



## A Rare Case of Hepatoid Adenocarcinoma in the Lung and Literature Review

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### Abstract

Hepatoid Adenocarcinoma (HAC) is a rare type of adenocarcinoma with adenoid and hepatocyte-like differentiation that occurs outside liver. It has high malignancy, strong invasiveness and poor prognosis. The tumor can occur in multiple organs, most often in stomach, and cases of primary lung are extremely rare with few reports. Here, we report a case of Hepatoid Adenocarcinoma of the Lung (HAL) which was admitted to the Affiliated Hospital of Jiangnan University.

**Keywords:** Lung neoplasms; Hepatoid adenocarcinoma; Immunohistochemistry; Prognosis

### Introduction

HAL is an extremely rare malignant tumor originating from the lung with hepatocellular carcinoma and adenocarcinoma-like characteristics. The tumor cells can secrete molecules such as AFP, HepPar1, HEA 125 and MOC31. This disease occurs mostly in middle-aged and elderly patients over 50 years old and is more common in men who have smoking history [1]. Usually, there is no specific clinical symptoms, most patients are not diagnosed until advanced stage and have poor prognosis. Because of the extremely low incidence and strong tumor heterogeneity, so far there is still no uniform treatment plan of HAL; therefore, the emergence of any new case will contribute to the research and classification of the disease, and improve our understanding. Now we report a case of HAL in our center recently, and also review the literature to further study the clinicopathological features, immunophenotype, diagnosis, treatment and prognosis of HAL to improve the understanding of this rare disease.

### Case Presentation

The patient, male, 67 years old, was admitted to the hospital on 06-02-2018 for "physical examination of right lower lung lobe mass 3 days". During the course of the disease, the patient had no symptoms such as cough, chest distress, chest pain and hemoptysis. He had a history of hypertension for more than 10 years and no history of smoking, no history of hepatitis, no other history of stomach and testicular tumors. No positive signs were found in physical examination. CT examination: there is an irregular mass in the right lower lobe, the size is about 4.1 cm × 3.5 cm and uneven enhancement can be seen, the edge of the tumor is not clear, bilateral pleural thickening, there are some small lymph nodes in mediastinal and right hilar. Abdominal CT showed no tumor in the liver (Figure 1A). ECT: there are no clear signs of bone metastasis (Figure 1B). PET-CT: there is abnormal FDG metabolism in the right lower lobe mass, and pleural decompression is not clear,  $SUV_{max} = 19.02$ , the FDG metabolism of right hilar lymph nodes increased,  $SUV_{max} = 3.82$ , considering the possibility of metastasis; several small lymph nodes were seen in the mediastinum, and no significant abnormal increase in metabolism was observed in FDG; no significant abnormal increase in FDG metabolism was observed in PET imaging of the whole body (Figure 1C). Laboratory examination: AFP: >2000 ng/ml, CY211: 4.63 ng/ml, liver function is normal. After completing preoperative examination and excluding surgical contraindications, the patient was received right lower lobe resection and lymph node dissection under thoracoscopic on 06-27-2018. Postoperative pathology: poorly differentiated adenocarcinoma of the right lower lobe with local necrosis, size 5.5 cm × 4.0 cm × 3.8 cm, no lymph node metastasis (0/9) (number of metastases/total number of lymph nodes), 2<sup>nd</sup> group of lymph nodes (0/2), 7<sup>th</sup> group of lymph nodes (0/2), 10<sup>th</sup> group of lymph nodes (0/2), 11<sup>th</sup> group of lymph nodes (0/3); no tumor thrombus was seen in the vascular tube, no

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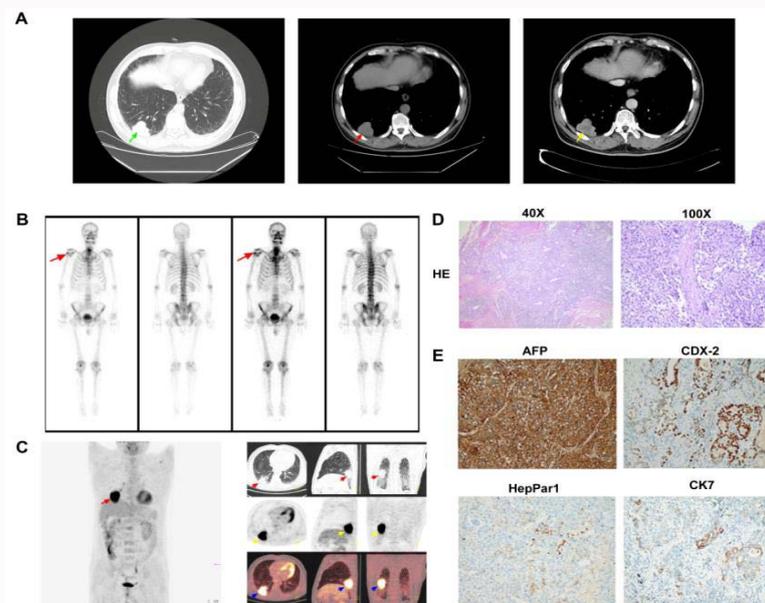
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**Figure 1:** A. CT of the patient (left, lung window; middle, mediastinal window) showed a soft tissue mass (green and red arrowhead) with its size about 4.1 cm x 3.5 cm in the right lower lobe. The lesion (yellow arrowhead) showed mild heterogeneous enhancement on the contrast CT image (Right). B. ECT of the patient showed the metacarpal osteogenesis of the right humeral head is increased (red arrowhead), and it is recommended to follow up. There is no obvious abnormality in the remaining bone imaging. C. PET-CT of the patient showed there is abnormal FDG metabolism in the right lower lobe mass,  $SUV_{max}=19.02$  (A, red arrowhead), B showed CT (red arrowhead), PET (yellow arrowhead) and PET-CT (blue arrowhead) of the tumor; no significant abnormal increase in metabolism was observed in FDG; no significant abnormal increase in FDG metabolism was observed in PET imaging of the whole body. D. Pathology of hepatoid adenocarcinoma of the lung showed poorly differentiated adenocarcinoma with local necrosis. (HE staining, A: 40x; B: 100x). E. Immunohistochemistry results of HAL. (Upper left: AFP positive; Upper right: CDX-2 partial positive; Lower left: HepPar1 small positive; Lower right: CK7 small positive).

invasion was observed in the nerve, no cancer was involved in the bronchial margin, and the pleural surface of the tumor was close to the cancer tissue (Figure 1D). Immunohistochemistry results: AFP (+), CDX-2 (partial +), CK7 (small +), CK20 (individual +), HepPar1 (small +), ALK (-), P40 (-), PE10/SPA (-), Napsin A (-), CK5/6 (-), Syn (-), CgA (-), PLAP (-), CD30 (-), CD56 (-), CD117 (-), Vimentin (-), P63 (-), TTF-1 (-), considering poorly differentiated cancer with hepatic differentiation (Figure 1E). The patient was discharged a week after surgery.

## Discussion

HAC is a rare malignant tumor that occurs outside the liver. It is similar to hepatocellular carcinoma in morphology and has adenocarcinoma-like characteristics. The tumor can occur in multiple organs; Metzgeroth et al. [2] reviewed the clinical features of 261 cases of HAC and found that the most common site of HAC was stomach (63%), and other parts including ovary (10%), lung (5%), gallbladder (4%), pancreas (4%), and uterus (4%). Given the rareness of the disease, complete clinical presentation and morphological description, biological behavior, and prognosis of any new case may contribute to the research and classification of the disease. Therefore, we discuss this case of HAL in detail to increase the understanding of the rare diseases. The origin of HAL remains unclear. Ishikura et al. [1] thought that HAL most likely originate from ectopic hepatocytes or germ cells in the lung tissue and respiratory epithelium during embryonic development. Some lung cancers may differentiate into hepatocytes, therefore, resulting in HAL. Saka et al. [3] considered this disease to be an intrapulmonary manifestation of extragonadal germ cell cancer syndromes. Sinard et al. [4] believed that hepatocytes have abnormal differentiation in other parts of the body (outside the liver) leading to HAC. HAL usually occurs at the older age; mostly patients

are over 50 year's old male with history of smoking. Our case presented here is an elderly male patient with no history of smoking. Most of the patients with HAL have been in clinical progression, serum AFP levels are often elevated. In this case, the preoperative AFP level was >2000 ng/ml and declined to 1180.12 ng/ml one week post operation; two months later, the AFP level became normal. Tumors vary in size; most of them are larger than 5.0 cm. The maximum diameter of this tumor is 5.5 cm. The cut surface of the gross specimen is gray or gray-brown, with clear boundaries. The central necrosis is mainly composed of hepatic-like differentiation zone and non-hepatic-like differentiation zone, and the hepatic-like differentiation zone cancer tissue is nested and beam-like. The cancer cells are large, polygonal, cytoplasm rich, eosinophilic or transparent, with PAS-positive small body, the nuclear is large, dark staining and in abnormal shape, the interstitial can appear more sinusoids and often have necrosis. Non-hepatic-like differentiation areas can be seen in adenoid and papillary structures, and a few areas are poorly differentiated adenocarcinoma-like changes. Ishikura et al. [1] reported in 1990 that HAC can be diagnosed when a typical alveolar or papillary adenocarcinoma and a component similar to hepatocellular carcinoma are observed and AFP is expressed. However, with the increased number of cases reported, we found that AFP is not unique to HAC. Therefore, it is necessary to use other specific molecules for immunohistochemical staining to aid diagnosis. HepPar1 is a relatively specific hepatocyte marker, which has no obvious crossover with other tumors. Immunostaining of CK molecules also contributes to the diagnosis HAL. It is reported that CK18 is positive in HAL, while CK20 is negative, and CK7 staining may be positive or negative [5]. In this case, immunohistochemical AFP (+), CDX-2 (partial +), CK7 (small amount +), CK20 (individual +), and HepPar1 (small amount +) were observed, which were similar to those reported in the literature. In summary, we believe

that the diagnosis of HAL should mainly rely on the morphological characteristics similar to hepatocellular carcinoma, combined with immunohistochemical markers AFP, Hepatocyte, CK18 and other positively expressed molecules, and excluded by clinical pathology and Immunohistochemistry metastasis of diseases such as hepatocellular carcinoma. So far there is no standard treatment scheme of HAL. Surgical resection, adjuvant chemotherapy and radiation are common choices for the treatment of this disease [6]. In recent years, molecular targeted therapy has also shown some curative effect. Khozin et al. [7] reported the first case of treatment of HAL with the tyrosine kinase inhibitor crizotinib, which resulted in a reduction in tumor volume. Gavrancic et al. [8] recently reported the use of platinum combined with sorafenib in the treatment of a patient with stage IV HAL who achieved partial remission and remained stable for 11 months, which is the longest survival time for patients with stage IV whose tumor cannot be resected. Basse et al. [9] reported that immunotherapy was used for HAL, although programmed death ligand 1 (PD-L1) was negative in this patient's tumor cells and immune cells, the patient presented a partial response to immunotherapy, unfortunately, the patient eventually died of infection. Previous studies have shown that the prognosis of HAL is poorer than other common types of lung tumors. However, if the disease is found early and the tumor is small, the prognosis of some cases will be better after complete surgical resection [8]. In this case, the tumor stage was (pT3N0M0, IIB), no lymph node metastasis, no vascular and nerve invasion, but the degree of tumor differentiation was low, and the prognosis needs further follow-up. The poor prognosis of HAL may be due to: 1. extensive tumor invasion and biological behavior of distant metastasis; 2. AFP production, which has immunosuppressive properties, then the body's immune response to tumors declines. In addition, the prognosis of HAL is also related to tumor stage, Ki67 index, Vascular Endothelial Growth Factor (VEGF) expression and other factors.

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