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REVIEW

- 1535 Intracranial pressure monitoring: Gold standard and recent innovations
Nag DS, Sahu S, Swain A, Kant S

- 1554 Role of the brain-gut axis in gastrointestinal cancer
Di YZ, Han BS, Di JM, Liu WY, Tang Q

MINIREVIEWS

- 1571 Cholestatic liver diseases: An era of emerging therapies
Samant H, Manatsathit W, Dies D, Shokouh-Amiri H, Zibari G, Boktor M, Alexander JS

ORIGINAL ARTICLE

Basic Study

- 1582 Neural metabolic activity in idiopathic tinnitus patients after repetitive transcranial magnetic stimulation
Kan Y, Wang W, Zhang SX, Ma H, Wang ZC, Yang JG

Retrospective Study

- 1591 Neuroendoscopic and microscopic transsphenoidal approach for resection of nonfunctional pituitary adenomas
Ding ZQ, Zhang SF, Wang QH

- 1599 Safety and efficacy of transjugular intrahepatic portosystemic shunt combined with palliative treatment in patients with hepatocellular carcinoma
Luo SH, Chu JG, Huang H, Yao KC

- 1611 Leveraging machine learning techniques for predicting pancreatic neuroendocrine tumor grades using biochemical and tumor markers
Zhou RQ, Ji HC, Liu Q, Zhu CY, Liu R

Clinical Trials Study

- 1623 Development and validation of a model to determine risk of refractory benign esophageal strictures
Lu Q, Lei TT, Wang YL, Yan HL, Lin B, Zhu LL, Ma HS, Yang JL

SYSTEMATIC REVIEWS

- 1634 Hydatid cyst of the colon: A systematic review of the literature
Lataat-Córdoba MÁ, Ruiz-Blanco S, Sanchez M, Santiago-Boyer C, Soto-García P, Sun W, Ramia JM

CASE REPORT

- 1643** Colon cancer arising from colonic diverticulum: A case report
Kayano H, Ueda Y, Machida T, Hiraiwa S, Zakoji H, Tajiri T, Mukai M, Nomura E
- 1652** Endoscopic submucosal dissection as excisional biopsy for anorectal malignant melanoma: A case report
Manabe S, Boku Y, Takeda M, Usui F, Hirata I, Takahashi S
- 1660** Gastrointestinal infection-related disseminated intravascular coagulation mimicking Shiga toxin-mediated hemolytic uremic syndrome - implications of classical clinical indexes in making the diagnosis: A case report and literature review
Li XY, Mai YF, Huang J, Pai P
- 1671** A complicated case of innominate and right common arterial aneurysms due to Takayasu's arteritis
Wang WD, Sun R, Zhou MX, Liu XR, Zheng YH, Chen YX
- 1677** Multimodality-imaging manifestations of primary renal-allograft synovial sarcoma: First case report and literature review
Xu RF, He EH, Yi ZX, Lin J, Zhang YN, Qian LX
- 1686** Chronic progression of recurrent orthokeratinized odontogenic cyst into squamous cell carcinoma: A case report
Wu RY, Shao Z, Wu TF
- 1696** Gastric adenocarcinoma of fundic gland type after *Helicobacter pylori* eradication: A case report
Yu YN, Yin XY, Sun Q, Liu H, Zhang Q, Chen YQ, Zhao QX, Tian ZB
- 1703** Synchronous multiple primary gastrointestinal cancers with *CDH1* mutations: A case report
Hu MN, Lv W, Hu RY, Si YF, Lu XW, Deng YJ, Deng H
- 1711** Primary hepatoid adenocarcinoma of the lung in Yungui Plateau, China: A case report
Shi YF, Lu JG, Yang QM, Duan J, Lei YM, Zhao W, Liu YQ
- 1717** Liver failure associated with benzbromarone: A case report and review of the literature
Zhang MY, Niu JQ, Wen XY, Jin QL
- 1726** Giant low-grade appendiceal mucinous neoplasm: A case report
Yang JM, Zhang WH, Yang DD, Jiang H, Yu L, Gao F

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Primary hepatoid adenocarcinoma of the lung in Yungui Plateau, China: A case report

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Abstract

BACKGROUND

Hepatoid adenocarcinoma (HAC) occurs in extrahepatic organs such as the gastrointestinal tract, testes, ovaries, lungs, mediastinum and pancreas, and frequently produces α -fetoprotein (AFP). HAC of the lung (HAL) is rare, characterized by difficult treatment and poor prognosis. There are no reports of HAL in Yunnan-Guizhou Plateau, China.

CASE SUMMARY

A 60-year-old male patient was clinically diagnosed with HAL pT3N0M0, stage IIB. Chest computed tomography revealed a 7.5 cm \times 7.2 cm soft tissue mass located in the right lung upper lobe and the adjacent superior mediastinum. Right upper lobectomy was performed. The diagnosis of HAL was confirmed by pathological examination, and the patient received paclitaxel and carboplatin as adjuvant chemotherapy after surgery.

CONCLUSION

Clinical manifestations, pathological features, imaging findings, auxiliary examination, and treatment planning of HAL are presented to help clinicians improve their diagnosis and treatment.

Key words: Hepatic adenocarcinoma; Lung cancer; Immunohistochemistry; α -Fetoprotein; Case report

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Core tip: We present a patient with primary hepatoid adenocarcinoma of the lung (HAL) in Yungui Plateau, China. HAL is a rare tumor involving difficult treatment and poor prognosis. We discussed the clinical manifestations, pathological features, imaging

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INTRODUCTION

Hepatoid adenocarcinoma (HAC) is a rare neoplasm with aberrant hepatocellular differentiation, and morphological features similar to hepatocellular carcinoma^[1]. HAC occurs in extrahepatic organs, and the most common site of origin is the stomach^[2-4]. There have been a few reports of HAC in extrahepatic organs such as the ovaries, mediastinum and pancreas^[1]. Primary HAC of the lung (HAL) is rare.

HAL was first formally described by Ishikura *et al*^[3] in 1990. Compared with the other more common types of lung tumors, HAL has a poorer prognosis^[5-7] and its invasiveness may explain its high mortality rate^[3,7]. The clinical symptoms of HAL are uncertain, and its biological significance remains to be elucidated^[4]. Computed tomography (CT) images, combined with morphology and immunohistochemistry, may provide some indications for confirmation of this diagnosis. The following two points about diagnostic criteria of HAL were proposed by Ishikura^[3]: (1) Typical acinar or papillary adenocarcinoma; and (2) α -fetoprotein (AFP). AFP expression is positive and/or the level of AFP is elevated in most HAL cases^[8]. The present literature review found no relevant cases of HAL in Yunnan-Guizhou Plateau, China. The limited literature regarding HAL is summarized in [Table 1](#). Here, we present a case that was diagnosed as HAL, and the postoperative pathological stage was pT3N0M0, stage IIB.

CASE PRESENTATION

Chief complaints

A 60-year-old man was hospitalized with repeated coughing and expectoration for > 4 years, and the symptoms worsened for 1 mo.

History of present illness

The patient had no history of the present illness.

History of past illness

He had undergone esophageal polypectomy, and suffered from gastric ulcers for > 20 years.

Personal and family history

No specific personal and family history of disease.

Physical examination upon admission

Physical examination showed that thick breathing sounds could be heard in the upper right lung, along with moist rales.

Laboratory examinations

No obvious abnormalities were found in liver and kidney function. Serum AFP (1210.0 ng/mL), cancer antigen (CA) 125 (38.43 U/mL), carcinoembryonic antigen, CA15-3 and CA72-4 were normal. C antibodies, E antibodies and surface antibodies were all positive for six items of hepatitis B, and the rest were negative.

Imaging examinations

A 7.5 cm × 7.2 cm soft tissue mass in the right lung upper lobe and adjacent superior mediastinum was observed by CT. The boundary of the soft tissue was clear, and there was significant inhomogeneous enhancement after enhanced CT ([Figures 1 and 2](#)). Numbers of enlarged lymph nodes were found in the mediastinum. The largest

Table 1 Clinicopathologic characteristics of patient with hepatoid adenocarcinoma of the lung

Ref.	Year	Region	Age / Sex	Maximum diameter in cm	Ki-67	VEGF	Immunohistochemical AFP	Serum AFP as µg/L	Hepatocyte	Survival time
Bai <i>et al</i> ^[9]	2006	Shanghai	48/M	7	Low-medium level	no data	-	-	+	9 mo
Cao <i>et al</i> ^[12]	2008	Beijing	64/M	3	no data	no data	no data	2037	no data	12 mo
Feng <i>et al</i> ^[13]	2013	Shanghai	46/M	2.4	no data	no data	little +	586	little +	6 mo
Haninger <i>et al</i> ^[14]	2013	Louisville	51/M		lowly proliferative	no data				14 mo
Shaib <i>et al</i> ^[15]	2014	Atlanta	53/F		no data	no data				4 yr
Gavrancic <i>et al</i> ^[16]	2014	New York	64/M		no data	no data				2 mo
Che <i>et al</i> ^[17]	2014	Beijing	48/M		no data	no data				
Liu <i>et al</i> ^[18]	2014	Guangzhou	64/M		no data	no data				
Zhong <i>et al</i> ^[19]	2015	Jiangxi	61/M	5.7	40% +	no data	++	943	-	2 wk
Motooka <i>et al</i> ^[20]	2016	Kumamoto	69/M	4.3	no data	no data	+	4497	+	51 mo
Sun <i>et al</i> ^[21]	2016	Shandong	59/M		20%	no data				23 mo
Grossman <i>et al</i> ^[22]	2016	New York	54/M		no data	no data				3 mo
Hou <i>et al</i> ^[11]	2017	Shandong	59/M	4	20%	no data	-	-	no data	12 mo
YF Shi	2018	Yunnan	60/M	7	50% +	no data	no data	1210	weak+	15 mo

VEGF: Vascular endothelial growth factor; AFP: α-Fetoprotein; Ki-67: Nuclear-associated antigen 67.

lymph node diameter was 1.4 cm. There were calcified nodules in the right middle lobe, and subpleural nodules in the left upper lobe. Abdominal magnetic resonance imaging, including the liver, gallbladder, pancreas and spleen, and double kidney B ultrasound did not show any occupying lesions.

FINAL DIAGNOSIS

The specimen was sent for pathological examination after surgery. The diagnosis of HAL was confirmed by pathological examination.

TREATMENT

The patient had no surgical contraindications after examination. Resection of the right upper lung was performed. The tumor was located in the upper right lobe of the right lung, and measured about 7 cm × 7 cm × 5 cm. The 1st, 2nd, 3rd, 4th, 7th and 11th groups of mediastinal lymph nodes were resected. The specimens were sent for pathological examination after surgery.

OUTCOME AND FOLLOW-UP

Right upper lobectomy was performed. The diagnosis of HAL was confirmed by pathological examination, and the patient received paclitaxel and carboplatin as adjuvant chemotherapy after surgery. For economic reasons, we did not carry out detection of tumor histogenetics and immune-related indicators. Chemotherapy was given once in the first month after surgery. Paclitaxel and carboplatin were added. Because of a serious adverse reaction to chemotherapy, the patient did not continue with the chemotherapy and other treatment. He died 15 mo after surgery.

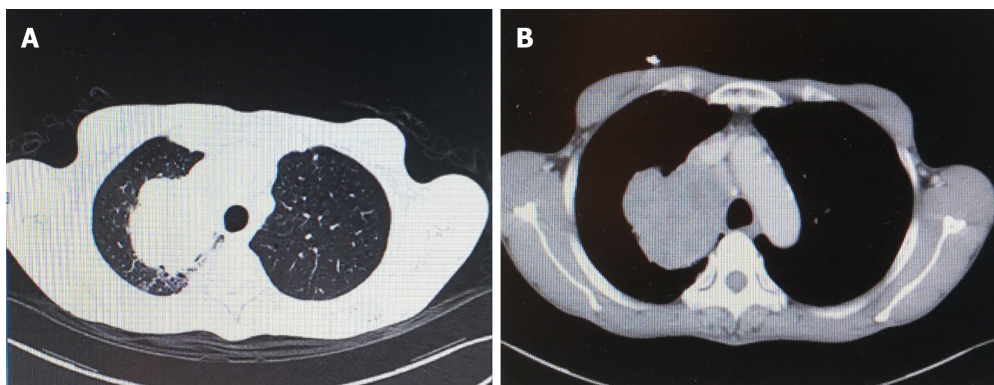


Figure 1 Computed tomography scan. A: Space-occupying lesion of the upper lobe of the right lung; B: Mediastinal window of the upper lobe of the right lung.

DISCUSSION

HAC is a rare tumor that was first recognized as a gastric tumor in 1985 by Ishikura *et al*^[8], and its etiology is still unclear. It has hepatocellular carcinoma-like differentiation and cytological characteristics. It is an aggressive tumor that most commonly arises from the gastrointestinal tract, and there are also a few reports in the ovaries, mediastinum, pancreas and other organs. Primary HAL is very rare. Ishikura *et al*^[3] showed that the pharynx, esophagus, upper gastroduodenal region, liver, gallbladder, pancreas and respiratory system below the throat all develop in the anterior intestine of the embryonic primitive digestive tract. Due to abnormalities in the differentiation process, certain adenocarcinomas of the lungs and other tissues may differentiate into hepatocytes. However, a small number of HACs are also seen in organs such as sweat glands, ovaries, endometrium, frontal sweat glands, and adrenal glands. In terms of embryonic histology, the above organs do not develop from the original digestive tract, or even from the endoderm. Therefore, further research and discussion are needed to explain the origin of extrahepatic HAC in relation to embryonic development.

HAL commonly occurs in older male patients aged > 50 years. It frequently occurs in the upper lobe, and metastasis of the adrenal gland and spine has been reported^[9]. The prognosis is closely related to the pathological stage, and the clinical manifestations are nonspecific. According to existing reports^[9], there may be symptoms in common with those of other lung tumors, such as cough, expectoration and hemoptysis, and other clinical manifestations of lumbar and back pain. The patient reported in this article only showed symptoms of repeated cough and expectoration. Most of the tumors were located near the hilar area, and the margins were more regular based on clinicopathological and radiographic findings. Tumor marker AFP was often elevated, but cases with normal AFP have also been reported. Postoperative pathological specimens were often grayish white, with a tough, well-defined mass, and internal necrosis. The lung mass was biopsied via bronchoscopy, revealing histopathological findings of carcinoma with hepatoid features. Tumor cells were large and irregular in shape. Circles and polygons were also visible. The cytoplasm was rich, acidophilic or transparent, with obvious heteromorphism. The nuclear mitotic figures were easy to see, and the nucleus was large and irregular. Positive corpuscle was seen in the cytoplasm by periodic acid-Schiff (PAS) staining. Immunohistochemical staining showed that tumor cells were positive for AFP, hepatocytes and cytokeratin (CK) 18. Compared with the reported cases, the clinical manifestations of this case were nonspecific, AFP level was abnormal, the mass was large, but there was no distant metastasis. Bronchoscopy features and immunohistochemical results were similarly to those reported previously.

The clinical manifestations of HAC are nonspecific, and the imaging features are often larger than those of typical lung cancer, but the boundaries are relatively neat. Bronchoscopy often shows dense, small blood vessels in tumor cells, and PAS-positive homogeneous transparent bodies. Elevated AFP is a useful index for the diagnosis of HAL, but lung metastasis of hepatocellular carcinoma must be excluded^[10]. However, there are still reports of AFP-negative HAC. Hou *et al*^[11] showed that preoperative patients have the following conditions that can be considered as HAL: (1) Symptoms in common with those of lung cancer, such as cough, expectoration, hemoptysis and other lung cancers; (2) Elderly men; (3) AFP positivity; and (4) Liver without space-occupying lesions. Preoperative diagnosis of HAL is difficult because there are no obvious clinical manifestations, nor clinical



Figure 2 Pictures of hepatoid adenocarcinoma of the lung.

copathological or radiographic features.

Although serum AFP levels are not high (Table 1), HAL can be considered when high levels occur before surgery and there is no space-occupying lesion in the liver. It is generally recognized that the diagnosis of HAL depends on the cytopathological characteristics of hepatocellular carcinoma, and immunohistochemical staining for AFP, hepatocytes and CK18. Simultaneously, we can exclude lung metastasis of hepatocellular carcinoma. However, there are also reports of HAL with negative immunohistochemical staining for AFP and hepatocytes (Table 1). Therefore, HAL is still diagnosed based on comprehensive evaluation, and there are no highly specific indicators. HAL is essentially a special type of lung adenocarcinoma, and guidelines for diagnosis and treatment of lung cancer should be followed. The general principle is that if there is distant metastasis, systemic chemotherapy and local radiotherapy should be performed after a clear diagnosis. If there is no distant metastasis, surgical treatment or local radiotherapy should be performed. Chemotherapy should be considered according to the postoperative stage of HAL. We strongly recommend that patients undergo genetic and immunological tests. However, there are different chemotherapy regimens at present, and the prognosis of patients varies. Therefore, the optimal chemotherapy scheme still requires further research. In the present case, right upper lobectomy was performed. The diagnosis of HAL was confirmed by pathological examination, and the patient received paclitaxel and carboplatin as adjuvant chemotherapy after surgery. For economic reasons, we did not carry out detection of tumor genetics and immune-related indicators. Chemotherapy with paclitaxel and carboplatin was given once in the first month after surgery. Due to a serious adverse reaction to chemotherapy, the patient did not continue with chemotherapy and other treatments, and he died 15 mo after surgery in December 2018. The prognosis of HAL is not clear, and there is no specific retrospective study at present, which may be related to the reported number of cases. Preliminary research has found that vascular endothelial growth factor is highly expressed in HAL, which may be associated with early vascular invasion. The expression of Ki-67 may be directly related to prognosis. It is difficult to review and evaluate the results because of the small number of reported cases and lack of data on the above indicators. It is suggested that Ki-67 is expressed in HAL at levels between 20%-40% (Table 1)^[9-22]. We could not perform statistical analysis due to incomplete follow-up data. Early vascular invasion may be the direct cause of early HAL metastasis and high degree of malignancy. However, this patient has a large primary mass, and postoperative pathology confirmed vascular invasion, although distant metastasis was undetected. Therefore, the above speculation needs further confirmation with retrospective studies.

CONCLUSION

Pathological examination revealed a lump of 7 cm × 7 cm × 7 cm in the upper lobe of the right lung. The patient was considered to have HAC because of the immunohistochemistry results and elevated AFP. Abdominal magnetic resonance imaging, including the liver, gallbladder, pancreas and spleen, and double kidney B ultrasound did not show occupying lesions. Investigation also found that there was

no pleural or bronchial invasion, but vascular tumor thrombus was seen. Immunohistochemical staining showed that tumor cells were positive for epidermal growth factor receptor, pan-CK, CK18, Napsin A (small focus), CK8 (weak), CD117 (small), Ki-67 (50%), and hepatocytes (weak). In contrast, TTF-1, Syn, CgA, PD-1, PAS, Villin, VIM and CK7 were negative. Finally, no lymph node metastasis was seen.

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