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Case Report

Hepatoid adenocarcinoma of the lung: a case report

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Abstract: Introduction: Hepatoid adenocarcinoma of the lung (HAL) is a rare type of lung cancer, with only 19 cases in English literature being reported. Its diagnosis is based on pathology and the standard treatment has not been established. Case report: We present a case of HAL. The patient was a 42-year old man with a primary complaint of dry cough. The chest computed tomography revealed a mass of the right lung with the diameter of the largest cross-section of 12.4 cm. The patient underwent surgery. Immunohistochemical staining of the specimen showed the tumor was positive forα-fetoprotein, Hepatocyte and CK, CK18. Gene test showed no epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) rearrangement or receptor tyrosine kinase (ROS1) mutation. The patient was diagnosed as HAL, stage IIIB and then received postoperational chemotherapy of pemetrexed. However, brain metastases were found and the disease free survival was merely 3 months.

Keywords: α-fetoprotein, chemotherapy, hepatoid adenocarcinoma, lung, pemetrexed

Introduction

Hepatoid adenocarcinoma (HAC) was defined as a mixture of tubular or papillary adenocarcinoma with α-fetoprotein (AFP) production, or the presence of cells with abundant, eosinophilic cytoplasm and centrally located nuclei in sheet-like or trabecular portions resembling those of hepatocellular carcinoma (HCC) [1]. The origin of HAC is still under debate. It is thought that some organs including liver, stomach and lung are derived from the primitive fore-gut during development. Some tumors of these sites could abnormally undergo hepatoid differentiation [2]. Cases of HAC of stomach, ovary, pancreas, etc. have been reported. Among them, hepatoid adenocarcinoma of the lung (HAL) is seldom seen and the standard treatment has not been established. It seems multimodality treatment of radical surgery and chemotherapy may not necessarily be sufficient, and the most effective regimen still needs to be explored. Here we report a case of HAL and reviewed all the literature of this rare type of tumor.

Case presentation

The patient was a 42-year old man presented with a primary complaint of dry cough for 1 month. The chest computed tomography (CT) of another hospital showed a 9.2 cm×7.9 cm mass in the upper and middle lobe of the right lung. No prior history of hepatitis B or C was noticed. He had a 20 pack-year history of smoking and no history of alcohol abuse. The physical examination revealed reduced respiratory sound of the right lung.

Complete blood count and biochemical tests were within normal range. Serological tests for hepatitis B and C were unrevealing. Of all the tumor markers checked, only neuron-specific enolase (NSE) was elevated to 22.66 ng/ml (range: 0-16.3 ng/ml). Carcinoma embryonic antigen, cytokeratin-19 fragments and squamous cell carcinoma associated antigen were all normal and the AFP level was not determined before treatment. The chest contrast-enhanced CT revealed a soft tissue mass in the upper and middle lobe of the right lung with the diameter of the largest cross-section of 12.4 cm and a nodule of the hilum of the right lung. Lymphangitis carcinomatosa of the right upper lung was suspected (**Figure 1**). Abdominal contrast-enhanced CT, bone SPECT-CT and brain enhanced magnetic resonance imaging (MRI) found no evidence of metastases. No tumor was seen during bronchoscope and the biopsy

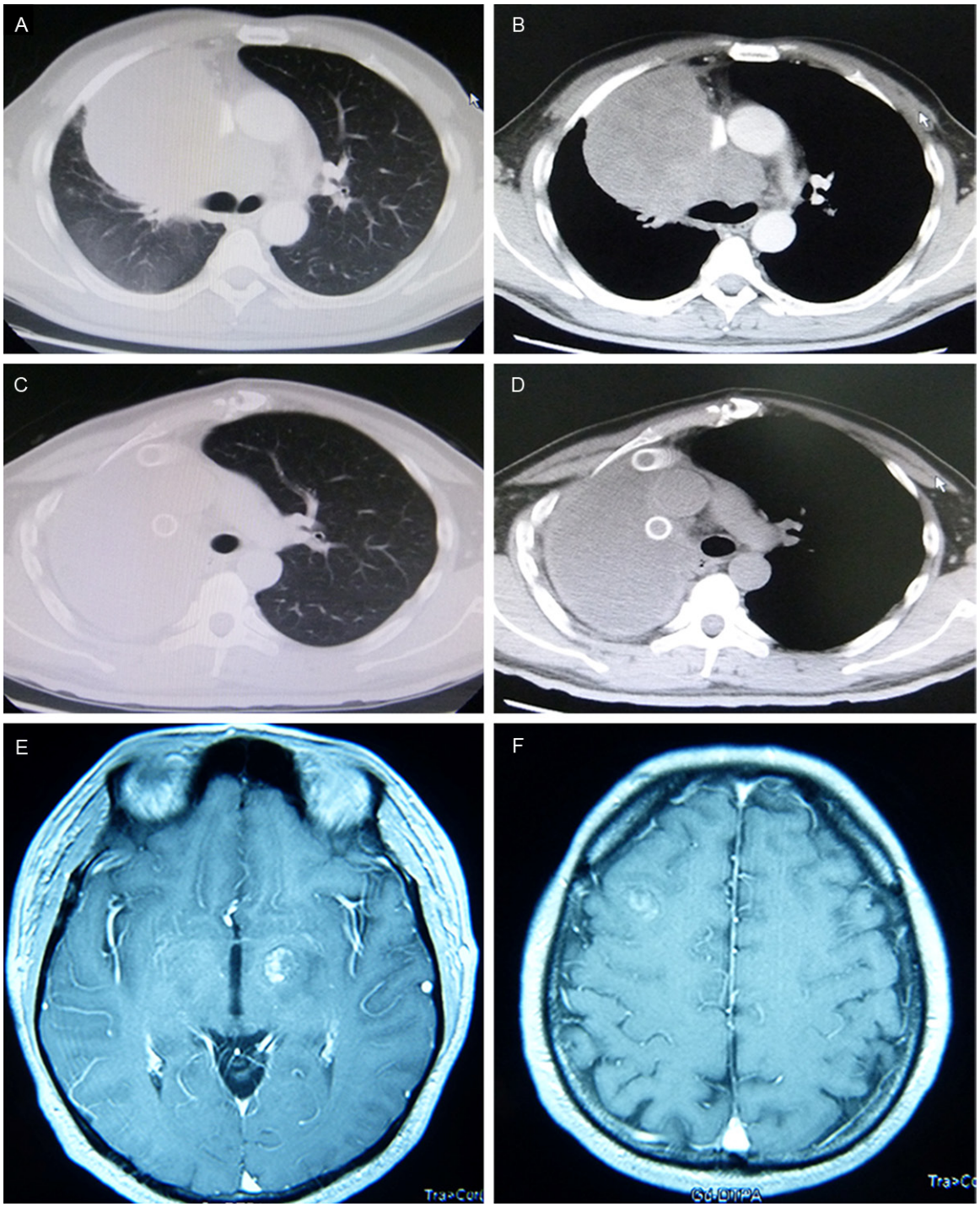

Figure 1. A, B. Pre-treatment CT showed a tumor of the right upper and media lobe with a diameter of 12 cm. C, D. post-operation CT. E, F Brain MRI showed multiple metastases after 2 cycles of chemotherapy.

of the anterior segment of the right upper lobe revealed just chronic inflammation. The patient underwent operation on 20 Apr 2015. A huge tumor of the right lung and enlarged mediastinal lymph nodes compressed heart and the big vessels and invaded the right pericardium, innominate vein and the superior vena cava (SVC). Group 2, 3 and 4 lymph nodes fused with the tumor and invaded mediastinal organs. Subcarinal lymph nodes were enlarged. Right

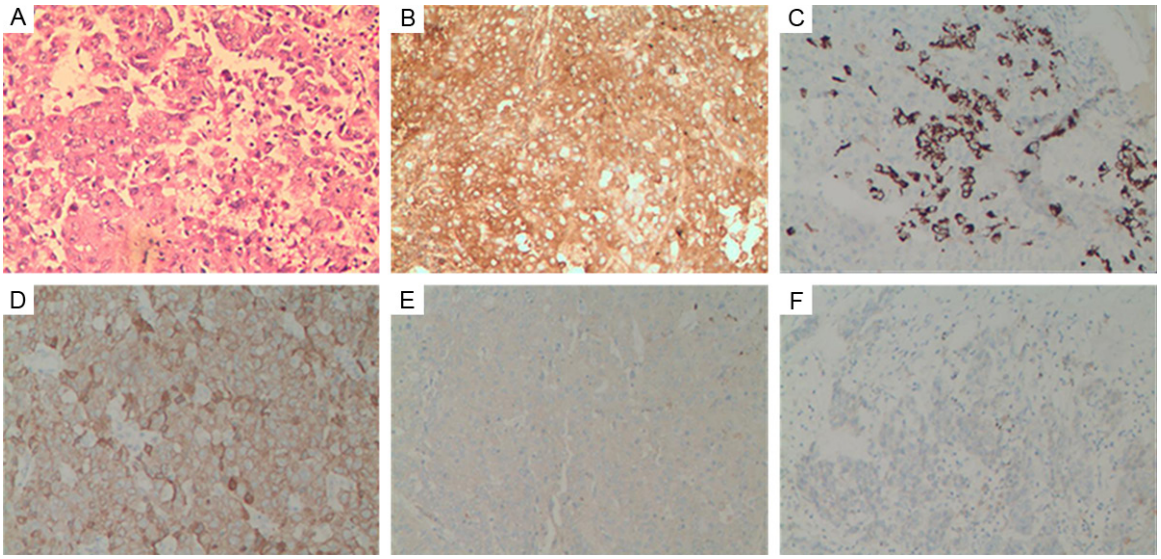

Figure 2. Histological and immunohistochemical findings of specimen. A. Morphology of HAL resembles that of HCC (hematoxylin and eosin staining; ×40); B. AFP (positive); C. Hepatocyte (focally positive); D. CK (positive); E. TTF-1 (negative); F. CK7 (negative).

pneumonectomy, systematic lymphadenectomy and innominate vein and the superior vena cava resection, left innominate vein, right atrium, right innominate vein-intrapericardial SVC artificial vessels reconstruction were performed.

On gross examination, a 20 cm×12 cm×5.5 cm tumor invaded pleura. Microscopically, low differentiated cancer tissue with abundant eosinophilic cytoplasm infiltrated the lung tissue. Margins were negative. Immunohistochemical staining showed the tumor cells were positive for AFP, Hepatocyte, CK (AE1/3) and CK18, but negative for TTF-1, CK7, Napsin A, P40, CD10, CgA, Syn and Vim, and Ki-67 25% (**Figure 2**). Gene test showed no epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) rearrangement or receptor tyrosine kinase (ROS1) mutation.

Postoperational AFP level was slightly elevated to 47.07 ng/ml (0-20 ng/ml), and NSE 17.22 ng/ml (0-16.3 ng/ml). Liver Gd-EOB-DTPA enhanced MRI and contrast-enhanced ultrasound found no mass of the liver.

The patient was diagnosed as hepatoid adenocarcinoma of the right lung, pT4N2M0, stage ⅢB. He received chemotherapy of pemtrexed 1.0 g (500 mg/m^2) d1. After two cycles, AFP level was elevated to 108.52 ng/ml (0-20 ng/ml). Thoracic CT showed no recurrence. No abnormality was found in abdominal CT and bone SPECT. But enhanced brain MRI revealed multiple metastases in right frontal occipital lobe, basal ganglia region and cerebellum (**Figure 1E**, **1F**). Disease free survival (DFS) was 3 months. The patient provided consent for publication in print.

Discussion

HAL is a relatively rare tumor of the lung, with 19 cases in English literature being reported (**Table 1**). Clinically, the cases of HAL share several common features. The majority of the patients were male (19/20), mostly smokers (16/20). The tumor sizes were large, ranged from 1 to 20 cm with a mean size of 7.6 cm. The masses were inclined to locate in the upper lobe (16/20). Most were at advanced stage at presentation, with Ib accounting for 10% (2/20), IIb 20% (4/20), IIIa 10% (2/20), IIIb 25% (5/20), and IV 35% (7/20). The tumors tended to metastasize, predominantly to brain (7/12), and then lung (6/12), adrenal gland (3/11), bone (3/11) and liver (2/12). HAC from different organs, although not exclusively HAL, appeared to share some features on CT. They were large tumors, isodense and moderately enhanced, with necrotic areas and lymphadenopathy [3].

The diagnosis of HAL depends on pathology. Differential diagnosis includes metastatic car-

Table 1. Clinical features and treatment of cases of hepatoid adenocarcinoma of the lung

Case	Age	Sex	Location	Size (cm)	AFP (ng/ml)	Stage	Treatment	Metastases	Survival (months)
Hayashi [17]	55	M	RU	6.5	Untested	pT2bN0M0, Ib	Surgery	--	Over 30
Carlifante [18]	82	M	LL	3.5	Untested	pT2bN0M0, IIa	Surgery	--	--
Wu [3]	50	M	RU	6	2.14	T2bN1M0, IIb	Surgery	--	Over 45
Lin [11]	66	M	RU	7.4	8686	pT3N0M0, IIb	Surgery, NP	--	48
Shaib [10]	53	F	RU	6.7	37810	pT3N0M0, IIb	Surgery, TP×3	--	Over 48
Kishimoto [19]	64	M	LL	7.5	673	pT3N0M0, IIb	Surgery	--	--
Che [8]	48	M	LU	10.0	6283	cT4N2M0, IIIa	Concurrent chemoradiation: 60Gy+TP×9, nedaplatin+TXT×5	Lung, liver	15
Hiroshima [20]	71	M	RL	10.5	7417	pT3N1M0, IIIa	Surgery	Lung, brain	12
Haninger [7]	51	M	RU	4.3	1.3	cT2N3M0, IIIb	Chemoradiation, debulking surgery	--	14
Arnould [12]	36	M	LU	10	11600	pT4N2M0, IIIb	Neoadjuvant BEP × 3, surgery, adjuvant doxorubicin + cyclophosphamide + cisplatin	Brain	7
Mokrim [13]	52	M	LU	11.8	5000	cT4NxM0, IIIb	NP×6	Lung	6-7
Papatsimpas [14]	28	M	RU	20	39000	cT4N0M0, IIIb	PC+bevacizumab×3, erlotinib	--	6
Terracciano [4]	49	M	LL	5	203320 IU/ml	IV	Surgery	Liver, adrenal gland, brain	2
Haninge [7]	52	M	RU	2.5	Untested	cT1bN0M1b, IV	Surgery, chemoradiation	Adrenal gland, brain, lung	Over 37
Haninger [7]	64	M	LU	3.2	untested	cT2aN0M1b, IV	Surgery, chemoradiation	Bone	10
Haninger [7]	54	F	LU	1	Untested	cT1aN0M1b, IV	Chemoradiation, debulking surgery	Bone, lung	Over 9 years
Haninger [7]	60	M	RU	11.2	4410	cT3N2M1b, IV	Chemoradiation	Brain	Over 1
Nasu [15]	63	M	RU	14.0	14000	cT4N2M1, IV	Irinotecan, cisplatin, carboplatin, fluorouracil, adriamycin, cyclophosphamide	Lung, adrenal gland, brain	11
Tatjana [16]	64	M	RU	3.8	181	cT2N2M1, IV	PC×4+sorafinib, vinorelbine×3+sorafinib, gemcitabine×1+sorafinib	Bone	11
Present	42	M	RU, RM	20	Untested	cT4N2M0, IIIb	Surgery, pemetrexed	brain	-- DFS 3

AFP, α-fetoprotein; M, male; F, female; RU, right upper lobe; LL, left lower lobe; RL, right lower lobe; LU, left upper lobe; RM, right middle lobe; NP, vinorelbine + cisplatin; TP, docetaxel + cisplatin; TXT, docetaxel; BEP, bleomycin +etoposide + cisplatin; PC, paclitaxe l + carboplatin; DFS, disease free survival.

cinoma from the liver, stomach and ovary, HAC from extrahepatic sites, and non-small-cell lung cancer (NSCLC) [1]. A final differential diagnosis can be reached, in most cases however, only through immunohistochemistry [4]. AFP positivity is often seen in HCC, cholangiocarcinoma, yolk sac tumors and tumors developing from the primitive foregut and not in the lung [5], but AFP production is often observed in HAL. Hepatocyte is specific to HCC with little cross-reactivity with other tumors [6], so the diagnostic specificity could be enhanced compared with AFP alone. Besides, CK18, HepPar1, CK7 and CEA could also be helpful [7-9].

Because of the rarity of it, conclusion of the standard treatment of HAL has not been drawn. Patients receiving surgery seemed to have a better prognosis. However, most cases were not at early stage while presentation, so systematic treatment was needed. The majority of the patients received platinum-based doublet therapy, which is the standard treatment for NSCLC. In the adjuvant setting, Shaib et al [10] presented a 53-year-old female patient with pT3N0M0, stage IIb disease who received cisplatin plus docetaxel for 3 cycles, and she was free of diseases for more than 4 years. As for another stage IIb patient who received vinorelbine and cisplatin for 6 months, DFS was also more than 4 year [11]. Arnold [12] reported a stage IIIb patient whose survival was 7 months after neoadjuvant chemotherapy of etoposide, cisplatin and bleomycin and then underwent surgery, and then doxorubicin, cyclophosphamide and cisplatin after recurrence and metastases. Che et al [8] presented a patient with stage IIIa disease who received concurrent chemoradiation. Radiation of 60Gy and taxol and platinum-based chemo were given. The survival was 15 months. Mokrim et al [13], Papatsimpas et al [14], Nasu et al [15] and Tatjana et al [16] presented patients with stage IIIb or IV diseases who received palliative chemotherapy. Mokrim's patient received vinorelbine and cisplatin for 6 cycles and the survival was 6-7 months. Papatsimpas's patient received paclitaxel and carboplatin for 3 cycles and erlotinib after progression and the survival was 6 months. Nasu presented a patient with stage IV disease treated with regimens of irinotecan, cisplatin, carboplatin, fluorouracil, adriamycin, cyclophosphamide successively and acquired a survival of 11 months. Different from other cases, Gavracic's patient received paclitaxel and carboplatin plus sorafinib, a drug usually used in HCC but failed to show survival improvement in NSCLC, and then vinorelbine and then gemcitabine plus sorafinib after progression. The survival of this case was 11 months. The other four cases did not specify whether the patient had received chemotherapy or not [17-20]. The case we presented here was the first one reported to use pemetrexed as systematic treatment but the efficacy of 3 months of DFS was disappointing. Nearly 50% of lung adenocarcinoma is driven by EGFR mutation. There are only two cases testing the EGFR mutation including the present one [7]. Unfortunately, EGFR mutation was detected in neither. ALK relocation and ROS1 mutation were not found. So the target therapy was not under consideration and the somatic mutation patterns of HAL still need accumulation of cases. To sum up, there doesn't seem to be an optimal regimen for the systematic treatment of advanced HAL, and whether a regimen covering both NSCLC and HCC could be more effective needs to be fully explored.

Generally, the prognosis of HAL seemed to be poor. Resectable cases tended to have longer survival, from 7 months to over 7 years, and a 9-year survival was reported for a patient of stage IV undergoing tumor debulking surgery [7]. As for unresectable disease, survival ranged from 2 to 15 months. However, although our patient received aggressive surgery, the prognosis was still not improved. All these cases strongly argue the stage is the most important prognostic factor for this kind of tumor. Because of the scarcity of HAL, there is still unknown territory needed to be explored. We suggest specifying the chemotherapy regimens used for HAL in future case reports.

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Disclosure of conflict of interest

None.

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