

Clinical Significance of a Rise in AFP in Lung Adenocarcinoma Patients with Liver Metastasis: One Case Report and Literatures Review

Yue'an Cao¹
Nanzhan Long¹
Chaosheng Peng¹
Ping Lu²
Jing Xia¹
Wei Wang¹
Wenxiu Xie¹

¹No. 3 Cadre Wards; ² Department of Pathology, Navy General Hospital of PLA, Beijing 100037, China.

Correspondence to: Yue'an Cao
E-mail: caoyuean2003@yahoo.com.cn

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CJCO <http://www.cjco.cn>
E-mail: 2008cocr@gmail.com
Tel (Fax): 86-22-2352 2919

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Introduction

Usually the alpha fetoprotein (AFP) concentration of patients with metastatic liver cancer is slightly raised. Most of the levels are lower than 400 ug/L^[1]. Following biopsies of lung and liver neoplasms, one patient with a clinical diagnosis of lung cancer plus liver metastasis was pathologically diagnosed having an adenocarcinoma. His serum AFP value was 100~300 times the normal value. In order to further explore the clinical significance of an elevation of the AFP level in patients with lung adenocarcinoma plus liver metastasis, and to precisely distinguish a simple liver metastasis from lung adenocarcinoma or from lung hepatoid adenocarcinoma (HAC), a clinical analysis of the patient, and a literature review was conducted.

Case Report

A 64-year old male patient, noting he had a space-occupying lesion in the right upper lung and liver over a 2-week period, was admitted to the hospital on May 18th, 2006. Two weeks before admission, the patient had visited another hospital because of prostatic hypertrophy. During a routine chest fluoroscopy, solitary tubercles in the right upper lung were found with a diameter of 1.4 × 2 × 3 cm, a limpid margin, a homogeneous internal density, and without intumescent lymph nodes. A multiple (3) intrahepatic nodular space-occupying lesion was shown by both abdominal ultrasound and MRI examinations, with a size of 1.8 × 2.0 cm or so, being diagnosed as a liver metastasis from lung cancer. No symptoms, such as cough, hemoptysis, chest pain and shortness of breath, or stomach ache etc. were found.

Physical examination after admission indicated that the patient's general health status was good, and mucocutaneous stained xanthochromia was not found. No large superficial lymph nodes were palpable, and no abnormalities were found upon examination of the heart, lung and abdomen functions. The lower extremities showed no swelling. Routine laboratory examinations showed that the blood, urine and stool were normal. The blood sedimentation rate was 6 mm/h, all 6 immune serum indices for viral hepatitis B were negative, but the serum AFP level was raised (see results). Values of the serum CEA, CA199, CA242 and CA50 were normal and there were no abnormalities of hepatic and renal functions. CT-guided puncture biopsies of the pulmonary and hepatic space-occupying lesions were respectively conducted on May 19 and June 6, 2006. CT-guided transcutaneous ar-

gon-helium knife radiation of the pulmonary and hepatic tumors was conducted on June 1 and 6, and 2 transcatheter hepatic-artery catheterization chemotherapy (pirarubicin, carboplatin and lipiodol embolism) were administered on June 22 and August 31. At present the tumor-bearing patient has survived for nearly 1 year since the final diagnosis, with a satisfactory general health status and an on-going symptomatic treatment. Observation of the patient's serum AFP level was conducted over a period of time, CT-guided puncture biopsy of the lung and liver space-occupying lesions performed, and pathological examination and immunohistochemical labeling analysis conducted.

The results of the AFP level were respectively 2,037 $\mu\text{g/L}$, 4,508 $\mu\text{g/L}$, 2,977 $\mu\text{g/L}$, 3,279 $\mu\text{g/L}$ and 2,502 $\mu\text{g/L}$ on May 19, June 21 and 27, September 4 and 7, 2006.

Pathologic results for the puncture biopsies of the lung and liver space-occupying lesions: pathological diagnosis indicated that both diseases, shown in Fig.1 and 2, were adenocarcinomas.

Fig.3. shows immunohistochemical labeling results of adenocarcinoma cells of the right upper lung: CK (AE1/AE3) (+), CK7 (+), CK17 (-), CEA (-), Syn (-); Fig. 4.shows the cells of adenocarcinoma of the liver: CK (AE1/AE3) (+), CK7 (-), CEA (-), AFP (-), hepatocyte (-).

Discussion

Adenocarcinoma of the lung itself does not result in an increase in the serum AFP level. When metastatic liver cancer occurs, the serum AFP level may be slightly raised. Usually, the level ranges from 25 $\mu\text{g/L}$ to 200 $\mu\text{g/L}$, or sometimes it has a transient increase, with less than 400 $\mu\text{g/L}$ in most instances. In our case, the patient did not suffer hepatitis or hepatic cirrhosis etc. After several assays, the serum AFP value ranged between 2,037 $\mu\text{g/L}$ to 4,508 $\mu\text{g/L}$ (normal value < 15 $\mu\text{g/L}$), which is about 100 to 300 times higher than the normal. Therefore in this case lung HAC was the preferred clinical diagnosis. HAC is an adenocarcinoma of a special type, occurring outside of the liver, with an adenoid and hepatocyte-like differentiations. Oncogenesis of this adenocarcinoma in the stomach has been frequently reported, however, HAC occurring primarily in the lung has only been reported several times^[2-4]. Like hepatic cellular cancer (HCC), there was an increase in the AFP level and positive AFP expression in the cancer cells in the serum of most HAC patients, nevertheless the AFP level did not rise in some of the patients. AFP expression is a distinctive expression of HAC, and AFP is an indication of primary HCC. It is well known that HCC, hepatoblastoma

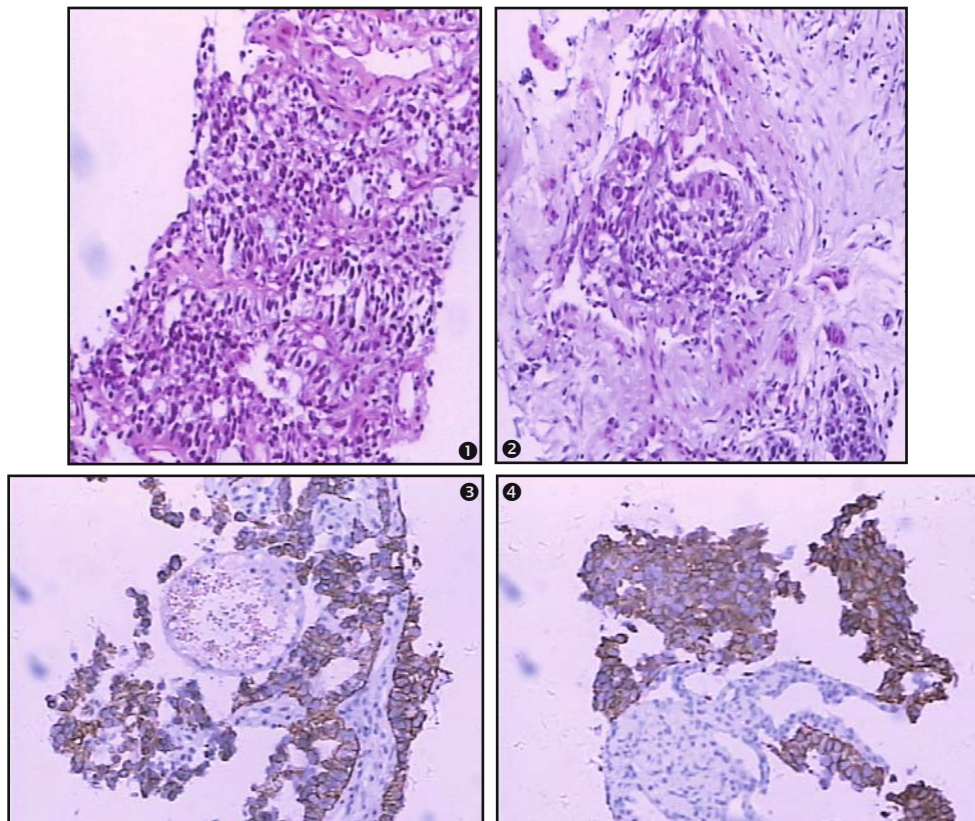


Fig.1. Adenocarcinoma of lung (H&E stain, $\times 100$). Fig.3. Immunohistochemical CK+ of the lung (H&E stain, $\times 100$).
Fig.2. Adenocarcinoma of liver (H&E stain, $\times 100$). Fig.4. Immunohistochemical CK+ of the liver (H&E stain, $\times 100$).

and germinoma may bring about elevated AFP. However, a possible reason for lung HAC to produce AFP may be that during the course of embryonic development, the organs such as lung, liver and stomach etc. arise from a common origin. Owing to an abnormality during the course of differentiation, adenocarcinoma occurring in organs such as lung etc. may differentiate towards liver cells^[5]. Besides displaying the characteristics of lung cancer, these cells can also produce a large amount of AFP and other HCC products etc., such as hemoglutin, ferroprotein and transferrin.

HAC has a strong tendency for invasion and metastasis, and liver metastases are concurrently confirmed in most of the patients when they are diagnosed with a primary lesion. So it should be noted that a diagnosis of HAC is different from extra-hepatic metastasis of primary HCC. Histo-morphology of the HAC is quite similar to that of the HCC, usually resulting in a very difficult differentiation. Most scholars emphasize that there is a multiclonal CEA expression in the HAC cytoplasm and mucous secretion can be found in the adenoid composition. However, the above characteristics are not found in HCC. Some authors describe an adenocarcinoma of the lung, with hepatocyte-like differentiated cancer cells, a morphological character similar to HCC, and a positive immunohistochemical expression of AFP, as a lung hepatoid adenocarcinoma. Although the specificity of AFP is very high, the sensitivity of AFP is poor. All HAC do not produce AFP, and positive expression of serum AFP is found in only a few adult HCC patients, with a patchy form and a weak positive expression. Therefore those adenocarcinomas with a morphological character of HCC but without production of AFP are called HAC with negative AFP^[6].

Morphologically, because lung HAC is difficult to differentiate from HCC, and both can develop metastasis, further clinical differentiation is needed to verify a diagnosis of HAC if lesions concurrently occur in the lung and liver. A preliminary differentiation can be based on the following: *i*) if AFP is positive, the preferential diagnosis should be pulmonary metastasis of HCC. However, if all pathologic findings indicate an adenocarcinoma, the possibility of HAC is to be considered and further immunohistochemical assays are necessary; *ii*) if AFP is negative, pulmonary metastasis of HCC and the HAC are possible, and a pathological examination for confirming the local lesions is needed; *iii*) primary hepatic carcinoma (PHC) is usually complicated with a variety of hepatitis or hepatic cirrhosis, but the above-mentioned symptoms seldom occur in hepatic metastasis of HAC. In accordance with these features, all pathological results for the pulmonary and hepatic lesions of our patient indicate an adenocarcinoma. At the same time, the AFP level obviously increased, without the diseases

such as hepatitis or hepatic cirrhosis. So the clinical diagnosis of lung HAC for this case is highly recommended. It has been reported that a strongly positive immunohistochemical expression of AFP was seen in PHC patients with a positive serum AFP expression^[7]. In our case, the adenocarcinoma patient expressed a positive serum AFP, but the immunohistochemical-labeled expression of AFP was negative. Therefore there is a need to probe the clinical significance of these results.

Few reports have been published on the prognosis of lung HAC, whereas there have been more studies on prognosis of stomach HAC. Chang et al.^[8] conducted a control study on HAC of the stomach comparing the positive and negative expression of serum AFP. They found that liver metastasis rates in the patients with positive and negative expressions were respectively 72% and 9.8%, and the 1, 3, 5 and 7-year survival rates in the patients were 38.7%, 11.6%, 11.6%, 11.6%, and 71.3%, 57.8%, 52.8%, 49.6%, respectively ($P < 0.01$). This shows that liver metastasis is prone to occur in patients with stomach HAC if AFP is positive. The higher the titer, the higher the rate of liver metastasis, and the poorer the prognosis. Based on our findings, we suggest that liver metastasis and an unfavorable prognosis are much more apt to occur in patients with positive AFP expression compared to those with negative expression. Further investigations on these tumors and related questions are necessary.

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