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Is it liver or lung cancer? An intriguing case of lung adenocarcinoma with hepatoid differentiation

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Abstract

We report the case of a 50-year-old man who was investigated for an incidental finding of a left lung mass following left shoulder pain over a three month period. He also had a significant raised serum alpha-fetoprotein (AFP) level of 29,000, which raised the suspicion of hepatocellular carcinoma with lung metastases. However, there was no detectable liver lesion on multiphase contrasted tomography of the liver and no significant hypermetabolic nodes or distant metastasis seen in the liver on positron emission tomography scan. A lung biopsy confirmed adenocarcinoma with hepatocellular differentiation that would explain the raised serum AFP level.

Keywords

Hepatocellular differentiation, lung carcinoma, alpha-fetoprotein, liver, metastasis, hepatoid adenocarcinoma

Introduction

Hepatoid adenocarcinoma (HAC) is a rare form of adenocarcinoma that is defined by morphological and functional hepatic differentiation. HAC occurs in extrahepatic organs such as gastrointestinal tract, testes, ovaries and lungs, and frequently produces alpha-fetoprotein (AFP). The diagnosis and treatment can be challenging due to the varied clinical presentation. However, morphological features and immunohistochemical analysis facilitate the diagnosis. We describe herein a case of lung adenocarcinoma with hepatoid differentiation, which, to the best of our knowledge, is the first case reported in Malaysia.

Case summary

A 50-year-old man presented with a complaint of left shoulder pain for three months. The pain was localised at the left scapular region, and was associated with numbness and weakness of the left arm. There was no significant loss of weight or loss of appetite, and he denied having any cough or shortness of breath. He had a smoking history of 40 pack-years. There was also a positive history of breast malignancy in his maternal aunt. Being a traffic police officer, he had been consistently exposed to vehicular fumes and dust throughout his adult life. Physical examination revealed features of left Horner's syndrome, as evidenced by left sided ptosis, meiosis, enophthalmos and anhidrosis. Features of left sided brachial plexopathy were also present, as demonstrated by reduced C8-T1 distribution sensory neuropathy and weakness of his left arm. Respiratory examination revealed features of left apical lung lesion with reduced air entry, reduced vocal resonance and dullness on percussion over the left apex. The clinical impression was of a Pancoast's tumour. His tumour markers showed a significant raised AFP level of 29,000, which raised the suspicion of hepatocellular carcinoma with lung metastases. His chest radiograph confirmed the presence of an apical lung mass. Bronchoscopy

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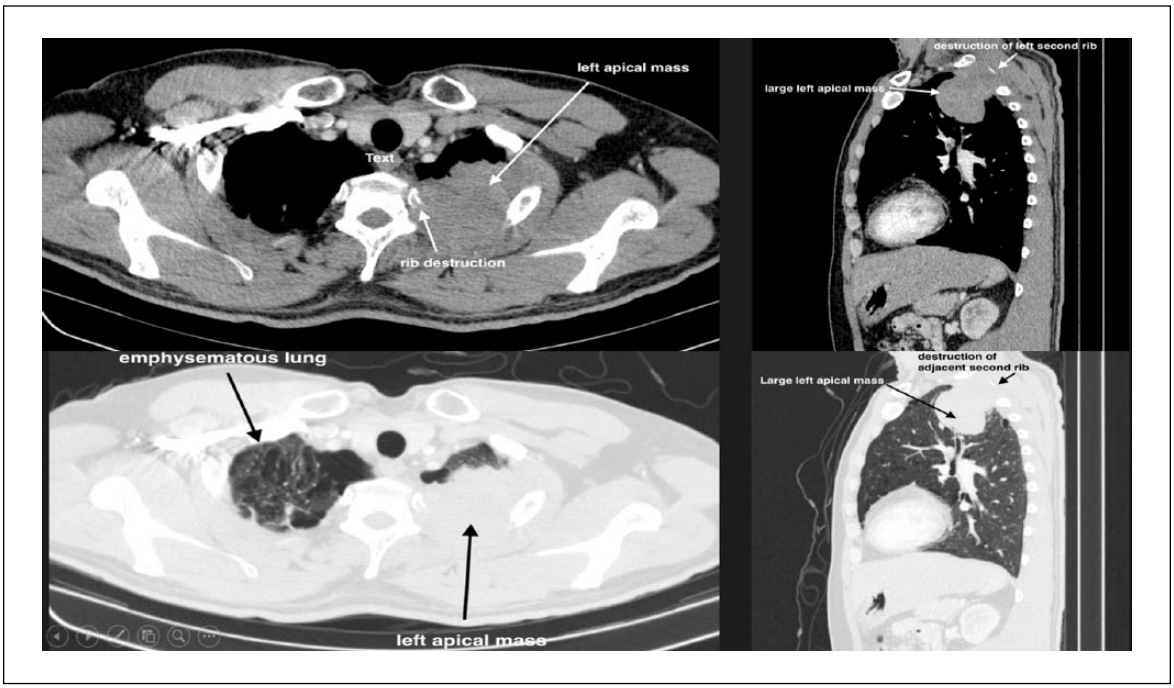

Figure 1. Axial and sagittal view of CT thorax, showing a left apical mass with destruction of adjacent second rib.

was normal. Contrasted tomography (CT) thorax showed an ill-defined large mass in the left apical region measuring 6 × 5 × 6 cm^3 with possible thoracic wall involvement at the upper part of the mass (Figure 1).

The CT guided lung biopsy subsequently performed revealed infiltrating malignant cells, arranged in solid nests with surrounding sinusoidal vessels, and occasional broad trabeculae formation. The malignant cells were polygonal with large amount of eosinophilic cytoplasm and central hyperchromatic nuclei with prominent nucleoli, resembling hepatocellular carcinoma (Figure 2). There were frequent mitotic figures. Focal mucin production was evident within the tumour. Immunohistochemical stain showed the malignant cells were positive for CKAE1/3, hepatocyte paraffin 1 (HepPar 1) and TTF-1 (cytoplasmic), focally positive for CK7, while negative for CK20, AFP, Napsin A, S100 protein, PLAP and p63.

The tumour was diagnosed as poorly differentiated adenocarcinoma with prominent hepatocellular differentiation. Subsequent CT liver revealed no detectable liver lesion. His positron emission tomography (PET) scan confirmed an avid tumour extending from left upper lobe into adjacent ribs, vertebra and muscle with no significant hypermetabolic nodes or distant metastasis seen. Based on his clinical presentation of a left Pancoast tumour, complemented by radiological absence of hepatic lesion and histological confirmation of poorly differentiated carcinoma, he was treated as a stage IIIB non-small cell lung cancer. In view of detrimental effects of the pain, he was treated with radical radiotherapy upfront to a total dose of 60 Gy in 30 fractions. His pain improved with radiotherapy, with lower requirement for opiates. He was planned for sequential chemotherapy following radiotherapy; unfortunately his performance status deteriorated to ECOG 2–3 within a month post treatment. Three months post-irradiation, he then progressed with cord compression at T1–T2 level due to primary tumour infiltration. Unfortunately he succumbed to his condition which worsened with concomitant sepsis and shock. The patient survived merely 7 months from the time of diagnosis.

Discussion

AFP-producing lung carcinoma is a rarely reported neoplasm and was first described by Ishikura et al. in 1990.[1] AFP production is observed in lung HAC that is typically large tumour commonly associated with regional lymphadenopathy and distant metastasis, with predilection for older patients and it is also an extremely aggressive tumour with poor prognosis.[2] The patient profile in our case is a middle-aged man with multiple risk factors for malignancy. His chronic smoking history, positive family history of malignancy, and significant occupational exposure are typical risk factors for malignancy. However, his clinical presentation was atypical that was left shoulder pain, in contrast to the majority of patients with lung cancer that typically present with chronic cough, haemoptysis and shortness of breath. Another atypical feature in this patient was that there were no constitutional symptoms of weight or appetite loss. It is unusual that he had features of Pancoast's tumour and Horner's syndrome while not having any respiratory symptoms. Adding to the curiosity of his presentation was his elevated AFP level. The clinical differential diagnosis was, could this be a hepatocellular carcinoma with lung metastasis or could it be dual primary malignancy or synchronous tumour? The HPE and immunohistochemical findings together with the absence of liver lesion in his multiphase CT liver and PET scan finally help to shed some light in his diagnosis. Differentiating HAC of lung from liver metastasis would be challenging in patients with both lung and liver

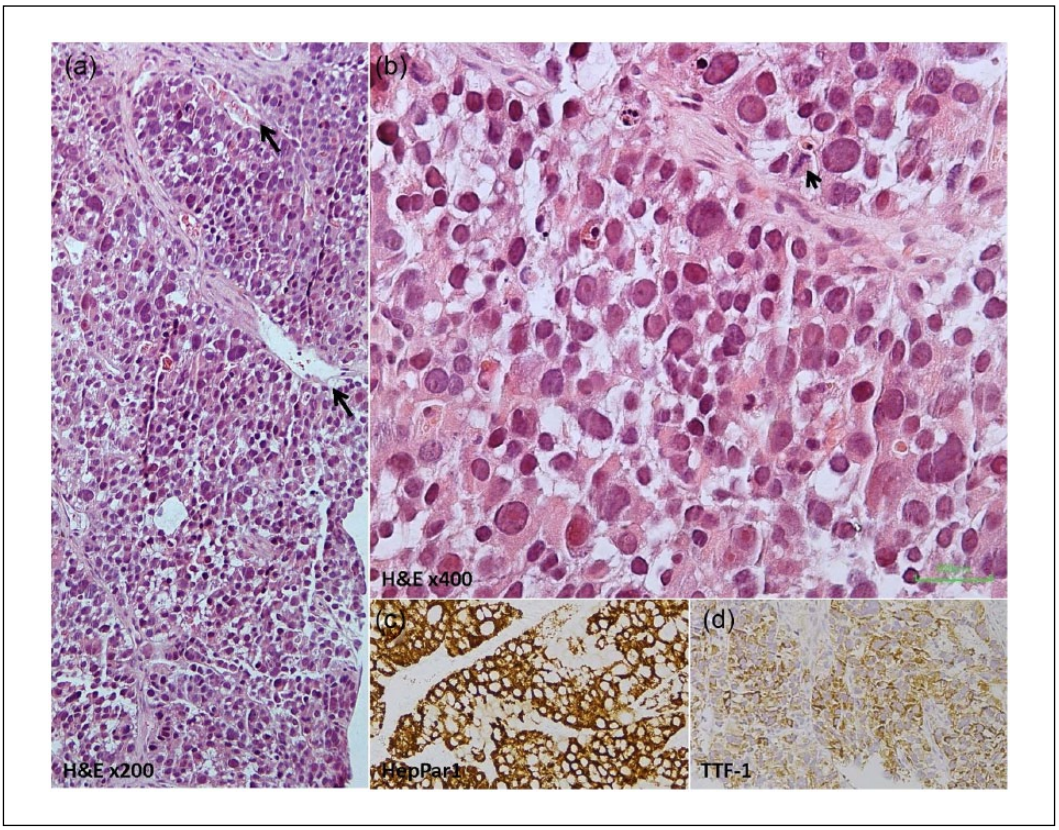

Figure 2. (a) CT guided lung biopsy showing infiltrating malignant cells arranged in solid nests with surrounding sinusoidal vessels (arrow; H&E ×200). (b) Polygonal malignant with large amount of eosinophilic cytoplasm, central hyperchromatic nuclei and prominent nucleoli; mitoses seen (short arrow; H&E ×400). Immunohistochemical (IHC) stain showing diffuse positivity for (c) HepPar1 and (d) TTF-1 (IHC ×200). H&E: haematoxylin and eosin.

masses,[3] but no liver mass was seen in this patient. Hence a multidisciplinary correlation between the treating respiratory physicians, radiologists, oncologist and pathologists is paramount important to conclude that this is an atypical, rare case of lung adenocarcinoma with hepatocellular differentiation, lung HAC. The patient subsequently was referred to the oncologists for further treatment of his lung malignancy, and he had poor response to primary radiotherapy. The diagnosis of his HAC was primarily based on the morphological features and immunohistochemical stains, with help of radiological modality that rule out the differential of metastatic hepatocellular carcinoma. The possibility of pulmonary metastasis from hepatocellular carcinoma was finally excluded in this case as there was no evidence of liver lesion or tumour on either CT multiphase liver or PET scan.

Several hypotheses have been postulated to explain AFP production. These include the 'ectopic hepatoma' theory that postulates tumours arising from ectopic germ cells or liver cells in the lung or respiratory epithelium progenitors. Another hypothesis suggested that hepatoid differentiation may occur at many diverse sites as another direction of differentiation of primitive neoplastic cells in an adenocarcinoma.[4]

There is no published consensus on treatment of HAC of the lung to date. At present they are treated as per any non-small lung cancer. Within the literature, there are less than 20 reported cases of HACs. Of these cases, the patients were described with majority male gender, large mass, advanced presentation and poor prognosis. Patients with localised tumour undergo surgery while those with distant metastasis are treated with concurrent chemoradiation. The combined treatment of surgical resection and adjuvant chemotherapy is also a common approach for selected cases. On the other hand, radiotherapy to the mediastinum with concurrent chemotherapy is appropriate and indicated to prevent tumour progression and compression to the adjacent structures.[4] Patients survive the longest after undergoing curative resection and multimodality adjuvant treatment. In our case, as majority of the HACs in the literature, surgical intervention was not possible due to his advanced disease.

Although AFP expression is not requisite for diagnosis of HAC, as the diagnosis depends on the recognition of characteristic histological features, serum AFP could offer a useful indicator to monitor tumour progression and treatment response.[6] The increased production of AFP is an indicator for poor prognosis because it possesses immunosuppressive properties. The poor prognosis is considered to be associated with extensive venous invasion and locally advanced or metastatic presentation.

Conclusion

This case illustrates an atypical presentation and a rare type of lung carcinoma. It also highlights the importance of having

a multidisciplinary approach to diagnosis and management. An accurate and early diagnosis using immunohistochemistry with the support of imaging modalities played important roles in optimising care of the patient. Further larger studies are needed to establish standard treatment approach for this rare type of lung cancer.

Declaration of Conflicting Interests

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