Cavitary Form of Lung Metastasis from Advanced Hepatocellular Carcinoma

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The most common site of extrahepatic metastasis in cases of advanced hepatocellular carcinoma is the lung. A 60-year-old Korean male had been previously diagnosed with hepatocellular carcinoma and was treated several times with transcatheter arterial chemoembolization prior to a regime of sorafenib after multiple bone metastases were detected. Despite 2 months of systemic treatment, the disease progressed, and newly developed cavitary nodules and ground glass opacities were observed on a chest computed tomography scan. Initially the patient was diagnosed with septic pneumonia and was subsequently treated with antibiotics over 2 weeks, with no observable improvement. A percutaneous transthoracic needle aspiration biopsy was performed to ascertain the noninfectious origin of the lung lesions. As a result, a rare form of pulmonary metastasis from hepatocellular carcinoma was discovered. Unfortunately, there were no available treatment options for the patient and so end-of-life care was recommended. (Korean J Med 2015;88:202-206)

Keywords: Hepatocellular carcinoma; Infection; Metastasis

INTRODUCTION

In advanced hepatocellular carcinoma, metastasis is most often seen intrahepatically, while the lung is the most common site of extrahepatic metastasis [1]. The typical radiologic findings of pulmonary metastases are multiple, round, variously sized nodules, generally in the peripheral parenchyma, combined with diffuse interstitial thickening [2]. Because multiple cavitary pulmonary nodules can have diverse etiologies such as septic pneumonia, fungal infections, Mycobacterium tuberculosis infection, vasculitis, and lung metastasis, identifying their origin can be difficult.
This case highlights the importance of considering pulmonary metastasis of a hepatocellular carcinoma, even when disease symptoms present with unusual or novel features.

CASE REPORT

A 60-year-old Korean male was diagnosed 7 years previously with chronic hepatitis B with related liver cirrhosis and hepatocellular carcinoma, which was diagnosed 3 years ago. He had undergone transcatheter arterial chemoembolization five times because of intrahepatic recurrences and metastases. When bone metastases were detected after a work-up to investigate back and chest pain, he underwent palliative radiation therapy to his sternum and his cervical and thoracic spine to alleviate bone pain. Subsequently, sorafenib, a tyrosine kinase inhibitor, was prescribed. After 2 months on sorafenib, he was admitted to our hospital with a fever, progressive dyspnea upon exertion, and general weakness. A chest radiograph identified multiple peripheral nodules with cavitation in both lungs. The patient had never smoked and his baseline lung function was normal. A chest computed tomography (CT) scan performed 3 years prior revealed no abnormal pulmonary parenchymal lesions, which would suggest emphysema.

The patient underwent a complete work-up, including computed tomography of the chest. The CT revealed multiple cavitary lesions, patchy consolidation, and ground glass opacities in both lungs (Fig. 1). At this time, serum levels of acute phase proteins were high (C-reactive protein [CRP], 21.45 mg/dL), fever was sustained, and radiological findings supported an infectious condition. Metastasis was not immediately suspected, despite a marked increased in tumor marker expression (alpha-fetoprotein [AFP], 379.8 ng/mL), as cavitary nodular lung metastases are rarely encountered in hepatocellular carcinoma. Septic pneumonia appeared to be a more likely diagnosis based on the fever, high CRP levels, and multiple peripheral nodules with cavitation. Despite our efforts to uncover a septic cause, none could be determined. However, during CT scan and echocardiogram of the abdomen we observed progression of the hepatocellular carcinoma with portal vein tumor thrombus. After several days of antibiotic treatment, the patient’s fever did not subside and radiographic findings showed no improvement. No causative microbiological factors were identified despite a multi-
disciplinary approach culturing sputum, blood, and urine as well as bronchoscopic alveolar lavage fluid. Considering the possibility of combined radiation pneumonitis, a short-term systemic steroid was administered intravenously, and the patient’s fever subsequently subsided. However, his condition still showed no clinical or radiographic improvements. His continued lack of response to treatment for pneumonia suggested a noninfectious condition. Therefore, a percutaneous transthoracic needle aspiration biopsy of the lung was performed to ascertain the etiology of the cavitary lesions (Fig. 2). Histological examination of the specimen revealed a poorly differentiated carcinoma (Fig. 3A). Immunohistochemistry identified tumor cells positive for cytokeratin 7, and AFP (Fig. 3C and 3D, respectively) and negative for thyroid transcription factor-1 (Fig. 3B). Subsequently, the multiple cavitary lung lesions were identified as metastasis from the primary hepatocellular carcinoma. At this time antibiotic treatment was terminated. Unfortunately, there were no further treatment options for the patient and end-of-life care was recommended. Administration of sorafenib was also discontinued. Although the patient had been taking it regularly, the drug had no effect on the progression of the disease. After discontinuation of the systemic steroid, the patient’s fever returned; however, there were no other signs or symptoms suggestive of an infection. The patient was sent to a convalescent hospital for supportive care, and

**Figure 3.** Histopathological findings of the lung. (A) Hematoxylin and eosin staining; original magnification 200×. (B) Immunonegativity for thyroid transcription factor-1 (immunohistochemistry [IHC], 400×). (C) Immunopositivity for cytokeratin 7 (IHC, 400×). (D) Immunopositivity for alpha-fetoprotein (IHC, 400×).
did not return to the outpatient clinic.

**DISCUSSION**

Hepatocellular carcinoma is the sixth most common form of cancer worldwide, with predominance in Asia over other regions. While it can be successfully treated if diagnosed at an early stage, it remains the third-leading cause of cancer-related deaths globally [3]. Although intrahepatic recurrence and metastasis of hepatocellular carcinoma occur frequently, they can be managed successfully through various multidisciplinary modalities including surgical resection, transcatheter arterial chemoembolization and percutaneous ablation or alcohol injection [4]. Therefore, intrahepatic recurrence and metastasis can be reasonably managed, prolonging patient survival. Due to the development of new diagnostic techniques extrahepatic metastasis is now more frequently diagnosed than previously, making it an important indicator of prognosis. The most commonly observed site of extrahepatic hepatocellular carcinoma metastasis is to the lung. Hepatocellular carcinoma with extrahepatic metastasis is regarded as a terminal condition as there are currently no standard treatment courses available [1].

In most cases of pulmonary metastasis from hepatocellular carcinoma, the classic radiologic findings include multiple, round nodules of various size, usually in the peripheral parenchyma, combined with diffuse interstitial thickening [2]. Previously, Assed et al. reported a case of a 26-year-old female, with no history of disease, who presented with multiple nodules, of various size, in both lungs by CT and multiple hyperechoic nodules in the liver, as shown by abdominal ultrasonography. Liver and pleural biopsies were performed, and she was diagnosed with primary hepatocellular carcinoma with multiple pulmonary metastases. The patient died 3 months later despite receiving systemic chemotherapy. Typical pulmonary metastases were reported in this case [5].

Multiple cavitary pulmonary lesions can have various causes, which may be of infectious or noninfectious etiology. Infectious causes are diverse and include bacterial (e.g., *Mycobacterium tuberculosis*), fungal, parasitic, septic embolism, abscesses, and aspiration pneumonia. Noninfectious causes of cavitary lesions include primary tumors and metastasis, various granulomatous diseases, such as sarcoidosis and Wegener’s granulomatosis, arteriovenous malformation, pneumoconiosis, and rheumatoid arthritis [6]. Cavitary lesions are detected in only 4% of metastatic nodules, of which approximately 70% are metastatic squamous cell carcinoma [7]. To our knowledge, this is the first report of cavitary pulmonary metastasis from hepatocellular carcinoma. We believe that central necrosis may have occurred in the rapidly growing metastatic nodules or that intratumoral necrosis may have been the cause of cavitary lung metastasis in our patient. These atypical findings may aid clinicians in cases in which a pulmonary metastasis is difficult to distinguish from an infectious condition or where the appropriate treatment plan is unclear. Furthermore, while early lung metastasis is relatively asymptomatic, severe respiratory difficulties could develop as disease progresses [8]. Additional confounding factors, specifically in our case, included elevated CRP levels, which can be related to tumor burden; and fever, which can be triggered by pyrogenic cytokines produced by the liver in cases of hepatocellular carcinoma [9,10].

In conclusion, pulmonary metastasis from an advanced hepatocellular carcinoma should be considered even if typical pulmonary features are observed. Careful analysis of tumor markers is recommended in these cases.

중심 단어: 간세포암; 감염; 전이

**REFERENCES**


