Case Report

Establishing the First Diagnosis of Hepatocellular Carcinoma in Lung Biopsy in a 47-Year-Old Man: A Case Report

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Hepatocellular carcinoma (HCC) is a primary tumor of the liver. The most common metastatic sites include lung, lymph node, and bone. The diagnosis of HCC is usually through radiological examination and liver biopsy. The first diagnosis of HCC through a metastatic site is very rare. Here, we report a case that the first diagnosis of HCC was not through liver biopsy, but rather by a lung biopsy. The patient was a 47-year-old man with elevated AFP level. Abdominal CT and MRI showed liver nodules and lung nodules. A liver biopsy was performed, showing cirrhotic liver with extensive fibrosis. No malignancy can be identified. A lung biopsy was performed. Microscopic examination showed abundant polygonal cells with eosinophilic cytoplasm forming trabecular pattern with endothelial wrapping. These cells are positive for HepPar-1, and focally positive for Glypican-3, and negative for CK7, CK20, TTF-1, Napsin A, synaptophysin and chromogranin, consistent with metastatic hepatocellular carcinoma. The negative staining results of PAX-8, CD10, and EMA do not support differential diagnosis of metastatic renal cell carcinoma. This case raises the awareness that the first diagnosis of HCC can be through a metastatic site, especially when well-differentiated HCC is difficult to distinguish from benign hepatic masses, such as macroregenerative nodules, adenoma, or focal nodular hyperplasia. *[N A J Med Sci. 2025;18(1):005-008. DOI: 10.7156/najms.2025.1801005]*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, accounting for over 80% of liver cancers globally, and is a leading cause of cancer-related deaths.[1] Typically diagnosed in the setting of chronic liver disease such as cirrhosis, HCC frequently metastasizes to sites like lung, lymph node, and bone.[2] Diagnosis relies on a combination of imaging, serum markers like α-fetoprotein (AFP), and liver biopsy, however, establishing an initial diagnosis of HCC via a metastatic site is exceedingly rare.

We present a unique case where a lung biopsy provided the first definitive diagnosis of HCC after a liver biopsy revealed no malignancy.

CLINICAL PRESENTATION

A 47-year-old man with a history of hypertension, pulmonary hypertension, alcohol-induced cirrhosis with esophageal and splenic varices, and upper gastrointestinal bleeding presented with a serum AFP level of 11.0 ng/mL. Imaging studies, including computed tomography (CT) and liver ultrasound, were performed to evaluate multifocal HCC. CT revealed the presence of both liver and lung nodules, while liver ultrasound showed innumerable cysts and/or hypoattenuated lesions throughout the liver. Subsequent magnetic resonance imaging (MRI) demonstrated numerous ill-defined T2 hyperintense foci in the liver and multiple nodular opacities in both lungs.

RESULTS

Liver biopsy revealed extensive fibrosis without evidence of malignancy (**Figures 1A** and **1B**), as confirmed by reticulin stain (**Figure 1C**) showing normal plates of hepatocytes (1-2 cells thick) and nodularity attributed to reticulin collapse. Immunohistochemical staining was negative for Glypican-3 (**Figure 1D**). In contrast, lung biopsy showed normal lung tissue in some areas, along with clusters of polygonal cells with eosinophilic cytoplasm arranged in a trabecular pattern and demonstrating endothelial wrapping (**Figures 2A** and **2B**). Immunohistochemical stains show that the tumor cells were focally positive for Glypican-3 (**Figure 2C**) and diffusely strong positive for HepPar-1 (**Figure 2D**), consistent with metastatic HCC. Stains for CK7, CK20, TTF-1, Napsin A, synaptophysin, chromogranin, PAX-8, CD10, and EMA were all negative.

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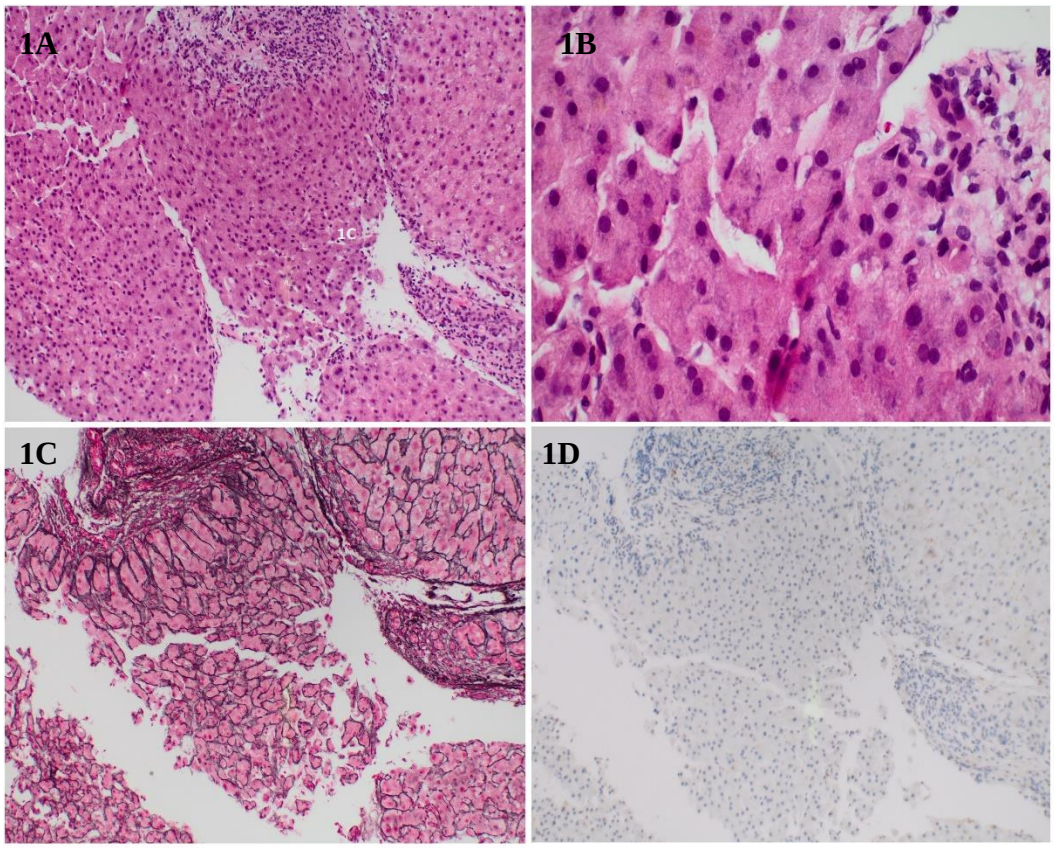

Figure 1. Liver Biopsy. **1A.** Hematoxylin and Eosin stain, 100X. **1B.** Hematoxylin and Eosin stain, 400X. **1C.** Reticulin stain, 100X. **1D.** Glypican-3 stain, 100X.

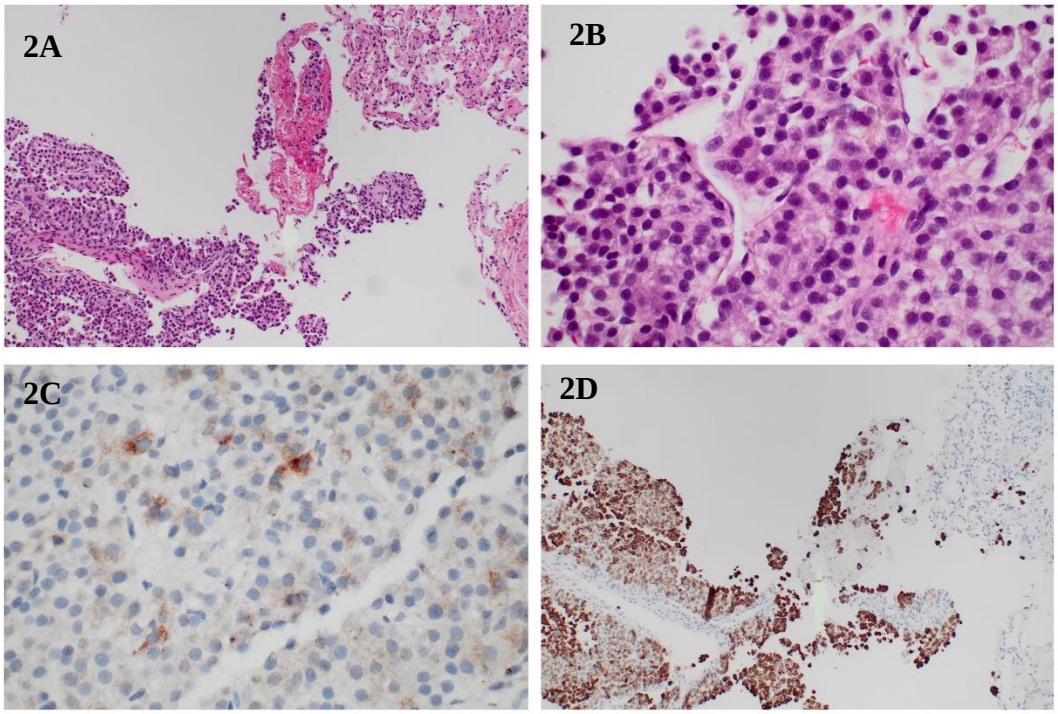

Figure 2. Lung Biopsy. **2A.** Hematoxylin and Eosin stain, 100X. **2B.** Hematoxylin and Eosin stain, 400X. **2C.** Glypican-3 stain, 100X. **2D.** HepPar-1 stain, 100X.

DISCUSSION

HCC is the sixth most common cancer worldwide and the third leading cause of cancer-related deaths, with a rising global incidence and high mortality rate.[1,3] HCC typically arises in the setting of chronic liver disease, such as cirrhosis or chronic hepatopathy, and is also associated with hereditary conditions like hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency.[3] Common sites of metastasis include the lungs (47%), followed by regional and distant lymph nodes, the musculoskeletal system, adrenal glands, kidneys, and bone marrow.[1]

The diagnosis of HCC is typically achieved through imaging modalities such as ultrasound, contrast-enhanced CT, or MRI, often complemented by the measurement of AFP, a widely used biomarker for HCC surveillance and diagnosis. AFP is elevated in 70-90% of cases, with a sensitivity of 60% and specificity of 90%.[1,2] Histology or cytology may also be employed for a definitive diagnosis. The degree of differentiation reflects the similarity of tumor cells to normal hepatocytes. Well-differentiated HCCs are typically small (< 2 cm) and display mild atypia, arranged in a thin trabecular pattern with occasional pseudoglandular structures. Moderately differentiated HCCs are often larger (> 3 cm), composed of polygonal tumor cells in a thick trabecular pattern with frequent pseudoglandular arrangements. Poorly differentiated HCCs consist of pleomorphic tumor cells forming a solid or compact growth pattern.[4]

Regarding well-differentiated HCC, histological examination reveals that the tumor cells closely resemble hepatocytes in function, cytologic features, and growth patterns. The cells are polygonal, exhibit mild atypia, and have granular eosinophilic cytoplasm.[5] The tumors predominantly grow in a trabecular pattern that mirrors normal liver architecture, with cords of tumor cells separated by vascular sinusoids. A notable pathological feature of HCC is lipid accumulation, which is commonly observed in well-differentiated HCC but occurs less frequently in poorly differentiated variants.[6]

Because well-differentiated HCC closely mimics benign hepatic masses such as macroregenerative nodules, hepatocellular adenomas, or focal nodular hyperplasia, diagnosing it can be challenging. In cases where liver biopsy findings are normal or inconclusive, performing a biopsy of suspicious metastatic sites may help confirm the diagnosis of well-differentiated HCC. This approach can guide appropriate treatment strategies, ultimately improving patient outcomes and survival rates.

Immunohistochemistry plays a crucial role in the diagnosis and differential diagnosis of HCC. Hepatocyte Paraffin 1 antigen (HepPar-1) is one of the most sensitive and specific markers for confirming hepatic origin, demonstrating cytoplasmic granular positivity in most well-differentiated HCCs but less than 50% of poorly differentiated cases.[3] However, its low sensitivity limits its utility in diagnosing poorly differentiated and scirrhous HCCs.[5] Although Arginase-1 immunostaining has a higher sensitivity and specificity than HepPar-1 for HCC diagnosis,[9.10] as a relatively new HCC marker, Arginase -1 immunostain is not available in many labs. The reticulin stain is the most widely used histochemical stain to support an HCC diagnosis. A loss of the normal reticulin staining pattern is indicative of hepatocellular carcinoma.[7] Glypican-3 (GPC-3), an oncofetal protein, is expressed in fetal tissues and trophoblastic cells but shows minimal or no expression in normal adult liver tissues and other non-neoplastic liver lesions. It is expressed in 64% to 90% of HCC cases, making it a valuable diagnostic marker.[3] Compared to other commonly used markers, such as HepPar-1, AFP, cytokeratin profiles, and CD10 (which highlights intercellular canaliculi), GPC-3 is more sensitive and specific. For well-differentiated HCC, GPC-3 expression has been observed in 78% of cases.[8]

In our case, the liver biopsy revealed extensive fibrosis without evidence of malignancy. GPC-3 stain was negative, and reticulin staining demonstrated normal hepatocyte plate thickness, precluding a definitive diagnosis of HCC based on liver tissue. Conversely, the lung biopsy revealed neoplastic cells positive for HepPar-1 and focally positive for Glypican-3, consistent with metastatic HCC. These findings underscore the importance of examining suspicious metastatic sites with biopsy and staining for confirming diagnosis.

Treatment options for HCC include chemotherapy, liver resection, liver transplantation, and ablative therapies such as radiofrequency ablation, transarterial embolization, and percutaneous ethanol injection, with the choice depending on the tumor stage at diagnosis.[2] Surgical resection may still be considered for some patients with pulmonary metastases.[2] Despite these interventions, HCC has a dismal prognosis, with over 90% of affected individuals dying from the disease, particularly in cases with lung metastases, which are associated with an especially poor outcome.[2]

CONCLUSION

This case underscores the importance of considering metastatic sites for biopsy when liver biopsy findings are inconclusive in patients suspected of having hepatocellular carcinoma. Diagnosing well-differentiated HCC can be particularly challenging due to its resemblance to benign hepatic masses. Incorporating metastatic site analysis with immunohistochemical markers like Glypican-3 and HepPar-1 can aid in confirming the diagnosis and guiding appropriate management strategies, ultimately improving patient outcomes.

CONFLICT OF INTEREST DISCLOSURES

The authors have no conflict of interest to disclose.

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REFERENCES

1. Yang JD, Hainaut P, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16:589-604.

2. Uka K, Aikata H, Takaki S, et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol. 2007;13:414-420.
3. Schlageter M, Terracciano LM, D'Angelo S, Sorrentino P. Sorrentino P. Histopathology of hepatocellular carcinoma. World J Gastroenterol. 2014;20:15955-15964.
4. Choi JH, Thung SN. Pathology and diagnostic approaches to well-differentiated hepatocellular lesions: a narrative review. J Yeungnam Med Sci. 2025;42.5.
5. Dimitroulis D, Damaskos C, Valsami S, et al. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. World J Gastroenterol. 2017;23:5282-5294. doi: 10.3748/wjg.v23.i29.5282. PMID: 28839428; PMCID: PMC5550777.
6. Suzuki H, Kohjima M, Tanaka M, et al. Metabolic Alteration in Hepatocellular Carcinoma: Mechanism of Lipid Accumulation in Well-Differentiated Hepatocellular Carcinoma. Can J Gastroenterol Hepatol. 2021;2021:8813410. doi: 10.1155/2021/8813410. PMID: 33681091; PMCID: PMC7910064.
7. Yasir S, Chen ZE, Said S, Wu TT, Torbenson M. Biopsies of hepatocellular carcinoma with no reticulin loss: an important diagnostic pitfall. Hum Pathol. 2021;107:20-28. doi: 10.1016/j.humpath.2020.09.015. Epub 2020 Oct 8. PMID: 33039370; PMCID: PMC9177079.
8. Yamauchi N, Watanabe A, Hishinuma M, et al. The glypican 3 oncofetal protein is a promising diagnostic marker for hepatocellular carcinoma. Mod Pathol. 2005;18:1591-1598.
9. Yan BC, Gong C, Song J, et al. Arginase-1: a new immunohistochemical marker of hepatocytes and hepatocellular neoplasms. Am J Surg Pathol. 2010;34:1147-1154. doi: 10.1097/PAS.0b013e3181e5dffa. PMID: 20661013; PMCID: PMC3160135.
10. Radwan NA, Ahmed NS. The diagnostic value of arginase-1 immunostaining in differentiating hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma as compared to HepPar-1. Diagn Pathol. 2012;7:149. doi: 10.1186/1746-1596-7-149. PMID: 23111165; PMCID: PMC3500209.