

Primary Hepatic Small-Cell Carcinoma Developed during Antiviral Treatment for Chronic Hepatitis B

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Key Words

Primary small-cell carcinoma · Liver · Chronic hepatitis B · Cirrhosis

Abstract

Previously reported cases of primary hepatic small-cell carcinoma were all detected at progressed state with associated symptoms. Therefore, the natural course of primary hepatic small-cell carcinoma remains unknown. This case shows the natural course of primary hepatic small-cell carcinoma. We detected a 1.2 cm hypodense nodule 6 months ago in a patient with cirrhosis who had been taking entecavir. It was suspected to be a regenerating or degenerating nodule. Three months later, liver computed tomography (CT) revealed that the mass was increased to 2.1 cm with the same characteristics. The patient wanted to do a follow-up CT scan after 3 months instead of a biopsy. Another 3 months later, the mass was markedly increased, involving the whole left lobe and was confirmed as small-cell carcinoma on biopsy. Here, we report the first case of primary hepatic small-cell carcinoma developed during treatment for chronic hepatitis B with cirrhosis.

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Introduction

Most small-cell carcinomas (SCC) arise from cells in the lung, and only 2–4% of SCCs are from cells in extrapulmonary organs [1, 2]. Since the first report of extrapulmonary small-cell carcinoma (EPSCC) by Duguid and Kennedy in 1930 [3], many EPSCCs have been reported. However primary hepatic SCC, which originates from the liver, is still very rare. Since Hsueh et al. [4] first described the presence of primary hepatic SCC, only a few cases have been reported worldwide [4, 5]. In previous reported cases of primary hepatic SCC, patients

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usually present with abdominal pain or discomfort because most cases had a huge mass on initial imaging scan. In the operable stage, the optimal treatment of primary hepatic SCC is surgical resection [5, 6]. However, its prognosis is poor because most primary hepatic SCCs are found as inoperable with extensive progression of the disease at the time of diagnosis. Here, we report a patient whose primary hepatic SCC was developed during antiviral treatment for chronic hepatitis B with liver cirrhosis. To date, no report of primary hepatic SCC in chronic hepatitis B or liver cirrhosis has been reported. While primary hepatic SCCs were extensive in previous reports, we found an early primary hepatic SCC of small size in a patient who experienced rapid growth of the tumor within 6 months.

Case Presentation

A 49-year-old man was admitted due to progressive epigastric pain, which had presented 5 days earlier. He had been diagnosed with chronic hepatitis B and liver cirrhosis 15 years ago. Three years ago, he had started to take entecavir 0.5 mg every day because of elevated alanine aminotransferase (ALT) with high HBV DNA titers (433,590 copies/ml). On physical examination, there was mild epigastric tenderness with splenomegaly. Laboratory examinations revealed a white blood cell count of 8,010/mm³, a hemoglobin level of 12.6 g/dl, a platelet count of 60,000/mm³, total protein of 6.2 g/dl, albumin of 3.6 g/dl, total bilirubin of 0.94 mg/dl, AST/ALT of 29/35 IU/l, alkaline phosphatase (ALP) of 98 IU/l, and a prothrombin time (PT) of 13.9 s. Virological markers revealed the following: HBsAg(+), anti-HBs(-), HBeAg(-), anti-HBe(+), and anti-HCV(-). HBV DNA was undetectable. Alpha fetoprotein (AFP) was elevated to 18.8 ng/ml, which was lower than that of 1 month earlier. Des-gamma-carboxy prothrombin (PIVKA-II) and carbohydrate antigen 19-9 (CA 19-9) were normal.

He had been having regular liver CT scans, and a 6 months earlier scan showed a 1.2-cm-sized hypodense lesion in hepatic segment II (fig. 1a). It was suspected to be a regenerating or degenerating nodule. Three months later, the size of the low-density lesion was increased to 2.1 cm (fig. 1b). Liver biopsy was recommended to the patient, but he refused to undergo it. He wanted close imaging follow-up instead. After another 3 months, we performed an emergent CT scan because he complained of severe epigastric pain. On CT scan, the lesion was markedly increased and involved hepatic segments II, III, and IV, with multiple lymph node enlargement (fig. 1c).

On liver magnetic resonance imaging (MRI), the mass was of low signal intensity during arterial phase but of high signal intensity on T2-weighted image. Histology showed round-shaped small cells with dense, hyperchromatic nuclei and scanty cytoplasm on light microscope (fig. 2a). Immunohistochemical staining was positive for synaptophysin, chromogranin A, and CD56, but negative for carcinoembryonic antigen (CEA), AFP, Hep Par 1, CK7, and CK19 (fig. 2b, c). Thyroid transcription factor-1 (TTF-1), a tumor marker profile consistent with small-cell lung cancer, was also negative (fig. 2d).

We performed chest CT, esophagogastrosocopy, and colonoscopy to identify the primary origin site. However, we could not find any other lesion. He was finally diagnosed with primary SCC of the liver. Palliative systemic chemotherapy consisting of etoposide and cisplatin was initiated. He received 5 cycles, but the disease progressed on CT scan. Second-line chemotherapy consisting of irinotecan and cisplatin was administered. After 2 cycles, the mass increased and the patient passed away 1 month later.

Discussion

Based on the 2010 World Health Organization (WHO) histological classification, a neuroendocrine tumor can be classified as a 'well-differentiated neuroendocrine tumor', a 'well-differentiated neuroendocrine carcinoma', or a 'poorly differentiated neuroendocrine carcinoma'. Poorly differentiated neuroendocrine carcinomas are highly aggressive malignant tumors, and most of them are SCCs. The majority of SCCs arise from the lung. EPSCCs account for only 4% of all SCCs [7]. EPSCCs can originate from the female genital tract (26%), the gastrointestinal tract (23%), the genitourinary tract (19%), the head and neck (16%), or an unknown primary site (13%) [8]. In the gastrointestinal tract, common primary sites include esophagus, stomach, and large intestine. Primary hepatic SCC is extremely rare. There has been no report of primary hepatic SCC in a patient with underlying liver disease such as chronic hepatitis B or liver cirrhosis [9]. Neuroendocrine tumors arise from embryonic neural crest cells that migrate to the bronchopulmonary system or gastrointestinal tract during development. These cells seldom migrate to the liver, which might be the reason why primary hepatic neuroendocrine tumors are rare [10].

Primary hepatic SCC was first described in 1983 by Hsueh et al. [4] in an 8-year-old girl with a tumor size of 17 cm. In other reports, the tumor sizes were all above 5 cm. Most of them were found as extensive disease with regional lymph node invasion or distant metastasis accompanied by subsequent symptoms such as jaundice or abdominal pain. In our case, we detected a 1.2-cm-sized primary hepatic SCC in a patient who had no symptoms at the time. After 3 months, the size of the tumor was increased to 2.1 cm without symptoms. Another 3 months later, the tumor was increased dramatically and the patient complained of epigastric pain. This might help us understand the natural course of primary hepatic SCC, because primary hepatic SCC is so rare and most primary hepatic SCCs are discovered as extended state.

It is important to exclude hepatic metastasis of small-cell cancer from other primary sites. Lung is the most common organ in which small-cell cancer develops. Therefore, it is important to reveal whether small cell originated from the lung. Immunohistochemical stain on biopsy specimen is usually performed because light microscope alone cannot differentiate small-cell lung cancer with EPSCCs. Neuroendocrine cells secrete various neuroendocrine proteins, which stain positively to chromogranin A, synaptophysin, NSE, and TTF-1 [11, 12]. Because chromogranin A and NSE are also positive in 40 and 60% of EPSCCs, respectively, they are not helpful in differentiating primary hepatic SCC from metastatic hepatic SCC [13]. In our case, CD56, chromogranin A, and synaptophysin were positive on immunohistochemical stain. TTF-1 is usually positive (96%) in small-cell lung cancer but negative in EPSCC [14]. In our case, TTF-1 was negative. There is a report of deletion of distal 3p (chromosome 3) on EPSCC [15]. However, chromosome study was not performed in this study. Above all, the natural course of tumor in this case could be the strongest evidence of primary hepatic SCC.

In this case, the patient was diagnosed as chronic hepatitis B with cirrhosis. He started antiviral therapy 3 years ago with regular imaging checkup at 6-month intervals using abdominal ultrasonography or liver dynamic CT. The initially discovered 1.2-cm-sized hypodense mass on CT scan was thought a regenerating or dysplastic nodule. We planned to do short-term imaging follow-up because most malignancies of the liver in liver cirrhosis are hepatocellular carcinomas. Other carcinomas are extremely rare. From this case, we can learn that additional attention should be paid to possible primary hepatic SCC when a hypodense lesion is observed in a patient with liver cirrhosis, despite its rarity.

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Conclusion

Here, the case of a 49-year-old man with primary hepatic SCC who had been treated for chronic hepatitis B and liver cirrhosis was reported, together with a literature review. Hopefully, this contributes to developing knowledge on the natural course of primary hepatic SCC.

Statement of Ethics

The author has no ethical conflicts to disclose. This report was approved by the Institutional Review Board (IRB file No. 2015-04-005), and the need for a written informed consent was waived.

Disclosure Statement

The authors has no conflicts of interest to disclose.

References

- 1 Richardson RL, Weiland LH: Undifferentiated small cell carcinomas in extrapulmonary sites. *Semin Oncol* 1982;9:484–496.
- 2 Frazier SR, Kaplan PA, Loy TS: The pathology of extrapulmonary small cell carcinoma. *Semin Oncol* 2007;34:30–38.
- 3 Duguid JB, Kennedy AM: Oat-cell tumors of mediastinal glands. *J Pathol Bacteriol* 1930;33:93–99.
- 4 Hsueh C, Tan XD, Gonzalez-Crussi F: Primary hepatic neuroendocrine carcinoma in a child. Morphologic, immunocytological, and molecular biologic studies. *Cancer* 1993;71:2660–2665.
- 5 Kim KJ, Yim HJ, Kim MJ, Choung RS, Yeon JE, Lee HS, Byun KS, Lee SW, Choi JH, Ryu HS, Lee CH, Hyun JH, Lee ES, Kim YS: A case of primary small cell neuroendocrine carcinoma of the liver. *Korean J Gastroenterol* 2006;48:37–41.
- 6 Lobins R, Floyd J: Small cell carcinoma of unknown primary. *Semin Oncol* 2007;34:39–42.
- 7 Cohen MH, Matthews MJ: Small cell bronchogenic carcinoma: a distinct clinicopathologic entity. *Semin Oncol* 1978;5:234–243.
- 8 Brennan SM, Gregory DL, Stillie A, Herschtal A, Mac Manus M, Ball DL: Should extrapulmonary small cell cancer be managed like small cell lung cancer? *Cancer* 2010;116:888–895.
- 9 Brenner B, Tang LH, Klimstra DS, Kelsen DP: Small-cell carcinomas of the gastrointestinal tract: a review. *J Clin Oncol* 2004;22:2730–2739.
- 10 Levenson RM Jr, Ihde DC, Matthews MJ, Cohen MH, Gazdar AF, Bunn PA Jr, Minna JD: Small cell carcinoma presenting as an extrapulmonary neoplasm: sites of origin and response to chemotherapy. *J Natl Cancer Inst* 1981;67:607–612.
- 11 Hainsworth JD, Johnson DH, Greco FA: Poorly differentiated neuroendocrine carcinoma of unknown primary site. A newly recognized clinicopathologic entity. *Ann Intern Med* 1988;109:364–371.
- 12 Johnson FD: Ectopic ACTH syndrome in APUD tumors. *Oncology* 1982;39:358–361.
- 13 Tsuchimochi S, Nakajo M, Inoue H, Miyazono N, Noguchi I, Matsushita T, Senba I, Yoshida A, Yoshida H: Primary hepatic neuroendocrine carcinoma with multiple metastases: a case report. *Radiat Med* 1995;13:183–185.
- 14 Ordonez NG: Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217–1223.
- 15 Johnson BE, Whang-Peng J, Naylor SL, Zbar B, Brauch H, Lee E, Simmons A, Russell E, Nam MH, Gazdar AF: Retention of chromosome 3 in extrapulmonary small cell cancer shown by molecular and cytogenetic studies. *J Natl Cancer Inst* 1989;81:1223–1228.

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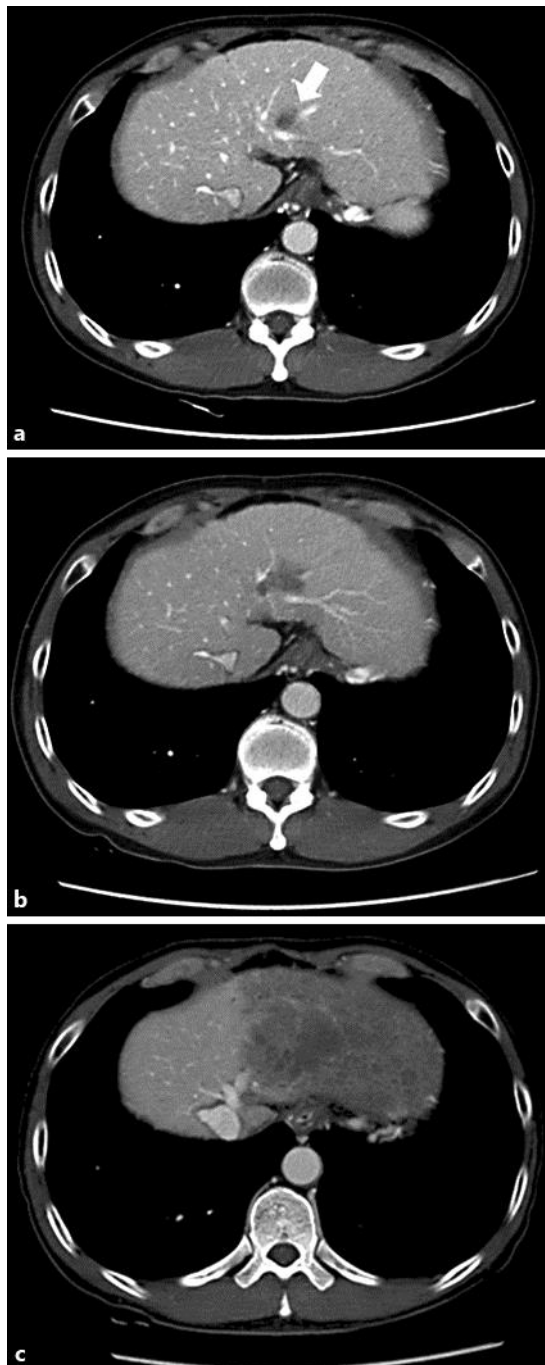


Fig. 1. Three-phase dynamic liver CT findings. **a** A new mass was detected 6 months ago, showing a 1.2-cm-sized low-attenuated nodular lesion in hepatic segment II (arrow). **b** The size of the lesion was increased to 2.1 cm after 3 months. **c** The lesion was markedly increased, involving hepatic segments II, III, and IV after 6 months.

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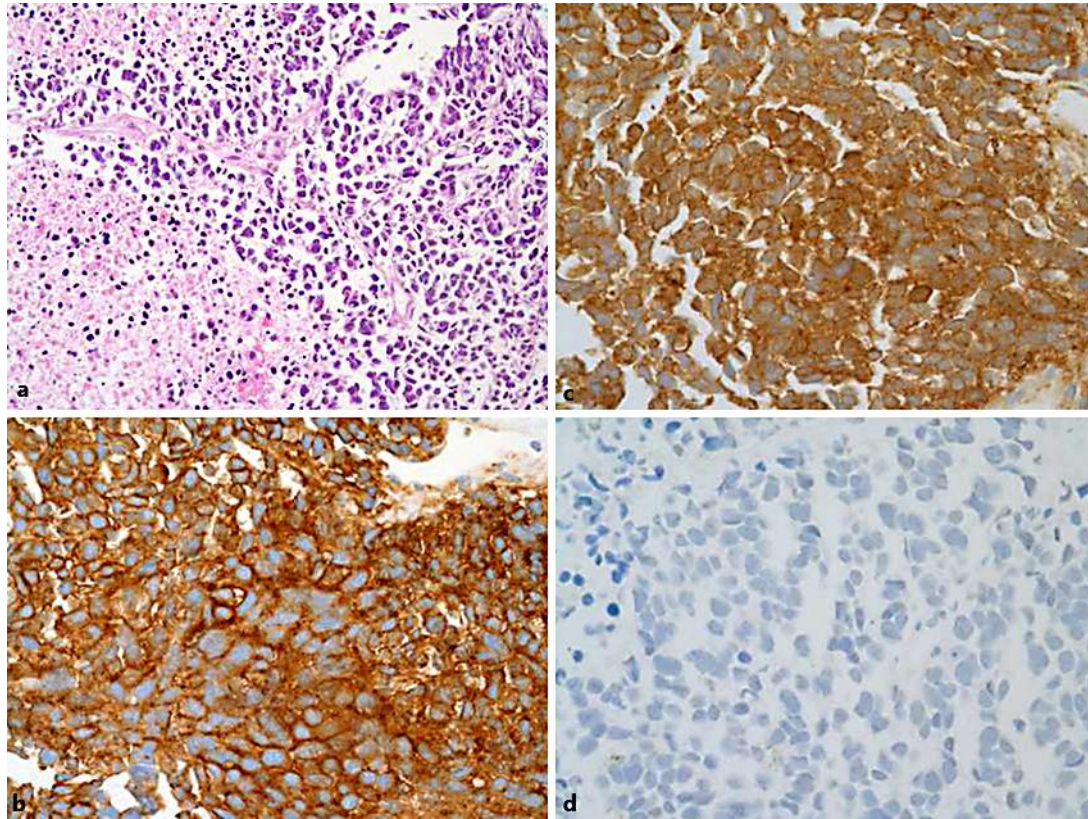


Fig. 2. Pathological findings. **a** HE stain. $\times 200$. The tumor cells show enlarged hyperchromatic nuclei and scanty cytoplasm. Most tumor cells show a strong positive reaction on immunohistochemical staining for CD56 (**b**) and synaptophysin (**c**), but a negative reaction on immunohistochemical staining for TTF-1 (**d**).