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Case Report

Rare sarcomatoid liver carcinoma composed of atypical spindle cells without features of either HCC or ICC: a case report

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Abstract: The patient was a 68-year-old male with a history of chemotherapy for malignant lymphoma which had achieved a complete remission. As he was infected with the hepatitis C virus, he was followed periodically, and 7 years after chemotherapy completion computed tomography revealed a 51 mm-in-diameter tumor in the right lobe of the liver. F-Fluorodeoxyglucose positron emission tomography with computed tomography showed a maximum standardized uptake value of 14.6. The patient had no history of transcatheter arterial chemoembolization, percutaneous ethanol injection therapy or radiofrequency ablation. The alfa fetoprotein level was 5.9 ng/ml. Malignant lymphoma recurrence was thus suspected. The tumor was surgically resected and examined. There was no pathological evidence of malignant lymphoma. The entire tumor area was composed of atypical spindle cells with no components of either hepatocellular carcinoma or intrahepatic cholangiocarcinoma. Immunohistochemically, the tumor cells were diffusely positive for cytokeratin 7 and vimentin, indicating a poorly differentiated carcinoma. The appearance of the adjacent liver parenchyma was consistent with chronic hepatitis. Based on tumor location, clinically limited to the liver, this patient was diagnosed with sarcomatoid liver carcinoma. This malignancy is rare, with an unusual clinical course and histological features.

Keywords: Sarcomatoid liver carcinoma, HCC, ICC

Introduction

Sarcomatoid liver cancer is reportedly very rare. In a study of liver cancer conducted in Japan, 19,499 cases were found to have hepatocellular carcinoma (HCC) and 905 intrahepatic cholangiocarcinoma (ICC), with only nine liver sarcoma cases being identified, between January 2004 and 31 December 2005 [1].

Sarcomatoid HCC and sarcomatous ICC consisted mainly of sarcomatoid components with the respective foci showing the usual features of HCC and ICC [2-14]. The patients presented herein had a hepatic neoplasm consisting solely of spindle cell type sarcomatoid carcinoma. None of the usual HCC or ICC components were identified, despite an extensive histopathological investigation. Our search of the literature yielded no similar cases.

Sarcomatoid changes in HCC frequently develop in patients who have undergone transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection therapy (PEIT), or radiofrequency ablation (RFA) [6-8], suggesting these procedures to be the origin of such changes. Our present case had not undergone TACE, PEIT or RFA. However, he did have a history of diffuse large B-cell lymphoma (DLBCL), which had been treated with rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone approximately 7 years prior to the current presentation. Several investigators have noted a relationship between malignant lymphoma and hepatitis C virus (HCV) infection.

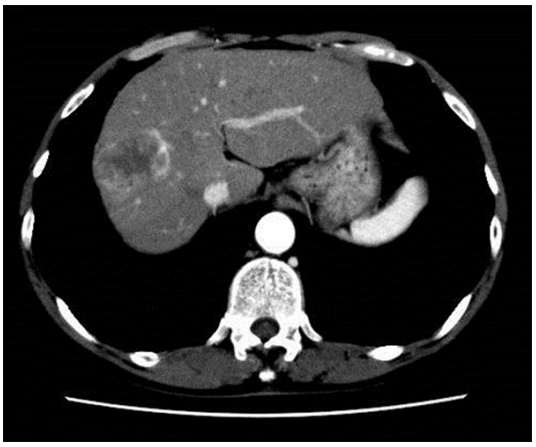

Figure 1. Enhanced computed tomography showed a 51 mm-in-diameter low-density area in liver segment 8. It appeared to have a lobular pattern.

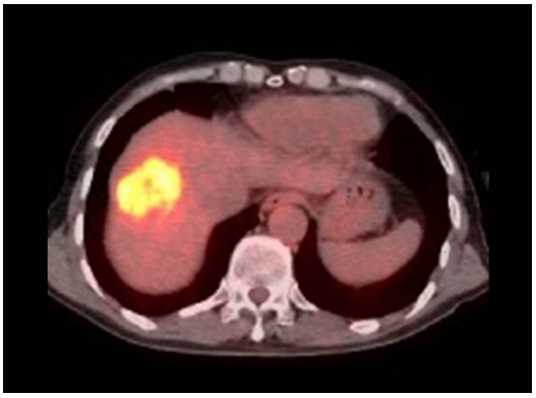

Figure 2. Positron emission tomography with computed tomography (PET-CT) (SUVmax 14.6).

However, to our knowledge, there are no case reports describing sarcomatoid carcinoma of the liver developing after chemotherapy for DLBCL.

Based on its occurrence after DLBCL and the rare histological features of a pure sarcomatoid tumor cell component, we describe the clinical course, radiological imaging data and histopathological findings of this case in detail.

Case report

A 68-year-old man, with a history of DLBCL treated with rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone, remained recurrence free for seven years. He was already infected with HCV at the time of DLBCL diagnosis. He was thus followed-up for both tumor recurrence and HCV. Seven years after the completion of chemotherapy, computed tomography (CT) showed a hepatic tumor (51 mm in diameter) in segment 8 of the right lobe of the liver. Laboratory testing showed that HCV ribonucleic acid was genotype 2A and the fixed quantity of HCV was 6.7 log copies/mL. Blood studies showed mild elevations of aspartate aminotransferase (85 IU/L) and alanine aminotransferase (52 IU/L), a slightly low platelet count ($12.6\times10^4/mm^3$), and low total bilirubin (0.39 mg/dl) and albumin levels (3.0 g/dL). The prothrombin time international normalized ratio was 1.07. There was no evidence of either ascites or hepatic encephalopathy. The Child-Pugh classification was A. The α-fetoprotein (AFP) level was 5.9 ng/mL and the concentration of protein induced by vitamin K absence or antagonist-II was 15 mAU/m. The carcinoembryonic antigen level was 2.5 ng/mL, and that of soluble interleukin-2 receptor was slightly elevated at 827 U/mL.

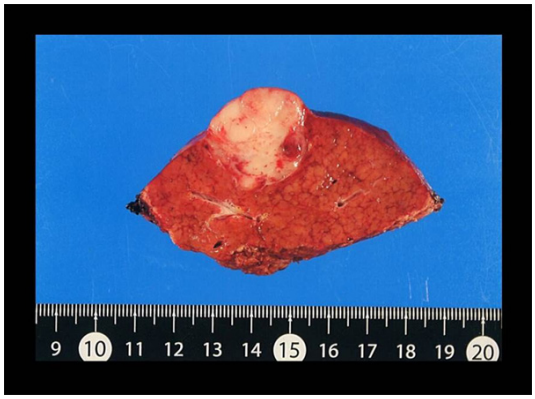

Figure 3. Macroscopic appearance of the resected hepatic tumor (40 mm) in segment 8 of the right lobe of the liver.

Enhanced CT showed a 51 mm-in-diameter low-density area in liver segment 8. It appeared to have a lobular pattern. Lymph node swelling was noted in the hepatic portal area and mediastinum. The diagnosis based on enhanced CT was ICC, HCC or malignant lymphoma (**Figure 1**).

Magnetic resonance imaging (MRI) confirmed the liver tumor in segment 8. No decreases in signal intensities were observed in the out-of-phase and in-phase images. There was no early deep dye staining on ethoxybenzyl (EOB) MRI. Furthermore, no internal partition enhancement was seen in either the portal or the late phase. This space occupying lesion appeared

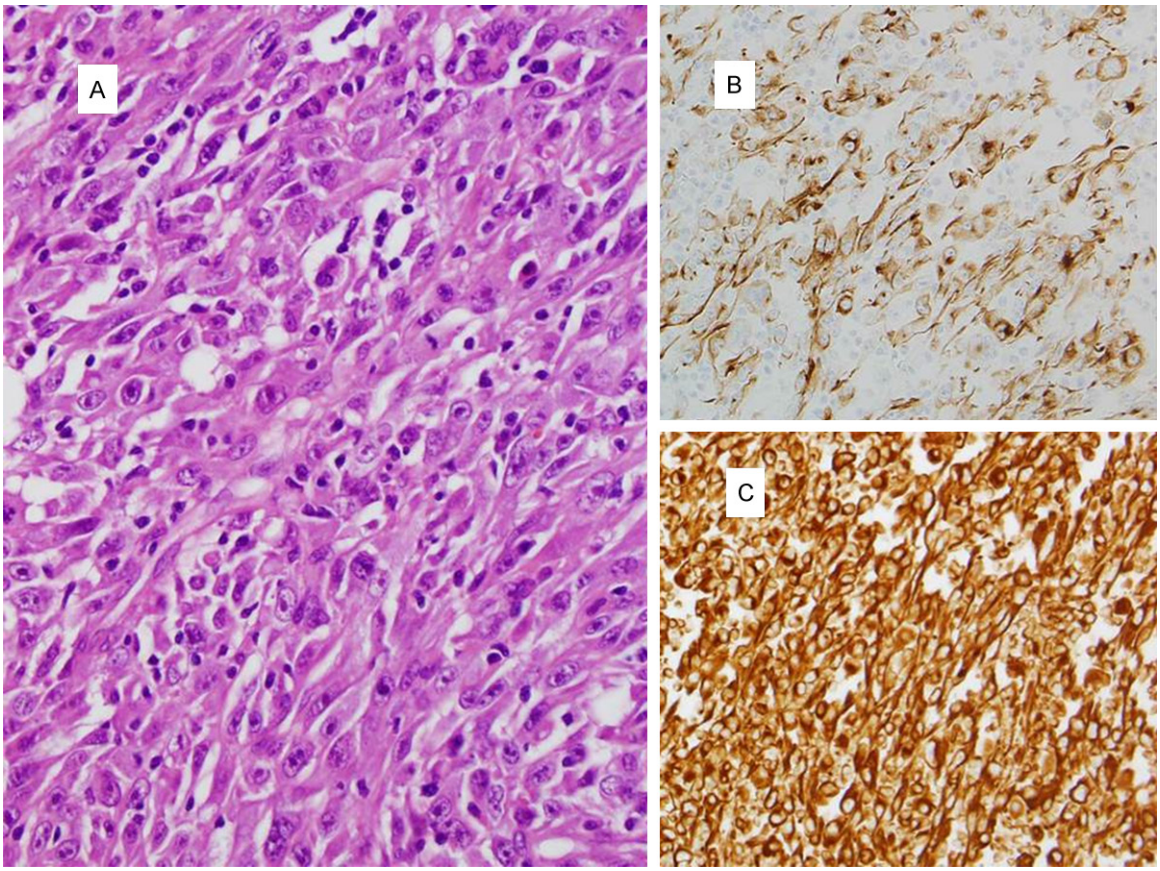

Figure 4. Histopathological examination of the resected specimen revealed the microscopic findings of the tumor. A. H&E staining, ×400 magnification. Atypical cells show proliferative features but without typical HCC and ICC findings. Though tumor cells can be difficult to distinguish from normal cells of epithelial or non-epithelial origin based only on H&E staining, the possibility of cells being malignant should not be ruled out. B. Immunostaining for Cytokeratin 7 (CK7), at magnifications of ×200. Tumor cells and bile duct epithelial cells are immunohistologically positive for CK7, whereas hepatocytes and non-epithelial cells are negative. C. Immunostaining for vimentin, ×200 magnification. Tumor cells and non-epithelial cells are immunohistologically positive for vimentin.

to represent cancer umbilication. The EOB MRI findings suggested HCC, an ICC metastatic liver tumor or malignant lymphoma recurrence.

Positron emission tomography (PET) 18 F-fluorodeoxyglucose (FDG) showed a highly integrated standardized uptake value (SUV). The maximum SUV (SUVmax), 14.6, was in the area of liver segment 8. The swollen bronchial, parietal and mediastinal lymph nodes had SUVmax of 9.5. Lymph nodes in the para-aortic area were also swollen, with SUVmax of 8.6. The PET CT findings suggested a diagnosis of malignant lymphoma. Therefore, we considered this patient to have developed a recurrence of the malignant lymphoma from seven years earlier (**Figure 2**). Neither esophago-gastro-duodenoscopy nor colonoscopy yielded clinically relevant findings.

Since we initially considered the tumor to be recurrent malignant lymphoma rather than HCC or ICC, it was surgically resected and histopathologically examined. Macroscopically, the border between the tumor and surrounding tissue was clear (**Figure 3**). The entire tumor area was sufficiently sampled for the pathological examination, and the following findings were obtained. Microscopically, the tumor was composed of proliferative atypical spindle cells including giant cells and multi-nucleated cells indicative of sarcomatoid features (**Figure 4A**). There were no findings of HCC, ICC, or combined hepatocellular-cholangiocarcinoma. We detected no typical morphological features of atypical spindle cells transforming into either HCC or ICC. We detected no evidence of malignant lymphoma recurrence. The non-tumorous area showed chronic active hepatitis with bridging

Table 1. Clinical characteristics of patients with sarcomatoid liver carcinoma Blanks indicate that the data were not provided

References	Age/ Gender	Local Therapy (TACE)	Virus	Adjacent Liver	Follow up	Histology	AFP ng/ml	Tumor Size
Giunchi et al.	54/M	No	HBV	Chronic Hepatitis	2 month	Pure Sarcomatoid	3	29×22 mm
Eriguchi et al.	65/M	No	Non B, Non C		3 month	Pure Sarcomatoid	3.2	100×85 mm
Haratake et al.	73/M	No	Non B	Liver Cirrhosis		Pure Sarcomatoid	82	
Present Case	68/M	No	HCV	Liver Cirrhosis	22 month	Pure Sarcomatoid	5.9	51×47 mm

fibrosis, probably caused by HCV infection, but no cirrhosis. Immunohistologically, atypical spindle cells were diffusely positive for cytokeratin (CK) 7 (**Figure 4B**) and vimentin (**Figure 4C**). Small foci and scattered areas of positivity for Cluster of Differentiation (CD) 56 and epithelial membrane antigens (EMA) were noted. Hepatocytes were negative for Glypican 3, AFP, CK19, CK20, CK5/6, CD117, alpha-smooth muscle actin, D2-40, WT-1, CD3, CD20, and CD79a. Considering that the tumor was immunohistologically positive for CD56 and EMA, it was thought to have originated from the bile duct epithelium rather than hepatocytes. However, the CD56 and EMA positive foci were very small and scattered. Most of the tumor cells were negative for CD56 and EMA, making these findings non-definitive. Atypical spindle cells were considered to be poorly differentiated or undifferentiated malignant epithelial neoplastic cells, rather than a true sarcoma. Thus, we herein use the term "pure sarcomatoid liver carcinoma". The tumor origin was not identified, despite detailed histopathological investigation. However, the tumor location being limited to the liver, i.e. involving no other organs, raised the possibility of either sarcomatoid HCC or sarcomatous ICC.

Discussion

Previous studies have shown FDG-PET to be useful for evaluating various liver tumors. Only two prior case reports described preoperative FDG uptake in sarcomatoid HCC. The SUVmax values were determined for all three patients, including our case, with sarcomatoid HCC. The SUVmax values for these three sarcomatoid HCC (SUVmax 14.6, 18.6 and 25.0) were higher than that of a poorly differentiated HCC (mean SUVmax 5.7). Thus, SUVmax was reported to possibly be a useful diagnostic tool for preoperative evaluation of the aggressiveness of primary liver cancers such as sarcomatoid HCC [15]. In our case, the SUV of the tumor was high on integrated PET-CT, i.e. the SUVmax was 14.6. This result supports those of previous reports. Integrated PET-CT suggested malignant lymphoma recurrence. However, the final diagnosis was pure sarcomatoid liver carcinoma. It is difficult to differentiate sarcomatoid liver carcinoma from malignant lymphoma employing only PET-CT.

Sarcomatoid HCC and sarcomatous ICC are both rare tumors [1-14]. In these tumors, one or more specialized sarcomatoid components are associated with a recognizable HCC or ICC component. Previous reports showed that sarcomatoid liver tumors generally have histological features consistent with an HCC or ICC origin. However, the surgical specimen from our case had neither HCC nor ICC components. Only three histologically similar cases have previously been reported [3-5].

Table 1 shows the clinical characteristics of reported cases with pure sarcomatoid liver carcinoma including our present patient. The mean age was 65 years and all four patients were men. Liver dysfunction was probably attributable to infection with HBV and/or HCV in 3 of the 4 cases, but was unknown in the other. Complications of viral hepatitis may or may not contribute to sarcomatoid carcinoma development. Considering the histological findings of the adjacent liver, the case reported by Haratake et al. [3] had liver cirrhosis but that described by Giunchi et al. [5] and our case had chronic hepatitis. Tumors varied in size from 29 mm to 100 mm and that in our patient was 51 mm. TACE, PEIT and RFA therapies, administered previously for HCC, have been suggested to be related to sarcomatoid change [6-8]. However, the four reported cases had not received these therapies. Levels of the tumor marker AFP were under 10 ng/ml in three cases, including ours. Considering solely the clinical evidence, the mechanism underlying

Table 2. Immunohistological examination results described in previous reports Blanks indicate that the data were not provided

References	Immunohistochemical Findings of Sarcomatoid Elements												
	AFP	AAT	CEA	EMA	Vimentin	Desmin	CK-7	CAM5.2	AE1/AE3	CK-8	CD34	CD117	SMA
Giunchi et al.						-	+			+	-	-	-
Eriguchi et al.				+	+			+	+				
Haratake et al.	-	-	-	-	-	-				+			
Present case	-			+	+		+		+		-	-	-

the development of sarcomatoid liver carcinoma may differ from that responsible for sarcomatous hepatic tumors.

It is difficult to distinguish sarcomatoid HCC and sarcomatous ICC from true sarcoma and pure sarcomatoid liver carcinoma based only on hematoxylin and eosin (H&E) staining. Immunohistological examinations were conducted in the earlier cases. Eriguchi et al. [4] reported the clinicopathological and immunohistochemical features of four cases with primary hepatic carcinoma with sarcomatoid elements. Macroscopically, all resected specimens consisted of a single nodule showing pericapsular growth. Based on immunohistochemical examinations, one of the four patients was diagnosed as having sarcomatoid cancer without HCC elements. Haratake et al. [3] noted their case, based on immunohistochemical examinations, to be negative for AFP, α1-antitrypsin, carcinoembryonic antigen, EMA, and vimentin, while being positive for CK8. Giunchi et al. [5] identified sarcomatoid components histopathologically, while immunohistochemical examinations revealed keratin 8(K8)/18 and K7/K19-positivity. Liver specimens from their case showed strong positivity for Glutamine Synthetase and Enhancer of Zeste Homolog 2, as well as focal positivity for heat shock protein 70 (HSP70). The sarcomatoid component was negative for Glypican 3, α-smooth muscle actin, caldesmon, desmin, Discovered on Gastrointestinal Stromal Tumour-1, CD34, CD31, CD117, CD56, and AFP, and also stained with Alcian Blue-Periodic acid-Schiff, as well as being negative for albumin messenger RNA. In our case, the tumor was immunohistologically negative for hepatocyte Par-1, Glypican 3, AFP, CK19, CK20, CK5/6, CD117, α-smooth muscle actin, CD3, CD20, and CD79a. Tumor cells were immunohistologically positive for both CK7 and vimentin. Prior reports described no characteristic immunohistological findings common to all sarcomatoid liver carcinoma cells (**Table 2**).

In conclusion, we were unable to ascertain the origin of our patient's tumor, i.e. hepatocyte or bile duct epithelium in the liver, despite extensive and detailed clinical, radiological and pathological examinations. The other three case reports were similar in this respect. Sarcomatoid HCC usually develops after the liver is exposed to various therapies. However, the 4 pure sarcomatoid carcinoma cases reported to date had no history of such treatments. Mechanisms underlying the development of this rare tumor may vary among sarcomatoid HCC cases.

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Disclosure of conflict of interest

None.

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References

[1] Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, Takayasu K, Nakanuma Y, Makuuchi M, Matsuyama Y, Monden M and Kudo M. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res 2007; 37: 676-691.

[2] Yamamoto Y, Ojima H, Shimada K, Onaya H, Hiraoka N, Mizuguchi Y, Kosuge T and Kanai Y. Long-term recurrence-free survival in a patient with primary hepatic carcinosarcoma: case report with a literature review. Jpn J Clin Oncol 2010; 40: 166-173.
[3] Haratake J and Horie A. An immunohistochemical study of sarcomatoid liver carcinomas. Cancer 1991; 68: 93-97.
[4] Eriguchi N, Aoyagi S, Okuda K, Hara M, Fukuda S, Tamae T, Ohdo M, Kanazawa N, Kawabata M, Kodama T, Nishimura K and Hamada S. Unusual liver carcinomas with sarcomatous features: analysis of four cases. Surg Today 2001; 31: 530-533.
[5] Giunchi F, Vasuri F, Baldin P, Rosini F, Corti B and D'Errico-Grigioni A. Primary liver sarcomatous carcinoma: report of two cases and review of the literature. Pathol Res Pract 2013; 209: 249-254.
[6] Yokomizo J, Cho A, Yamamoto H, Nagata M, Takiguchi N, Kainuma O, Soda H, Mori M, Narumoto S, Asano T, Ryu M and Kondo F. Sarcomatous hepatocellular carcinoma without previous anticancer therapy. J Hepatobiliary Pancreat Surg 2007; 14: 324-327.
[7] Morise Z, Sugioka A, Mizoguchi Y, Fujita J, Kato T and Hasumi A. Carcinosarcoma of the liver: a case report with interesting histologic and immunohistochemical features. J Gastroenterol Hepatol 2004; 19: 948-950.
[8] Marijon H, Dokmak S, Paradis V, Zappa M, Bieche I, Bouattour M, Raymond E and Faivre S. Epithelial-to-mesenchymal transition and acquired resistance to sunitinib in a patient with hepatocellular carcinoma. J Hepatol 2011; 54: 1073-1078.
[9] Komada N, Yamagata M, Komura K, Hayashi K, Maruyama T, Kataoka H, Koono M and Tsubouchi H. Hepatocellular carcinoma with sarcomatous change arising in primary biliary cirrhosis. J Gastroenterol 1997; 32: 95-101.
[10] Honda H, Hayashi T, Yoshida K, Takenaka K, Kaneko K, Fukuya T, Tateshi Y, Ro T, Maeda T and Masuda K. Hepatocellular carcinoma with sarcomatous change: characteristic findings of two-phased incremental CT. Abdom Imaging 1996; 21: 37-40.
[11] Yoshida N, Midorikawa Y, Kajiwara T, Yoshida N, Nakayama H, Sugitani M and Takayama T. Hepatocellular Carcinoma with Sarcomatoid Change without Anticancer Therapies. Case Rep Gastroenterol 2013; 7: 169-174.
[12] Ishak KG, Anthony PP, Sobin LH. Histological Typing of Tumours of the Liver: World Health Organization International Histological Classification of Tumors. 2nd edition. Berlin: Springer; 1997. pp. 27.
[13] Moulin-Romsee G, Spaepen K, Stroobants S and Mortelmans L. Non-Hodgkin lymphoma: retrospective study on the cost-effectiveness of early treatment response assessment by FDG-PET. Eur J Nucl Med Mol Imaging 2008; 35: 1074-1080.
[14] Goto H, Tanaka A, Kondo F, Takeshita K, Nagashima I, Hanawa N, Aiso M, Takamori Y, Kato K, Takahashi Y, Fukushima J, Furui S, Fukusato T, Asano T and Takikawa H. Carcinosarcoma of the liver. Intern Med 2010; 49: 2577-2582.
[15] Ijichi H, Shirabe K, Taketomi A, Yoshizumi T, Ikegami T, Mano Y, Aishima S, Abe K, Honda H and Maehara Y. Clinical usefulness of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography for patients with primary liver cancer with special reference to rare histological types, hepatocellular carcinoma with sarcomatous change and combined hepatocellular and cholangiocarcinoma. Hepatol Res 2013; 43: 481-487.