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Case Report

Non-B Non-C Related Hepatocellular Carcinoma with Sarcomatous Change due to Epithelial Mesenchymal Transition

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Abstract

We describe a case of non-B Non-C related hepatocellular carcinoma and sarcomatous change in a 91-year-old woman who had not undergone previous anticancer treatment. Ultrasonography revealed a 40 × 60 mm hyperechoic nodule in segment 4; contrast enhanced ultrasound and contrast enhanced computed tomography revealed hypervascularity in the early phase and defect in the Kupffer phase; super Paramagnetic Iron Oxide magnetic resonance imaging revealed defect on T2-weighted images; US-guided liver biopsy revealed mixed components of moderately- to poorly-differentiated hepatocellular carcinoma and pleomorphic- and spindle-cell type sarcoma. The background of the liver was almost normal and without liver cirrhosis. Immunohistochemical findings of the hepatocellular carcinoma component were as follows: positive for CAM5.2, AE1/AE3, CK20, AFP, Hepatocyte-paraffin-1 antibody and S-100p, and negative for CK7, vimentin (VMT), CK19, CD34, and αSMA. The sarcomatous component was positive for CAM5.2, AE1/AE3, S-100p, VMT, and negative for CK7, CK20, CD34, AFP, αSMA and hepatocyte-paraffin-1 antibody. The Ki-67 index was less than 5% in both hepatocellular carcinoma and sarcomatous components. Moreover, in terms of EMT, the hepatocellular carcinoma component was positive for E-cadherin, and the sarcomatous component was positive for Snail and HES-1 in the nucleus, and negative for E-cadherin and P-ERK. The above findings led to our diagnosis of the case as one of hepatocellular carcinoma with sarcomatous change attributed to EMT. Further study is needed to clarify the histogenesis of sarcomatous hepatocellular carcinoma not administered previous treatment for hepatocellular carcinoma.

Keywords: Epithelial Mesenchymal Transition (EMT); HES-1; Non-B Non-C Hepatocellular Carcinoma (HCC); Notch pathway; Snail; Sarcomatous change

Introduction

Hepatocellular carcinoma (HCC) with a sarcoma (sarcomatous HCC) feature is an uncommon neoplasm in the clinical settings. HCC and sarcoma have been defined as HCC that has undergone sarcomatous differentiation (sarcomatous carcinoma) according to WHO [1]. The histogenesis of the sarcomatous appearance of HCC has drawn two hypotheses: (1) the coexistence of sarcoma and HCC derived from hepatic stem cells and (2) transition in HCC [2]. Also, histogenesis involving Epithelial Mesenchymal Transition (EMT) of sarcomatous HCC remains to be clarified. Sarcomatous HCC has been described as induced by anticancer treatment such as Transcatheter Arterial Chemoembolization (TACE), Hepatic Arterial Infusion Chemotherapy (HAIC) [3] and Radiofrequency Ablation (RFA) [4].

Here, we describe non-B non-C related sarcomatous HCC in a 91-year-old woman not previously administered anticancer treatment. Immuno histochemical analyses disclosed biopsy specimens positive for parenchymal markers CAM5.2, AE1/AE3, and mesenchymal marker S-100p in both the HCC and sarcomatous components. Additionally, on the basis of the specimens being positive for Snail and HES-1 and negative for E-cadherin and P-ERK, the present case was considered more a sarcomatous HCC, because of transition of HCC induced by EMT, than the coexistence of HCC and sarcoma. To the best of our knowledge, this is the first case of HCC with sarcomatous change due to EMT and not administered previous anticancer treatment.

Case Report

A 91-year-old woman was admitted to our hospital for further examination of a 40 × 60 mm hypoechoic nodule in segment 4 of the liver (Figure 1a). She had no past history of alcoholism and had been under treatment for heart and renal failure for the past 20 years. Laboratory data on admission were shown in (Table 1). Contrast Enhanced Ultrasound (CEUS) revealed hypervascularity in the arterial predominant phase (Figure 1b) and defect in the Kupffer phase (Figure 1c). Plain Computed Tomography (CT) revealed hypoattenuation and Contrast Enhanced Computer Tomography (CECT) revealed hypervascularity, except for the central lesion in the early phase (Figure 1d) and defect in the delayed phase (Figure 1e). CT Hepatic Arteriography (CTHA) revealed hypervascularity and CT during Arterial Portography (CTAP) revealed perfusion defect. Magnetic Resonance Imaging (MRI) revealed hypointensity on T1-weighted images and hyperintensity on T2-weighted images. Control enhanced MRI was not carried out because of severe renal failure, but instead Super Paramagnetic Iron Oxide Magnetic Resonance Imaging (SPIO MRI) revealed defect on T2-weighted images (Figure 1f). From the above imaging findings, mostly HCC was suspected. US guided biopsy carried out for precise diagnosis of the nodule revealed mixed components of moderately- to poorly-differentiated HCC and pleomorphic and spindle-cell type sarcoma (Figure 2a,2b). The background of the liver was almost normal and without liver cirrhosis.

Figure. 1

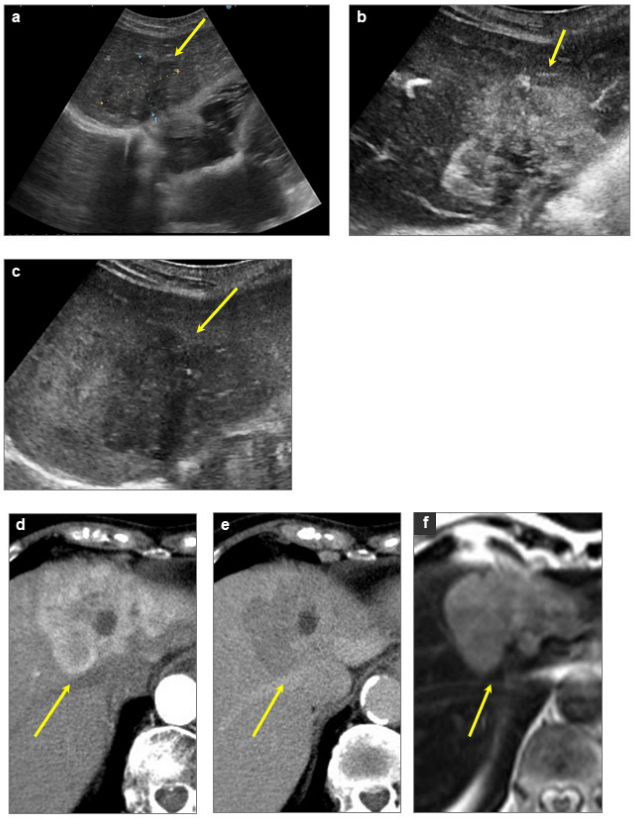

Figure 1: Imaging Findings. (a) US, 40 × 60mm hypoechoic nodule in segment 4. (b) CE-US, hypervascular in the arterial predominant phase. (c) CE-US, defect in the Kupffer phase. (d) CE-CT, hypervascular except for the central region in the early phase. (e) CE-CT, defect in the delayed phase. (f) SPIO MRI, defect on T2-weighted image.

Figure. 2

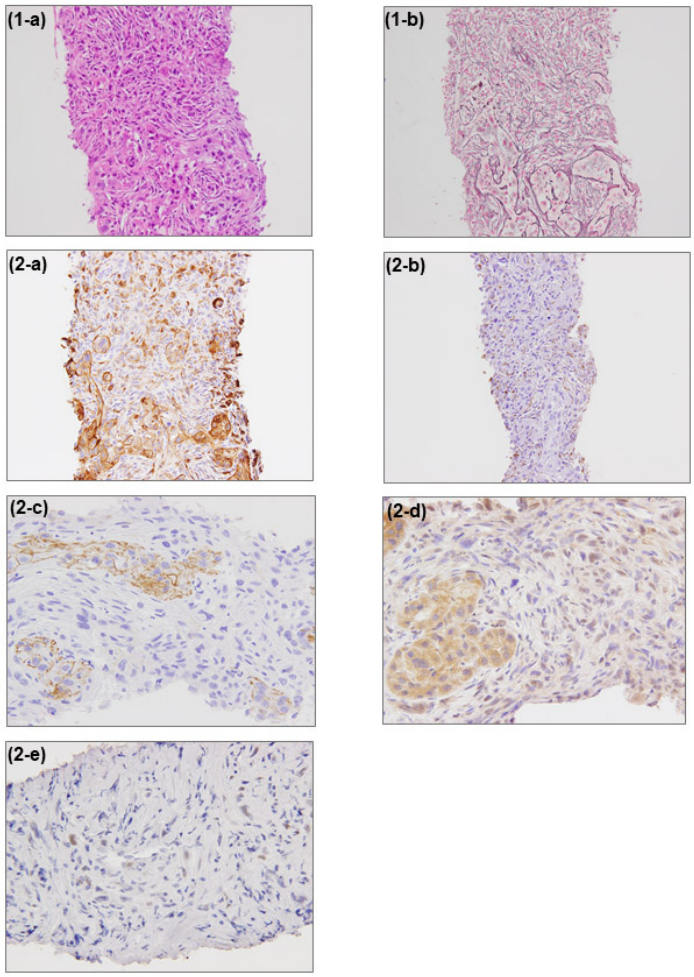

Figure 2: Pathological Findings. (1) HE and Silver staining. (a) HE staining; mixed components of moderately- to poorly-differentiated HCC and sarcoma. (×200). (b) Silver staining; mixed components of moderately- to poorly-differentiated HCC and sarcoma. (×200). (2) Immunohistochemical findings. (a) CAM5.2, both HCC and sarcomatous components are stained positive. (×200). (b) Vimentin is stained positive in the sarcomatous component. (×200). (c) E-cadherin is stained positive in the HCC component. (×400). (d) Snail is stained positive in the nucleus of the sarcomatous component. (×400). (e) HES-1 is stained positive in the nucleus of the sarcomatous component. (×400).

Hb (11.5〜15.0)	10.0 g/dl	HCVAb	(-)
PLT (13.4-34.9)	19.5 ×104/μl	HBsAg	(-)
AST (10-40)	17 IU/l	AFP (<10.0)	5.3 ng/ml
ALT (5-40)	8 IU/l	PIVKAII (<40)	826 mAU/ml
ALP (115-359)	218 U/L	CEA (<5.0)	3.0 ng/ml
T-Bil (0.2〜1.2)	0.6 mg/dl	CA19-9 (<37.0)	45.0 U/ml
* Hb, haemoglobin; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; HCVAb, Hepatitis C virus antibody; hepatitis B surface antigen; AFP, alpha-fetoprotein; PIVKAII, protein-induced vitamin K absence; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9. * inside ( ), normal data			

Table 1: Laboratory data on admission.

Immunohistochemically findings of the HCC component were as follows: positive for CAM5.2 (Figure 2 (2)-a), AE1/AE3, CK20, AFP, Hepatocyte-paraffin-1 antibody (HepPar 1) and S-100p, and negative for CK7, vimentin (VMT) (Fig. 2 (2)-b), CK19, CD34, and αSMA. The sarcomatous component was positive for AE1/AE3, CAM5.2 (Figure 2 (2)-a), VMT (Figure 2 (2)-b), S-100p, and negative for CK7, CK20, CD34, AFP, αSMA and HepPar 1. The Ki-67 index was less than 5% in both HCC and sarcomatous components. Moreover, in terms of EMT, the HCC component was positive for E-cadherin (Figure 2 (2)-c), and the sarcomatous component was positive for Snail (Figure 2 (2)-d) and HES-1 (Figure 2 (2)-e) in the nucleus, and negative for E-cadherin and P-ERK. From the above pathological findings, the nodule was diagnosed as sarcomatous HCC attributed to EMT. She denied any treatment for the liver tumor due to old age. She died due to heart failure seven months after diagnosis of the liver tumor.

Discussion

Several studies have described imaging findings of sarcomatous HCC. In the delayed enhancement phase of computed tomography, sarcomatous HCC appears as an irregular intrahepatic mass [5], although this feature has not been described in another series [6]. The most common CT feature of HCC with Sarcomatous Change (SC) is central necrosis [7]. This pattern of enhancement on enhanced CT is, however, not specific to SC and might represent metastases or liver abscesses. Thus, SC induces loss of the classic imaging features of HCC [8-10]. In our study, central necrosis was disclosed by CECT; however, SPIO MRI showed only an HCC pattern with no specific finding of SC, and the diagnosis was made based on liver biopsy findings. The sarcomatous component represents clonal evolution from a differentiated component (hepatocellular or cholangiocarcinoma). Morphology varies from spindled to epithelioid and pleomorphic. The mitotic rate is usually high, and atypical mitoses are frequent. These tumours are clinically aggressive with a poor prognosis [1]. In terms of the prognosis of patients, the overall survival rate of patients with a ≥70% sarcomatous component and a ≥40 mm tumor is significantly worse than that of patients with ≤30% sarcomatous tissue or a <40mm tumor (P = 0.0059) with a poor prognosis of patients with SC in primary liver carcinoma, especially those with a large sarcomatous component and a large tumor [11]. Compared with the foregoing study, the prognosis of our case was estimated to be poor because of tumor size (40 × 60 mm), although the percentage of the sarcomatous component could not be assessed due to the pathological analysis of a biopsy sample.

Among 579 autopsy cases of HCC, of 55 (9.4%) exhibiting a sarcomatous appearance 20.9% had undergone anticancer therapy and 4.2% had not [3]. Among the cases administered various anticancer therapies, the sarcomatous appearance was most frequent in 27.6% of cases administered repeated TACE. The sarcomatous appearance, assumed as caused by phenotypic change of HCC cells under anticancer therapy, such as TACE, HAIT and RFA [4], may accelerate the proliferation of the sarcomatous cells present in the original tumour as histological components [12]. The sarcomatous appearance is characterized as treatment-resistant and rapid-growing in sarcomatous HCC [3]. A study of several sarcomatous HCC cases not administered anticancer treatment has described 308 HCC cases, with 6 (1.9%) showing partial (5 cases) or total (1 case) SC; only 1 case had received preoperative anticancer therapy among the 6, suggesting that SC is not always related to anticancer therapy [13]. The WHO definition also has not mentioned the effect of anticancer therapy such as TACE, HAIC and RFA as a histogenesis [1]. In our present case also, the patient had not received any anticancer therapy such as TACE, HAIC and RFA.

Irrespective of the WHO definition, the histogenesis of the sarcomatous appearance of HCC has not yet been clarified. The hypothesis that the histogenesis of the sarcomatous appearance of HCC is attributable to the coexistence of sarcoma and HCC derived from hepatic stem cells has been supported on the basis of Craig's definition of carcinosarcoma as a liver tumour with both hepatocellular carcinoma and non-spindle sarcoma such as osteosarcoma, chondrosarcoma, angiosarcoma, or malignant schwannoma [2]. The authors, through histological analysis, describe an autopsy case of carcinosarcoma of the liver where both foci of the hepatic tumour are composed of carcinomatous and sarcomatous components; also, through immunohistochemical analysis, they show that both cell types are strongly positive for Cytokeratin (CK) 18, VMT and AFP, but negative for CK subtypes 7, 8, 19, beta human chorionic gonadotropin (β-HCG) and CEA. Thus, the carcinomatous component represents spindle cell HCC, because (1) the finding of a hepatic tumour with immunoreactivity for AFP is suggestive of HCC, and (2) a hepatic tumour with expression of the normal HepPar 1 cytokeratin profile (CK8 and/or 18) and co-expression of VMT is strongly suspected to be HCC. The sarcomatous component is composed of hypercellular cartilage lobules at the periphery and osteoid production in the centre showing a strong immunoreactivity for VMT. Combination tumours originate from a single totipotent stem cell that differentiates into separate epithelial and mesenchymal directions [2].

Most researchers, however, support the hypothesis that the histogenesis of the sarcomatous appearance is attributable to transition in HCC [14-16], as shown through immunohistochemical techniques. Tumour cells in regions showing sarcomatous appearance are frequently found to be positive to Keratin (KRT) and VMT, whereas the percentage of positivity to Albumin (ALB), Fibrinogen (FBG), and AFP is not significantly different from that in ordinary HCC [14]. Spindle cell components, but not ordinary HCC ones, have revealed positive reaction to VMT in 8 (62%) tumours, S-100p and HAM-56 in 3 (23%), HHF-35 in 2 (15%) and

alpha-smooth muscle actin, desmin, and KP-1 in 1 (8%), and p53 overexpression has been found in two spindle HCC tumours [17]. Immunohistochemically analyses have revealed some spindle cells positive for both KRT and VMT, and chondrosarcomata's cells positive for S-100p [15]. Taken together, the above studies suggest that the sarcomatous appearance represents more a SC in HCC than a combination of HCC and sarcoma.

In the present study, immunohistochemical findings of the positivity of parenchymal markers CAM5.2 and AE1/AE3, and of mesenchymal marker S-100p in both HCC and sarcomatous components suggested sarcomatous HCC attributed to transition. Taken together with previous studies [14,15], the present case was considered more a sarcomatous HCC due to transition [14,15] than a mixed tumour of HCC and sarcoma [2]. Although the precise immunohistochemical findings have been described, no direct evidence has been shown in terms of the relation between SC and EMT [14-16]. It has been suggested that in carcinosarcoma, the sarcoma component may derive from EMT. EMT is involved in a number of developmental milestones, including gastrulation, neural crest formation and heart morphogenesis, which rely on the plastic transition between the epithelium [18] and the mesenchyme [19]. In our case, the findings of the positivity of Snail and HES-1 and the negativity of E-cadherin in SC were regarded as induced by EMT. There are numerous molecules that could explain EMT, including ZEB1, twist 1 and Snail; however, in oesophageal carcinosarcoma, ZEB1 has been suggested to serve a critical role in the EMT process [18].

The Notch pathway is frequently activated in various types of cancers including HCC and plays multiple roles including transition, differentiation, epithelial-mesenchymal transition, metastasis, and maintenance of cancer stem cells, although the mechanisms for its pleiotropic actions have remained unclear [20]. In human carcinogenesis, transcriptional factor HES-1 (hairy enhancer of split 1), a member of the transcriptional repressor family Basic Helix-Loop-Helix (bHLH), is a downstream target of the Notch signaling pathway. Moreover, Hes1 upregulation has been observed throughout the intestinal tumorigenesis in APC+/– mice [21], the pancreatic tumorigenesis in KrasG12D mice [22], and the development of mouse papillary tumors [23]. Increasing evidence supports that Hes1 regulates cancer cell proliferation [24,25], differentiation [24-27], senescence [24,28] and resistance to chemotherapy [29]. Increasing evidence supports the concept that inactivation or downregulation of the tumour suppressor PTEN triggers EMT of cancer cells, and evidence shows that HES-1 downregulates PTEN to activate the PI3K/Akt pathway, which may be one of the major mechanisms of HES-1-induced EMT-like phenotypes of NPC cells [18]. HES-1 overexpression has been reported in not only colon cancer [21,30], breast cancer [31], glioma [32], non-small cell lung cancer [33], head and neck squamous cell carcinomas [34], ovarian carcinomas [35], meningiomas [36] and medulloblastomas [37], but also in HCC [28]. The high expression of fibronectin and Snail, and the low expression of Ecadherin have been demonstrated as significantly associated with the gain of HES-1 expression in EMT in Nasopharyngeal Carcinoma (NPC) [18].

The interactions of the Notch pathway have been examined with other signalling pathways in a mouse hepatocarcinogenesis model using the Sleeping Beauty transposon-mediated somatic integration of various oncogenes in vivo. Although the introduction of Notch1 Intracellular Domain (N1ICD) does not induce liver tumours, the combination of N1ICD and HRASV12D has induced sarcomatous tumours involving the expression of VMT and Snail [20]. Although hepatocarcinogenesis in human and mouse models differs, the latter model is suggestive when considering human hepatocarcinogenesis. Taken together with the foregoing, our case was diagnosed as sarcomatous HCC attributed to EMT. Further study is needed to clarify the histogenesis of sarcomatous HCC.

Author Contributions

Kim SK conceived the case and wrote the manuscript; Kim SR and Imoto S observed the clinical course of the patient and made the figures; Fujii T, Fujii Y, Yuasa K and Ohtani A observed the clinical course of the patient; Kobayashi H conducted the radiological examinations; Koma Y, Yamamoto M and Nakashima O examined the histology of the specimens; Kumabe T and Kudo M interpreted the imaging findings.

Conflict of Interest Statement

Masatoshi Kudo received financial support from Taiho Pharmaceutical CO., LTD., Taiho Pharmaceutical CO., LTD., Chugai, Otsuka, Takeda, Sumitomo Dainippon, Daiichi Sankyo, grants and personal fees from MSD, Eisai, Bayer, Abbvie, Medico's Hirata, Astellas Pharma, Bristol-Myers Squibb.

The other authors have no conflicts of interest to declare.

Informed Consent Statement

Informed consent was obtained from the patient.

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