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【 CASE REPORT 】

Hepatocellular Carcinoma Arising in a Non-cirrhotic Liver with Secondary Hemochromatosis

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Abstract:
A 70-year-old man was admitted for treatment of a single liver nodule that was detected by contrast-enhanced computed tomography. Twenty years earlier, the patient had been diagnosed with myelodysplastic syndrome-refractory anemia and secondary hemochromatosis but had not received erythrocyte transfusions. The current histological, computed tomography, and magnetic resonance imaging findings revealed hepatocellular carcinoma (HCC) and non-cirrhotic liver hemochromatosis. The liver tumor was treated using radiofrequency ablation therapy. Secondary hemochromatosis may be a risk factor for HCC, even if the liver is not cirrhotic. In such cases, additional surveillance may be required to detect the development of HCC.

Key words: hepatocellular carcinoma, secondary hemochromatosis, non-cirrhotic liver

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death (1) and typically develops in cases of chronic liver disease [e.g., hepatitis B or C virus infection, nonalcoholic steatohepatitis, or hereditary hemochromatosis (HH)]. The risk of developing HCC in patients with HH is approximately 200 times than that in the normal population (2, 3). This difference may be related to free radicals caused by iron overload in HH, which lead to hepatocellular injury and subsequently HCC (1). Secondary hemochromatosis can also occasionally occur in patients with ineffective erythropoiesis, such as patients with myelodysplastic syndrome (MDS) or aplastic anemia, and patients who have received a large number of erythrocyte transfusions. These cases are also characterized by iron overload, similar to HH; however, only a few reports have described HCC arising in patients with secondary hemochromatosis. We herein report a case of HCC in a patient with secondary hemochromatosis in a non-cirrhotic liver.

Case Report

A 70-year-old man was admitted for treatment of a single liver nodule that was detected by contrast-enhanced computed tomography (CT). Twenty years earlier, the patient had been diagnosed with MDS-refractory anemia (MDS-RA) and secondary hemochromatosis. The risk of MDS, according to his International Prognostic Scoring System score, was considered to be low. He had been treated with daily oral vitamin B6 for MDS-RA and his hemochromatosis had been treated with deferoxamine (1,500 mg/day) for 20 years. This treatment helped his hemoglobin level recover from 6 g/dL to 10 g/dL. He also had a history of type 2 diabetes mellitus and a 5-year history of treatment using oral hypoglycemic drugs. He had no history of erythrocyte transfusion and received follow-up abdominal ultrasonography (US) or contrast-enhanced computed tomography (CT) every 6 months.

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Table 1. Laboratory Data on the Admission.

Variable		Variable	
White blood cells (/μL)	5,400	UIBC (μg/dL)	41
Red blood cells (10^4/μL)	440	Ferritin (ng/mL)	736
Hemoglobin (g/dL)	8.8	Total bilirubin (mg/dL)	0.5
MCV (%)	30.8	Direct bilirubin (mg/dL)	0.1
MCH (fL)	70	AST (U/L)	21
MCHC (pg)	20	ALT (U/L)	13
Platelets (10^4/μL)	13.4	LDH (U/L)	125
PT (%)	72	ALP (U/L)	305
APTT (s)	34.6	GGT (U/L)	31
TP (g/dL)	7.1	ChE (U/L)	137
Albumin (g/dL)	4.9	Glycated hemoglobin (%)	6.4
C-reactive protein (mg/dL)	0.03	Mac2BP (COI)	1.11
BUN (mg/dL)	17	Hyaluronic acid (ng/mL)	122.7
Creatinine (mg/dL)	0.60	Total AFP (ng/mL)	2.4
Iron (μg/dL)	167	PIVKA-II (mAU/mL)	27

MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, PT: prothrombin time, APTT: activated partial thromboplastin time, BUN: blood urea nitrogen, UIBC: unsaturated iron binding capacity, AST: aspartate aminotransaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: gamma glutamyltranspeptidase, ChE: cholinesterase, AFP: alpha-fetoprotein, PIVKA-II: prothrombin induced by vitamin K absence-II, Mac2: Mac-2 binding protein glycosylation isomer

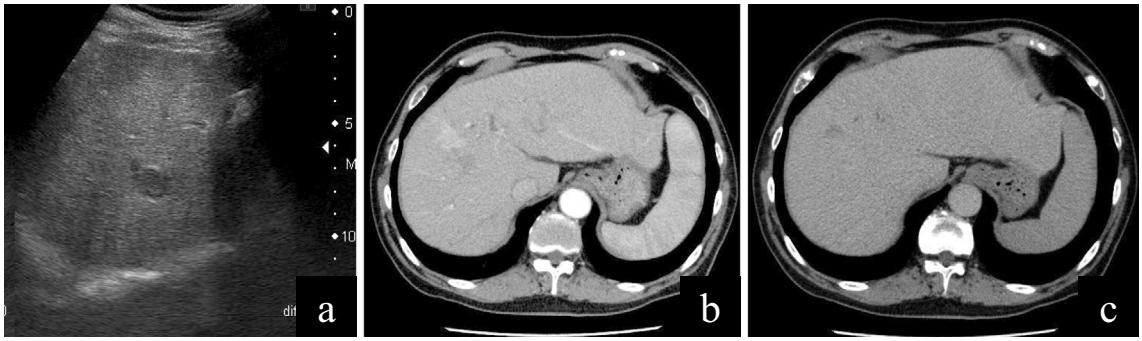

Figure 1. (a) Ultrasonography revealed that the tumor (segment 7) exhibited low echogenicity. (b, c) Early-phase computed tomography revealed hyperenhancement and a decrease to hypoenhancement during late-phase computed tomography (high-low).

Our physical examination revealed hepatosplenomegaly and no pigmentation. Laboratory testing revealed mild pancytopenia and high ferritin values, which were related to the MDS-RA. No elevated levels were observed for various tumor markers (alpha-fetoprotein, 2.4 ng/mL; des-γ-carboxy prothrombin, 27 mAU/mL; carcinoembryonic antigen, 1.6 ng/mL; carbohydrate antigen 19-9, 20 U/mL), and there was no evidence of hepatitis B or C virus infection. No fibrosis markers showed prominent elevation (M2BPGi, 1.11 COI; hyaluronic acid, 122.7 ng/mL) (Table 1), and their combination with thrombocytopenia reflected fibrotic changes but not cirrhosis. Abdominal US revealed a 25-mm lesion with low echogenicity in segment 7 of the liver (Fig. 1a); this nodule exhibited the characteristics of HCC with chronic liver change and splenomegaly on enhanced CT (Fig. 1b and c). The liver parenchyma had a higher density, relative to the spleen, on plain CT (Fig. 2a). Furthermore, the R2* map from magnetic resonance imaging (Fig. 2b) revealed a markedly elevated R2* value at the liver parenchyma (>800 Hz vs. a normal value of approximately 40 Hz). In addition, the liver's signal intensity on in-phase T1-weighted imaging was significantly lower than that on out-of-phase imaging (Fig. 2c and d), which was consistent with iron deposition caused by hemochromatosis. Magnetic resonance elastography (MRE) was also performed to evaluate the iron deposition; however, the results were obscured by the high level of iron deposition. A needle biopsy specimen revealed regenerative parenchymal hepatocytes that contained diffuse hemosiderin and Kupffer cells that rarely contained hemosiderin, with no evidence of severe fibrosis (Fig. 3a-c). The tumor was confirmed to be well differentiated HCC (Fig. 3d) with no iron granules. Radiofrequency

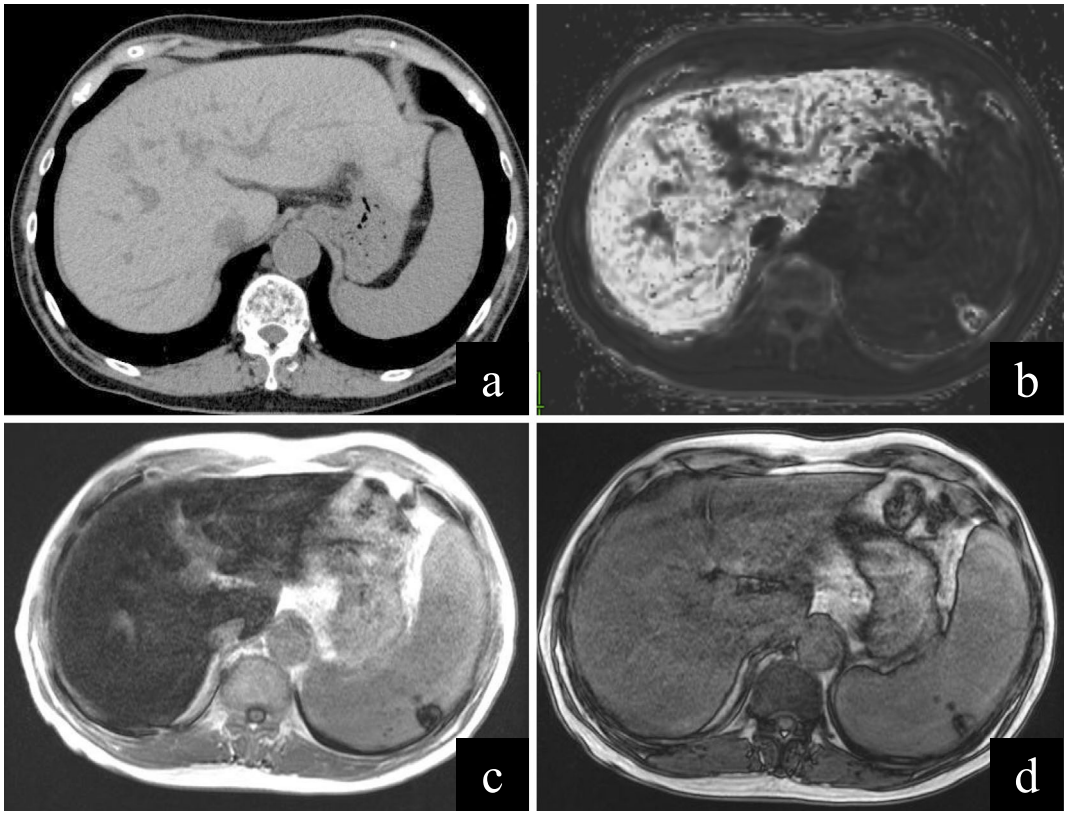

Figure 2. **Findings from (a) plain computed tomography, (b) R2* mapping, and (c) in-phase and (d) out-of-phase T1-weighted magnetic resonance imaging. The liver parenchyma also exhibited a markedly elevated signal on the R2* map, with a significantly low signal on the in-phase image (vs. the out-of-phase image), which reflected iron deposition.**

ablation was performed, which provided good results, and no recurrence has been observed during follow-up.

Discussion

This case highlights two important clinical issues. The first is that HCC can develop in cases of both HH and secondary hemochromatosis. In this context, HCC is a known major complication of HH and occurs in approximately 30% of cases (3), although there have only been four reported cases of HCC developing in patients with secondary hemochromatosis (4-7). The diagnosis of secondary hemochromatosis requires histological or imaging evidence of iron deposition in liver tissue (8). All five reported cases (including the present case) had histological findings of diffuse iron deposition in parenchymal hepatocytes, which supported the diagnosis of hemochromatosis, and three cases (including the present case) exhibited evidence of iron deposition on plain CT or magnetic resonance imaging (Table 2). The possibility of HH in the present case was excluded based on the medical history of MDS, the absence of a family history of HH, and a previous report that described low rates of two missense mutations (C282Y: 0%, H63D: 0.99%), which are associated with the risk of HH, in the Japanese population (9). Thus, the diagnosis was secondary hemochromatosis caused by ineffective erythropoiesis as a result of MDS. Our case and one other reported case involved MDS without a history of erythrocyte transfusion; another case involved MDS with a history of repeated erythrocyte transfusion, and the final case involved a coal miner with normal genetic results who might have had iron overload (4-7). MDS alone is a known risk factor for carcinogenesis, which may involve the attenuation of natural killer (NK) cell activity and chromosomal abnormalities (10, 11); however, there are no reports of coexisting HCC and MDS.

The second important clinical issue is that HCC can develop after secondary hemochromatosis even if the liver is not cirrhotic. In this context, liver cirrhosis is the most common risk factor for HCC, and iron overload is also associated with the risk of HCC, as HCC can develop in patients with iron overload but not cirrhosis (12-14). In our case, although no cirrhosis was detected in the needle biopsy specimen, splenomegaly and the swelling of the left lobe suggested the presence of liver fibrosis. Furthermore, results from an animal model of HCC (rats fed a high-iron diet) indicate that hepatic iron overload in the absence of cirrhosis is directly involved in the etiology and pathogenesis of HCC (15). Although iron is required for DNA synthesis and oxygen transport, excessive iron accumulation causes organ damage through increased oxidative stress, which is also a risk factor for HCC (16). Thus, we concluded that our patient developed HCC because of iron overload after secon-

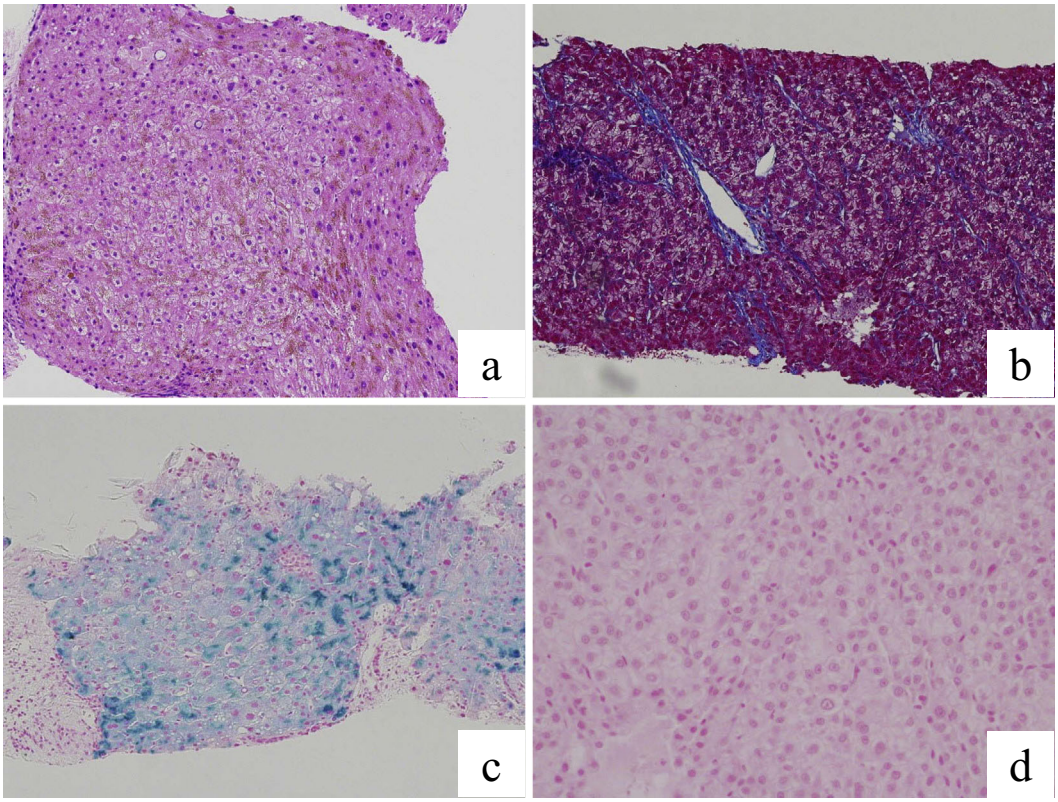

Figure 3. **Histological findings from the biopsy specimens. (a-c) The biopsy specimen from the non-tumor area revealed regenerative parenchymal hepatocytes that contained diffuse hemosiderin without fibrosis. (d) The biopsy specimen from the tumor nodule was confirmed to be well differentiated hepatocellular carcinoma. (a) Hematoxylin and Eosin (H&E) staining, ×200; (b) Masson trichrome staining, ×400; (c) iron staining, ×200; and (d) H&E staining, ×600.**

Table 2. **Presenting Clinical Features of 4 Cases of HCC Associated with Secondary Hemochromatosis and Our Patient.**

Case	Age (years)	Sex	Underlying disease	Iron deposition	LC	Treatment modality for HCC	Ref
1	61	M	Coal miner as a job	Yes	No	Right hepatectomy	4
2	56	M	MDS-RA Diabetes mellitus	Yes	Yes	Partial hepatectomy	5
3	40	M	MDS	Yes	No	TACE	6
4	67	M	MDS (RCMD-RS)	Yes	No	Partial hepatectomy	7
5	70	M	MDS-RA	Yes	No	RFA	Present case

HCC: hepatocellular carcinoma, MDA-RA: myelodysplastic syndrome refractory anemia, MDS: myelodysplastic syndrome, LC: liver cirrhosis, TACE: transarterial chemoembolization, RFA: radiofrequency ablation

dary hemochromatosis-despite the absence of liver cirrhosis-based on the histopathological and imaging evidence of iron deposition. Other reports have also indicated that HCC can occur without cirrhosis in patients with HH, which is associated with increasing hepatic iron storage (17). However, a needle biopsy specimen can only show a part of the liver parenchyma and "non-cirrhotic liver" is an imprecise term. In addition, iron deposition in sinusoidal Kupffer cells can predict the risk of fibrosis and histological changes leading to liver injury (18). Thus, other tests-such as MRE and blood testing for fibrosis markers-should be performed to identify liver fibrosis. In the present case, we performed needle biopsy, MRE, and blood testing for fibrosis markers. Although the MRE results were obscured by the high level of iron deposition in the liver, the blood levels of fibrosis markers were slightly elevated, which we suspect indicates that iron overload, rather than liver fibrosis, was involved in the carcinogenesis in the present case. Three of the four previously reported cases have also involved patients with a non-cirrhotic liver, while the remaining case involved compensated cirrhosis.

We suggest that surveillance for HCC every 6 months may help identify treatable early-stage HCC, as in the present case. Although the frequency of HCC after secondary hemochromatosis remains unclear, monitoring is likely essential. Furthermore, additional cases should be accumulated

to better understand the prevalence of HCC in cases of secondary hemochromatosis, as well as the prognosis after the treatment of HCC.

In conclusion, secondary hemochromatosis may be a risk factor for HCC, even if the liver is not cirrhotic. In such cases, additional surveillance may be required to detect the development of HCC.

The authors state that they have no Conflict of Interest (COI).

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