



# A case report of granulocyte colony-stimulating factor-producing hepatocellular carcinoma that recurred after long-term complete response

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## Abstract

The granulocyte colony-stimulating factor (G-CSF) is a glycoprotein that stimulates cell proliferation and differentiation of precursor cells in the bone marrow. Several cases of G-CSF-producing malignant tumors in various organs have been reported, but there are only nine cases of G-CSF-producing hepatocellular carcinoma (HCC) reported in the English literature. G-CSF-producing tumors grow rapidly and have a high probability of distant metastases; thus, they generally have a poor prognosis. Given that the mechanism of the carcinogenesis of G-CSF-producing HCC remains unclear, an efficient treatment strategy also remains to be elucidated. We report herein a case of G-CSF-producing HCC accompanied by leukocytosis and high serum G-CSF concentrations in the disease progression stage after long-term complete response. We also reviewed previous reports to investigate the clinical behaviors of G-CSF-producing HCC, including our case. Clinicians should consider G-CSF-producing HCC in patients with a hepatic mass and drastic leukocytosis, without any evidence of infection and blood disorders. Early diagnosis and prompt therapy, including radical resection, may provide a more favorable prognosis.

**Keywords** Hepatocellular carcinoma · Granulocyte colony-stimulating factor · Leukocytosis

## Introduction

Leukocytosis is often seen in patients with paraneoplastic syndromes and is related to granulocyte colony-stimulating factor (G-CSF) production. Robinson [1] reported that a colony-stimulating factor was found in the serum and urine in patients with malignant tumors. The granulocyte colony-stimulating factor (G-CSF) is a cytokine produced mainly by macrophages, fibroblasts, and endothelial cells, which functions to induce maturation and proliferation of the precursor of neutrophils in the bone marrow and recruit them into the periphery [2]. Asano et al. [3] first reported a G-CSF-producing lung cancer in 1997; subsequently, various types of G-CSF-producing tumors have been reported, such as the lung [4], bladder [5], gallbladder [6], pancreas [7], thyroid [8], and cervical cancers [9].

However, G-CSF-producing hepatocellular carcinoma (HCC) is extremely rare. G-CSF-producing tumors grow rapidly and have a high probability of distant metastases; thus, they generally have a poor prognosis. Given that the

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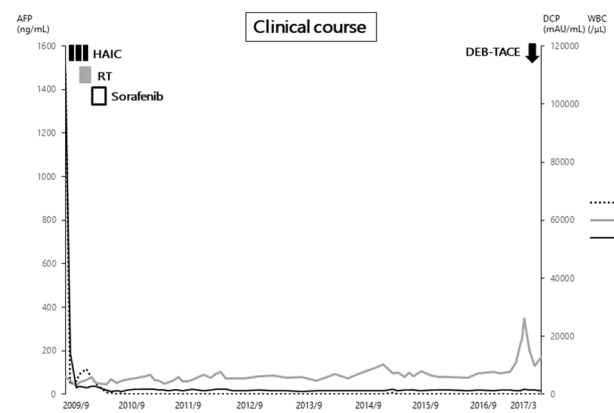
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mechanism of the carcinogenesis of G-CSF-producing HCC remains unclear, an efficient treatment strategy also remains to be elucidated.

Here, we report a case of G-CSF-producing HCC accompanied by leukocytosis and high serum G-CSF concentrations in the disease progression stage.

## Case report

A 78-year-old man with chronic hepatitis C was admitted to our hospital in September 2009 due to general fatigue. Contrast-enhanced computed tomography (CT) showed a 70-mm hepatic mass in the right lobe with peripheral enhancement, and right hepatic vein invasion, with metastasis of both lungs (Fig. 1a, b). The levels of tumor markers on the first admission were elevated as follows: alfa-fetoprotein (AFP), 1528 ng/mL; AFP-L3 fraction, 26.5%; and des-g-carboxy prothrombin (DCP), 110,020 mAU/mL. We, therefore, diagnosed the hepatic mass as HCC; however, the findings of the contrast-enhanced CT showed an unusual enhancement pattern for typical HCC. The patient had initially undergone hepatic arterial infusion chemotherapy (HAIC) with radiotherapy (RT). The HAIC involved cisplatin and a continuous infusion of fluorouracil, referred to as NewFP [10]. RT (50 Gy, in 25 fractions) for the right hepatic vein invasion was initiated with the first cycle of HAIC. After receiving sorafenib, followed by HAIC and RT, he maintained complete response (CR) for several years, and the levels of tumor markers decreased as follows: AFP, 16 ng/mL; AFP-L3 fraction, 0.5%; and DCP, 27 mAU/mL (Fig. 2).

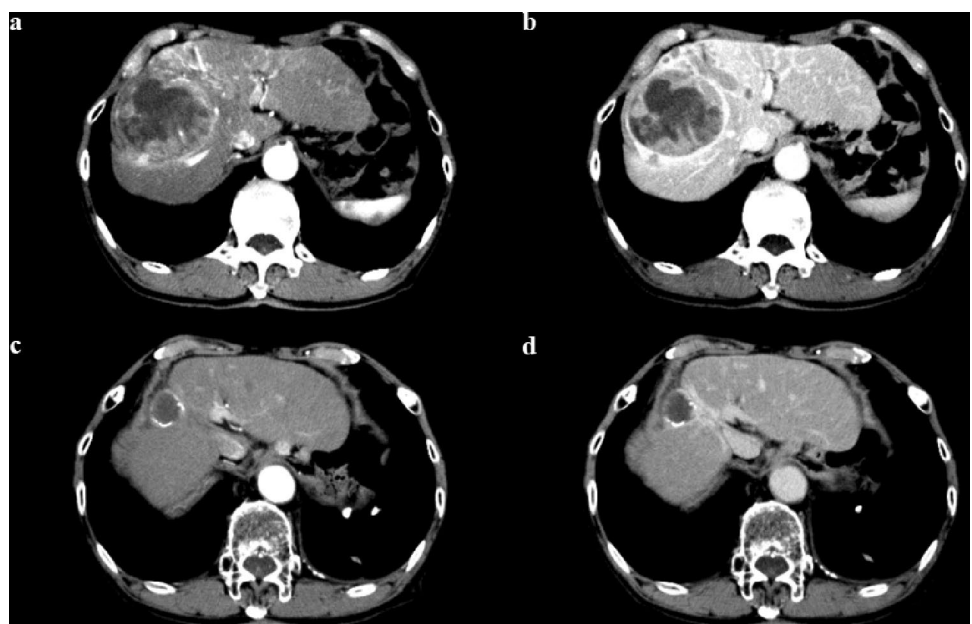


**Fig. 2** Clinical course and changes in the tumor maker and white blood cell count (WBC) levels. After the patient had undergone hepatic arterial infusion chemotherapy (HAIC) with radiotherapy (RT) and sorafenib, he maintained complete response for several years, and the levels of tumor markers decreased remarkably. In March 2017, a peripheral blood count analysis revealed leukocytosis of up to 26,070/ $\mu$ L at the time of hepatocellular carcinoma recurrence. DCP, des-g-carboxy prothrombin; DEB-TACE; drug-eluting bead transarterial chemoembolization

Then, the patient underwent imaging studies regularly, and contrast-enhanced CT revealed a low-density area in the treated location (Fig. 1c, d). This lesion gradually increased over time since February 2016; however, the AFP, AFP-L3, and DCP were not elevated, and we initially suspected biloma and could not determine whether HCC had recurred. We, therefore, followed up the lesion with 4-monthly imaging studies. In December 2016, gadoxetic acid-enhanced magnetic resonance imaging (MRI) showed that the lesion had grown to 50 mm in size, with high

**Fig. 1** Imaging findings.

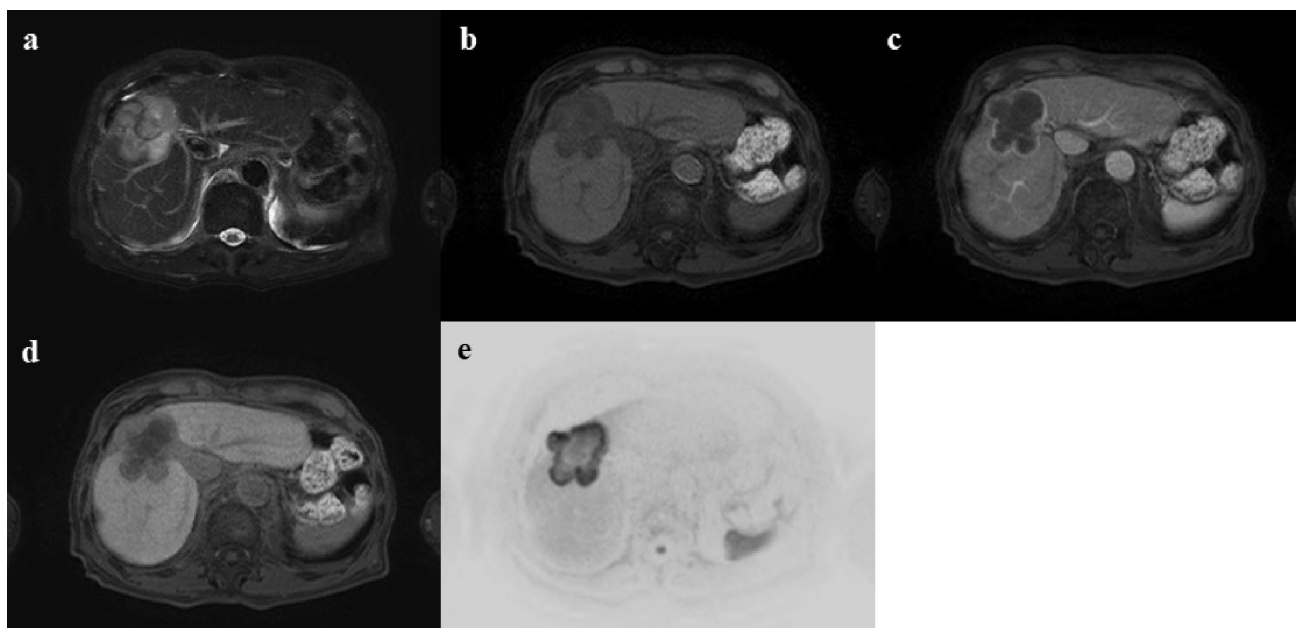
Abdominal contrast-enhanced computed tomography showed a liver mass in the right lobe, approximately 70 mm in size, with peripheral enhancement and right hepatic vein invasion at the first occurrence in September 2009. **a** Arterial phase; **b** equilibrium phase. After the treatment with hepatic arterial infusion chemotherapy with radiation therapy and sorafenib, the tumor obtained complete response for several years; however, abdominal contrast-enhanced computed tomography performed thereafter showed a low-density area in the treated location in February 2016. **c** Arterial phase; **d** equilibrium phase



signal intensity on T2-weighted image with fat suppression in the anterior segment of the liver. The lesion showed hypo-vascularization in the arterial phase, but peripheral enhancement in the portal phase, and washout appearance in the 20-min delayed phase with restriction on diffusion characterized by high signal on diffusion-weighted imaging (Fig. 3). Since these imaging findings were atypical for HCC and the patient had no symptoms, he strongly desired to be managed with follow-up alone. In March 2017, the patient had loss of appetite and fever, with a body temperature of 37 °C. Physical examination revealed a hard fixed mass palpable at the right hypochondria. As shown in Table 1, a peripheral blood count analysis revealed leukocytosis of up to 26,070/ $\mu$ L with 88.5% neutrophilia, although no leukocytosis or neutrophilia was seen before March 2017. The levels of tumor markers, such as AFP, carcinoembryonic antigen, and carbohydrate antigen 19-9, were slightly elevated, whereas the DCP level was within the normal range. Before the treatment, the serum granulocyte colony-stimulating factor (G-CSF: 93.1 pg/mL; normal range, < 39.0 pg/mL) and interleukin-6 (IL-6 30.5 pg/mL; normal range < 4.0 pg/mL) levels were markedly elevated. In comparison to the grade of leukocytosis, the increase in serum C-reactive protein (CRP) level was lower, and no infection foci were detected by several imaging examinations. Thus, we consider that leukocytosis in this patient was related to the HCC recurrence.

Abdominal ultrasonography showed a hypoechoic mass with an irregular demarcation, approximately 100 mm in size and located in the anterior segment of the liver. Sonazoid-enhanced ultrasonography detected a vessel flowing in the marginal region of the tumor in the early vascular phase, which was not enhanced in the late phase. Abdominal contrast-enhanced CT revealed an irregularly demarcated mass, approximately 100 mm in size, located in the anterior segment with peripheral enhancement. The center of the mass was in a low-density area, which was suggestive of degeneration or necrosis (Fig. 4a–d). 18F-fluorodeoxyglucose positron emission tomography/CT imaging showed a liver mass with a maximum standardized uptake value of 13.91 (Fig. 4e).

Immunohistochemical examination was performed using samples obtained from a needle biopsy. The histopathological findings revealed atypical poorly differentiated cells with a sheet structure, and the tumor was composed of sarcomatous spindle-shaped cells with necrosis and neutrophilic infiltration (Fig. 5a). The poorly differentiated HCC lesion was found to be positive for cytokeratin (CK) CAM5.2 (Fig. 5b), and the sarcomatous component was found to be negative for CK CAM5.2. Furthermore, the tumor was positive for pankeratin (CK AE1/AE3) (Fig. 5c) and vimentin (Fig. 5d). Immunohistochemical examinations showed that the G-CSF was positive in some cancer cells in the poorly differentiated HCC lesion (Fig. 5e). We found that HCC



**Fig. 3** Imaging findings in December 2016. Gadoxetic acid-enhanced magnetic resonance imaging showed that the lesion had grown to 50 mm in size, with high signal intensity on a T2-weighted image with fat suppression (T2FSWI) located in the anterior segment of the liver. The lesion showed hypo-vascularization in the arterial phase,

but peripheral enhancement in the portal phase, and washout appearance in the 20 min delayed phase, with restriction on diffusion characterized by high signal on diffusion-weighted imaging (DWI). **a** T2FSWI; **b** arterial phase; **c** portal phase; **d** 20 min delayed phase; **e** DWI

**Table 1** Laboratory data of patients with HCC recurrence

Peripheral blood counts			Biochemistry			Serology		
WBC	26,070	/ $\mu$ L	TP	6.5	g/dL	CRP	1.28	mg/dL
Neut	88.5	%	Alb	3.1	g/dL	HBsAg	(–)	
RBC	$344 \times 10^4$	/ $\mu$ L	T.Bil	0.5	mg/dL	HBcAb	(+)	
Hb	10.0	g/dL	D.Bil	0.2	mg/dL	HBsAb	(+)	
Ht	30.5	%	AST	40	U/L	HCVAb	(+)	
Plt	$20.2 \times 10^4$	/ $\mu$ L	ALT	20	U/L	Tumor markers		
Coagulation			ALP	462	U/L	AFP	21	ng/mL
PT	119	%	$\gamma$ -GTP	73	U/L	AFP-L3	0.5	%
PT-INR	0.93		LDH	373	U/L	DCP	17	mAU/mL
APTT	31.3	s	BUN	19.2	mg/dL	CEA	6.3	ng/mL
Fibrinogen	404	mg/dL	Cr	0.77	mg/dL	CA19-9	39	U/mL
D-Dimer	2.6	$\mu$ g/mL				Others		
						G-CSF	93.1	pg/mL
						IL-6	30.2	pg/mL

WBC white blood cell, *Neut* neutrophil, *RBC* red blood cell, *Hb* hemoglobin, *Ht* hematocrit, *Plt* platelet, *PT* prothrombin time, *PT-INR* prothrombin time-international normalized ratio, *APTT* activated partial thromboplastin time, *TP* total protein, *Alb* Albumin, *T.Bil* total bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase,  $\gamma$ -*GTP*  $\gamma$ -glutamyl transpeptidase, *LDH* lactate dehydrogenase, *BUN* blood urea nitrogen, *Cr* creatinine, *CRP* C-reactive protein, *HBs* hepatitis B surface, *HBc* hepatitis B core, *HCV* hepatitis C virus, *AFP*, alfa-fetoprotein, *DCP* des-g-carboxy prothrombin, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *G-CSF* granulocyte colony-stimulating factor, *IL-6* interleukin-6

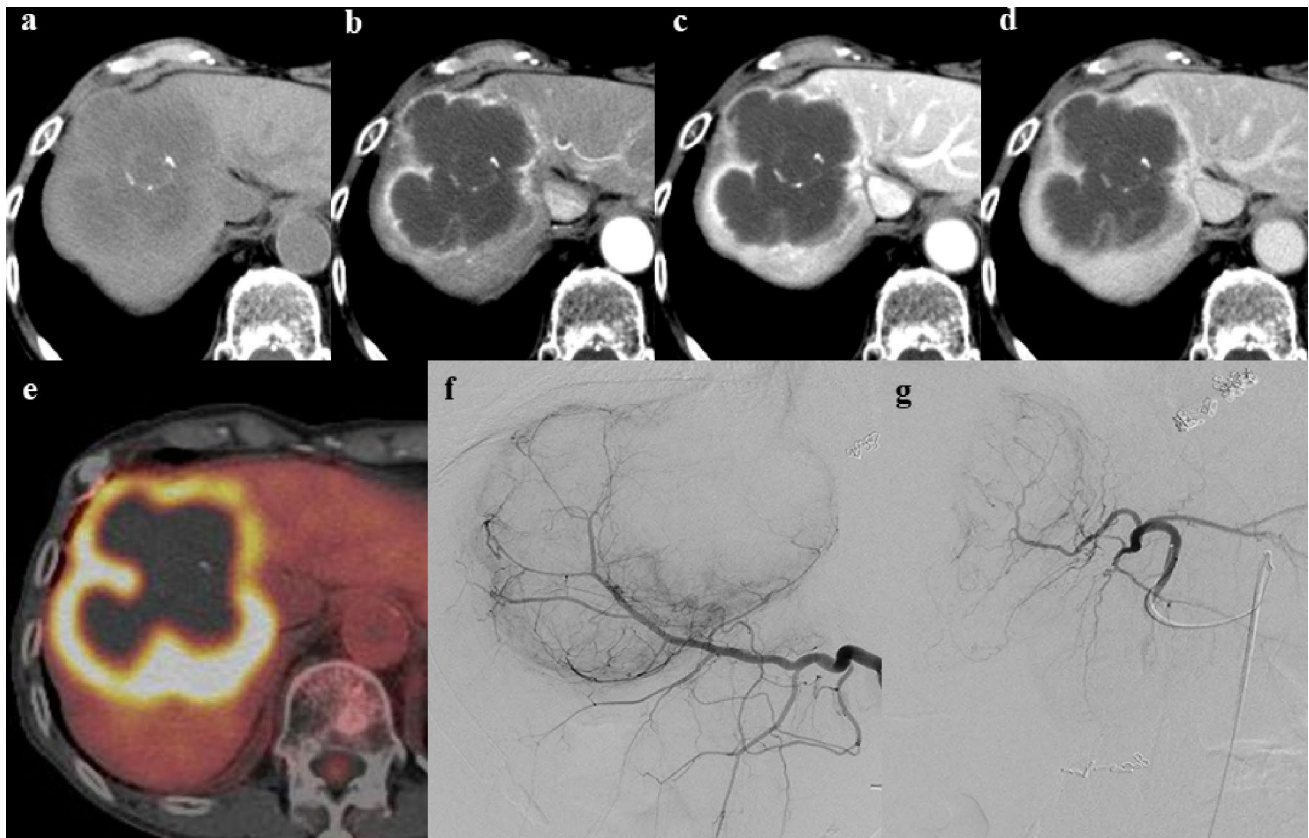
with sarcomatous changes produced G-CSF, according to the results of the G-CSF immunohistochemical study.

Given that the angiography via the superior mesenteric (Fig. 4f) and celiac (Fig. 4g) arteries showed a tumor stain in the marginal region of an irregular liver mass, the patient was treated by drug-eluting bead transarterial chemoembolization (DEB-TACE). The serum G-CSF levels decreased at 14 days after DEB-TACE to 41.6 pg/mL. Although the HCC in this patient partially and transiently responded to this treatment, it grew rapidly again, and the patient died from hepatic failure approximately 3 months after the diagnosis (in July 2017).

## Discussion

The disease course of this patient suggested two important clinical issues. Clinicians should consider G-CSF-producing HCC in patients with a hepatic mass accompanied by drastic leukocytosis, without any evidence of infection and blood disorders. In the process of dedifferentiation of cancer cells, it might be possible that the cancer cells changed the G-CSF-producing HCC.

G-CSF-producing HCC is extremely rare. To date, only nine cases have been reported in the English literature [11–19] (Table 2). The clinical manifestations of G-CSF-producing HCC included general malaise, loss of appetite, continuous fever, and high serum CRP. The characteristics of the CT and MRI findings of G-CSF-producing HCC did not show the same pattern. Some cases showed patterns typical of HCC that enhanced in the early phase of contrast medium infusion and washed out in the late phase; in contrast, some cases showed an unusual pattern that peripherally enhanced, with the center of the tumor in a low-density area, suggestive of necrosis or degeneration, as in our case. The G-CSF-producing tumor has been described as having the following clinical characteristics: (1) drastic white blood cell (WBC) increase; (2) elevation of G-CSF activity; (3) decrease in WBC count after tumor resection; and (4) evidence of G-CSF production in the tumor tissue [3]. In our case, the WBC count and the serum G-CSF level increased remarkably without any evidence of infection and blood disorders. Our case was not due to WBC decrease after tumor resection closely because of an unresectable HCC, and the WBC count and serum G-CSF level considerably decreased after DEB-TACE. In the present



**Fig. 4** Imaging findings at time of recurrence in March 2017. Abdominal contrast-enhanced computed tomography showed an irregularly demarcated liver mass with peripheral enhancement, 100 mm in size, located in the anterior segment of the liver. **a** Plain; **b** arterial phase; **c** portal phase; **d** equilibrium phase. An 18F-fluoro-

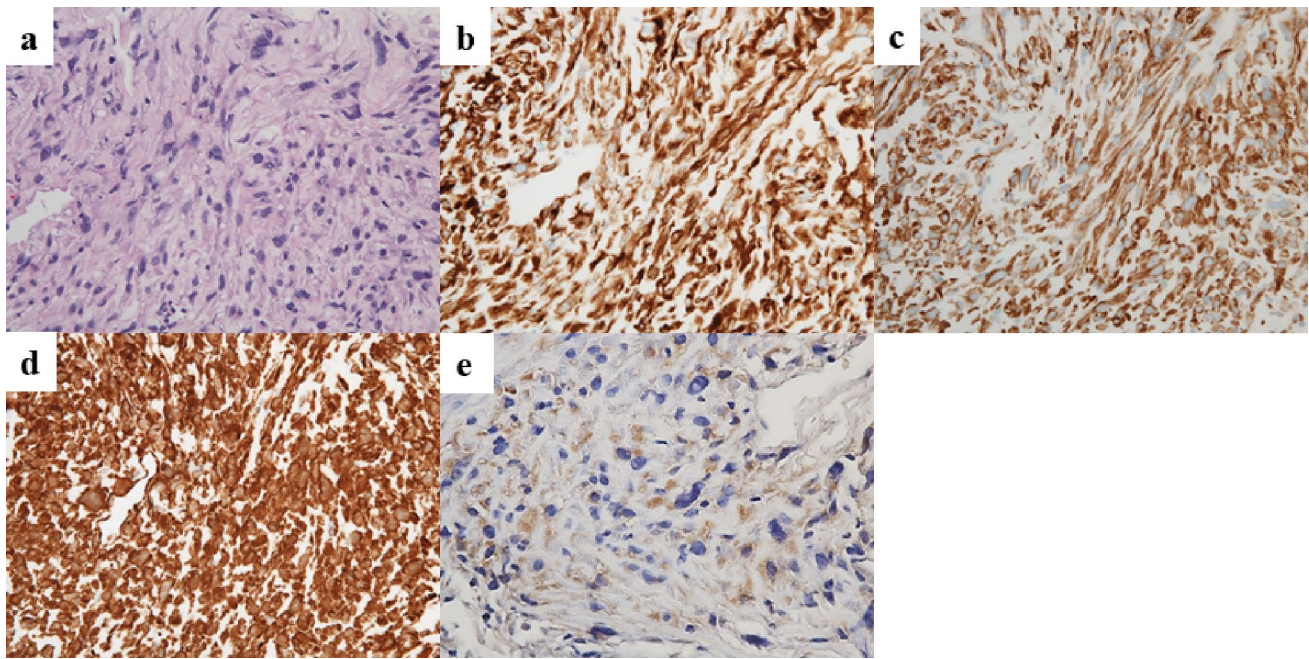
deoxyglucose positron emission tomography/computed tomography image showed the marginal region of the liver mass with a maximum standardized uptake value of 13.91 (**e**). Angiography via superior mesenteric artery (**f**) and celiac artery (**g**) showed tumor stain in the marginal region of an irregular liver mass

case report, the immunohistochemical study showed that G-CSF was positive in the tumor tissues, suggesting the production of G-CSF in HCC. The abovementioned findings supported the diagnosis of G-CSF-producing HCC in our case.

As shown in Table 2, among the ten reported G-CSF-producing HCC cases, including our case, six cases [60% (6/10)] were histologically diagnosed as poorly differentiated HCCs, three cases were moderate to poorly differentiated HCCs, and one case was a moderately differentiated HCC. Collectively, our case and previously reported cases might suggest that G-CSF-producing HCCs are poorly and/or moderately differentiated HCCs, not well-differentiated HCCs.

In the previous report by Yamamoto et al. [11], leukocytosis was not found at the initial diagnosis of HCC. The diagnosis of G-CSF-producing HCC was determined after the patient underwent treatments for HCC. Similarly, in our case, the WBC count was within the normal range at the early period of the first treatment for HCC. At 7 years after the first treatment, the HCC of our patient rapidly increased in size, as seen by contrast-enhanced CT, and the WBC count began to increase.

Although the mechanism of the production of G-CSF in HCC remains unclear, an intimate relationship between the production of G-CSF in cancer cells and their dedifferentiation has been reported [11]. Wang et al. [20] compared



**Fig. 5** Histopathologic findings. The tumor was composed of sarcomatous spindle-shaped malignant cells, pleomorphic cells with bizarre nuclei, an intense infiltration of neutrophils and histiocytes, focally admixed with poorly differentiated hepatocellular carcinoma with trabecular and compact patterns (a) (hematoxylin eosin staining,  $\times 100$ ). Immunohistochemical findings showed cytoke-  
 ratin (CK) CAM5.2 positivity in the cancer cells of a poorly differenti-

ated hepatocellular carcinoma (b) (CK CAM5.2,  $\times 100$ ). Immunohistochemical staining of CK AE1/AE3 (c) and vimentin (d) in the sarcomatous area of the tumor (CK AE1/AE3, vimentin,  $\times 100$ ). Immunohistochemical examination showed that granulocyte colony-stimulating factor was positive in a part of cancer cell (e) (granulocyte colony-stimulating factor,  $\times 400$ )

the production of G-CSF between well-differentiated and poorly differentiated HCCs using cell lines, and concluded that only the poorly differentiated HCCs tend to produce G-CSF. The number of patients with sarcomatoid liver cancers have been increasing since the late 1980s, when clinicians began to use transcatheter arterial embolization (TAE) as a treatment for HCC. In a previous report, sarcomatous changes were found in 27.6% of HCC cases treated with TAE frequently [21]. In our case, HAIC was used to treat HCC, which might induce sarcomatous changes. Thus, patients who maintained long-term CR of HCC should be monitored.

Generally, the G-CSF-producing tumors, including HCC, grow rapidly and have a poor prognosis, and the majority of the patients die within a few months after the initial diagnosis. Baba et al. [22] reported that G-CSF is associated with the rapid growth and metastasis of tumors as an autocrine growth factor in a gastric cancer cell line. Jana et al. [23] reported that G-CSF played an important role in the autonomous proliferation of Caco-2, which is a cell line derived from adenocarcinoma of the colon. The G-CSF-producing tumors induce some

inflammatory cytokines, such as IL-1 and IL-6 [24], and IL-6 has emerged as a cytokine involved in cachexia progression with some cancers [25]. Kyo et al. [9] described a case of cervical cancer that exhibited an aggressive clinical course, possibly due to the autocrine stimulation of cell growth by G-CSF and IL-6. In the present case, the G-CSF and IL-6 levels were also high, HCC progression occurred rapidly, and the patient had also a poor prognosis. We speculated that one approach to improve the poor prognosis of patients with tumors producing G-CSF or IL-6 would be the blockade of autocrine and/or paracrine growth-stimulating loops by the inhibition of cytokine production.

In conclusion, clinicians should consider G-CSF-producing HCC in patients with a hepatic mass accompanied by drastic leukocytosis. Early diagnosis and prompt therapy including, radical resection, may provide a more favorable prognosis. Further accumulation and studies of G-CSF-producing HCC are necessary, and other appropriate and effective treatments, such as immunotherapy, should be investigated.

**Table 2** Previously reported cases of G-CSF-producing HCCs

Case	Author (year)	Age	Sex	HBs antigen	HCV anti-body	WBC ( $\mu$ L)	G-CSF <sup>a</sup> (pg/mL)	Pathology	Sarcomatous change	Treatment	Prognosis <sup>b</sup>
1	Yamamoto [11]	67	M	-	+	234,000	251	Poorly differentiated HCC	-	TAE + chemotherapy	Dead (5 months)
2	Amano [12]	70	M	-	-	26,400	308	Poorly differentiated HCC/CCC	+	Palliative surgery	Dead (1 months)
3	Araki [13]	66	M	-	-	71,700	178	Poorly differentiated HCC	+	Radical Surgery + TAE	Dead (4 months)
4	Joshita [14]	66	M	-	-	25,450	62	Moderately differentiated HCC	-	Radical surgery	Dead (4 years)
5	Kohno [15]	46	M	+	-	51,670	195	Moderately to poorly differentiated HCC	+	Radical surgery + TAE + chemotherapy	Dead (7 months)
6	Snyder [16]	47	F	-	-	40,000	58.2	Poorly differentiated HCC	Unknown	Radical surgery	Dead (1 months)
7	Ito [17]	37	M	+	-	51,600	342	Moderately to poorly differentiated HCC	-	Radical Surgery + chemotherapy	Alive (2 years)
8	Nagata [18]	79	M	+	-	13,020	42	Poorly differentiated HCC	+	Radical surgery	Alive (6 months)
9	Sakamoto [19]	62	M	+	-	28,900	358	Moderately to poorly differentiated HCC	-	Radical Surgery + chemotherapy (+preoperative RT)	Alive (2 years)
10	Our case	85	M	-	+	26,070	93.1	Poorly differentiated HCC	+	DEB-TACE	Dead (3 months)

HBs hepatitis B surface, HCV hepatitis C virus, WBC white blood cell, G-CSF granulocyte colony-stimulating factor, HCC hepatocellular carcinoma, TAE transcatheter arterial embolization

<sup>a</sup>Granulocyte colony-stimulating factor (normal value: <39 pg/mL)

<sup>b</sup>Prognosis after diagnosis

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## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflicts of interest.

**Human/animal rights** All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** Informed consent was obtained from the patient for being included in this case report.

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