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A long-term survivor of undifferentiated carcinoma of the liver successfully treated with surgical treatments: A case report and literature review

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ABSTRACT

INTRODUCTION: Undifferentiated carcinoma of the liver is extremely rare. The biological characteristics and standard strategy for its treatment have not been established yet.
PRESENTATION OF CASE: A 45-year-old man was admitted because of fever elevation and shivering. Abdominal computed tomography revealed a hypovascular cystic mass in segments 6 and 7 of the liver measuring 11.5 × 9.0 cm with ring enhancement and partial solid component. A diagnosis of liver abscess was made, and percutaneous transhepatic abscess drainage was performed. Reddish brown-colored pus showed no bacteria or amoebas. However, cytology demonstrated malignant cells. After additional examinations of magnetic resonance imaging and the positron emission tomography, extended posterior sectionectomy with cholecystectomy was performed. The excised specimen showed a solid and irregular tumor with extensive central necrosis. A pathological examination revealed diffuse proliferation of oval- and spindle-shaped malignant cells. Immunohistochemically, the malignant cells were diffusely positive for AE1/AE3 and vimentin and focally positive for granulocyte colony-stimulating factor and cytokeratin 19; however, hepatocyte-specific antigen, glypican 3, cytokeratin 7, and CD56 were negative. Therefore, a diagnosis of undifferentiated carcinoma of the liver was made. He has remained well without any recurrence for three years since the operation.
DISCUSSION: Undifferentiated carcinoma of the liver might grow rapidly, resulting in necrosis with a cystic component. Therefore, it can be difficult to distinguish from liver abscess.
CONCLUSION: This disease has markedly different clinical and biological features from common primary malignant tumor of the liver. However, if the tumor is a solitary mass, surgical resection might lead to a good prognosis.

1. Introduction

Undifferentiated carcinoma of the liver is an extremely rare condition. In the literature, only two cases of undifferentiated carcinoma of the liver have been reported [1,2]. This type of disease is generally reported to be difficult to diagnose compared with primary malignant tumor of the liver and shows aggressive features and a poor prognosis [1,2]. However, due to its rarity, the biological features and standard therapeutic strategies have not been established yet.

We herein report a long-term survivor of undifferentiated carcinoma of the liver successfully treated with radical hepatectomy. This work has been reported in line with the SCARE criteria [3].

2. Case presentation

A 45-year-old man was admitted to our hospital because of fever elevation and shivering. He had a medical history of hepatitis B. A physical examination showed no tenderness in the abdomen.

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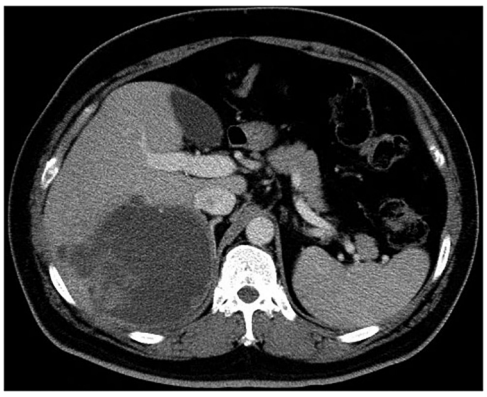

Fig. 1. Abdominal computed tomography revealed a hypovascular cystic mass in segments 6 and 7 of the liver measuring 11.5 × 9.0 cm with ring enhancement and partial solid component.

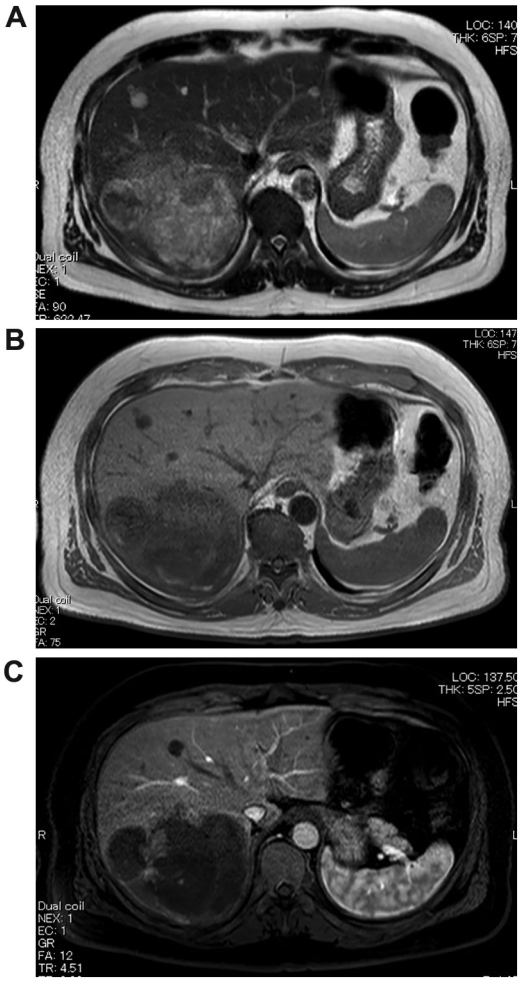

Fig. 2. Magnetic resonance imaging demonstrated a liver mass with cystic and irregular solid components measuring 11.5 × 9.0 cm. T1- and T2-weighted imaging showed a hypointense mass with partial hyperintensity and a nonuniform hyperintense mass, respectively (A, B). Dynamic contrast enhancement revealed a hypointense mass with a hyperintense area around the tumor (C).

The body temperature was 40.1 °C. His blood pressure and heart rate were 108/57 mmHg and 125 beats per minute, respectively. Laboratory studies on admission showed elevated inflammation markers (white blood cell count: 25,500/μl, C-reactive protein [CRP]: 10.13 mg/dl) and slight anemia (hemoglobin: 11.1 g/dl). Liver function markers, such as AST and ALT, were in the normal range. Tumor markers of carcinoembryonic antigen (CEA), CA19-9, pancreatic cancer-associated antigen (DUPAN-2), and s-pancreas-1 antigen (SPan-1) were also in the normal range. Serum viral markers for hepatitis B were positive (HBs antigen [+], HBe antigen [−], HBe antibody [+]), while hepatitis C were negative. The blood platelet count was in the normal range (374,000/μL). Abdominal computed tomography (CT) revealed a hypovascular cystic mass in segments 6 and 7 of the liver measuring 11.5 × 9.0 cm with ring enhancement and partial solid component (Fig. 1). Based on these findings, a diagnosis of liver abscess was made.

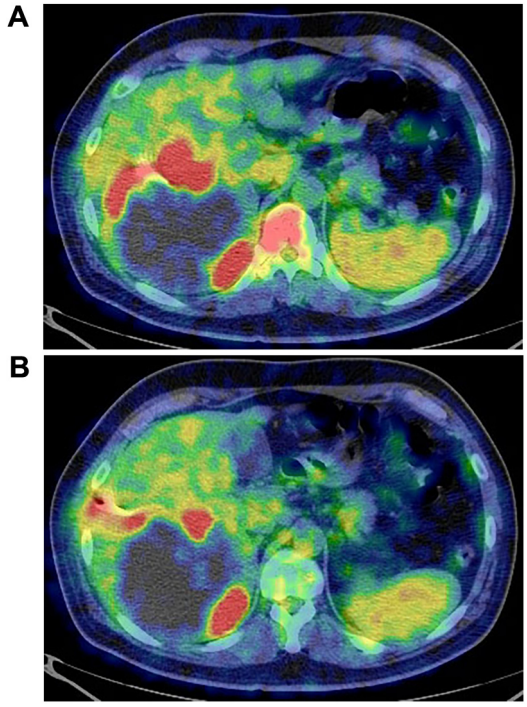

Fig. 3. Positron emission tomography showed a hypermetabolic lesion in the area surrounding the tumor (A), and a strong signal was also observed along the PTAD tube (B) (SUV_{max}: 4.80).

Percutaneous transhepatic abscess drainage (PTAD) was performed. Reddish brown-colored pus (100 mL) was drained. No bacteria or amoebas were detected in the aspirated sample. However, cytology demonstrated malignant cells. Therefore, magnetic resonance imaging was additionally performed at 12 days after the initial visit, showing a liver mass with cystic and irregular solid components measuring 11.5 × 9.0 cm (Fig. 2A–C). Positron emission tomography showed a hypermetabolic lesion in the area surrounding the tumor, and a strong signal was also observed along the PTAD tube (SUV_{max}: 4.80) (Fig. 3A, B). However, no other distant metastases or lymph node metastases were shown.

Based on these findings, radical operation was performed. The intraoperative findings showed that neither dissemination nor ascites were observed in the abdominal cavity. Extended posterior sectionectomy, cholecystectomy, and fistulectomy along the PTAD tube were performed. The excised specimen showed a solid and irregular tumor with central necrosis (Fig. 4). A pathological examination revealed the diffuse presence of oval- and spindle-type tumor cells (Fig. 5A). Immunohistochemical studies showed that AE1/AE3 and vimentin were positive (Fig. 5B, C), and cytokeratin 19 was focally positive. However, hepatocyte-specific antigen (HSA), glypican 3, cytokeratin 7, and CD56 were negative. Therefore, a diagnosis of undifferentiated carcinoma of the liver was made. An immunohistochemical study of granulocyte colony-stimulating factor (G-CSF) was additionally performed because the white blood cell count was extremely high before the operation. G-CSF was

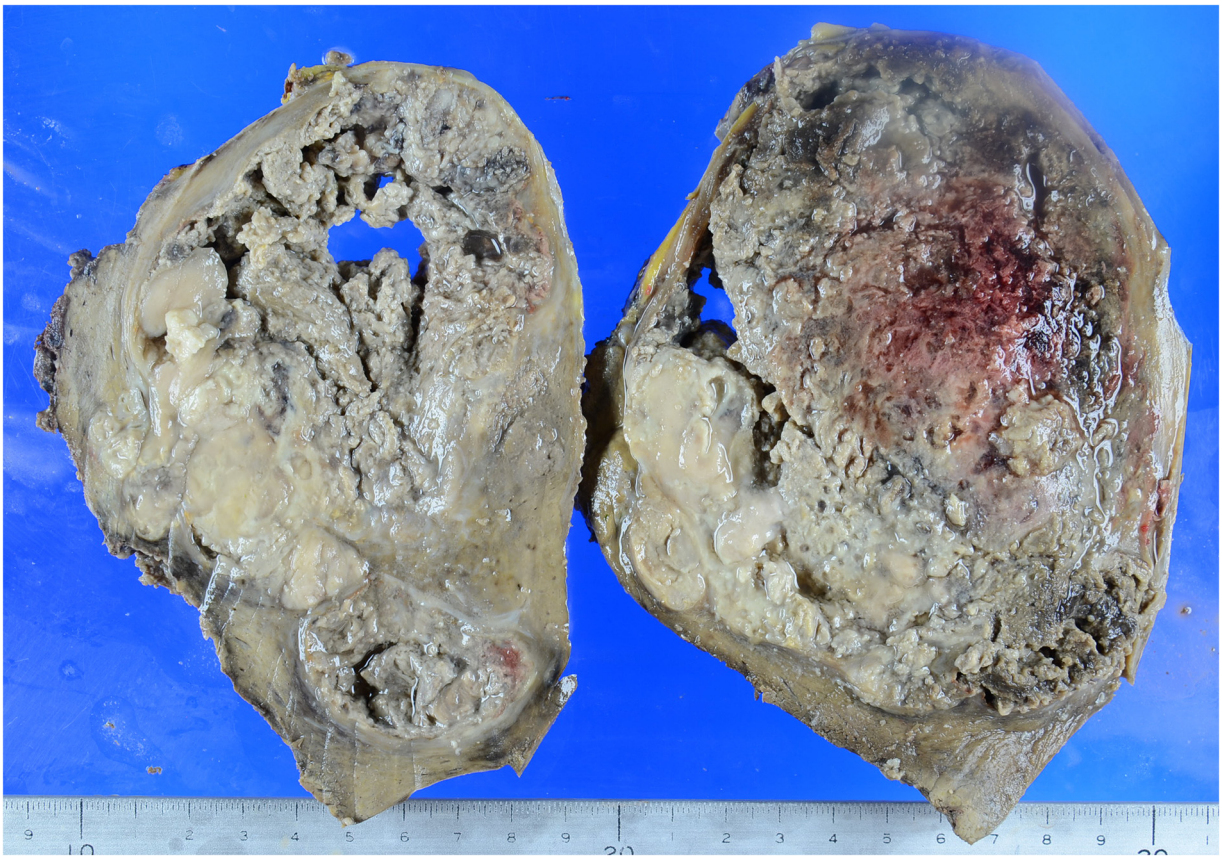

Fig. 4. The excised specimen showed a solid and irregular tumor with central necrosis.

found to be focally positive in the immunohistochemical study (Fig. 5D).

The patient has remained well without any recurrence for three years since the operation and has not received any additional chemotherapeutic treatment.

3. Discussion

Undifferentiated carcinoma of the liver is an extremely rare condition. A previous report found that only two cases had been documented in PubMed through December 2017 after searching with the key words "undifferentiated carcinoma" and "liver" [1,2]. Cases showing hepatocellular differentiation as confirmed by an immunohistochemical study were excluded. Because of the rarity of this entity, the biological features and standard treatment strategies have not been established yet. Table 1 shows three reports of undifferentiated carcinoma of the liver, including our own.

The imaging pattern for diagnosing undifferentiated carcinoma of the liver might differ markedly from primary malignant tumor of the liver. Hepatocellular carcinoma (HCC) is the most common liver cancer [4], and classical HCC normally shows arterial phase enhancement followed by washout in the portal and/or delayed phase on CT [5]. Regarding cholangiocarcinoma, which is the second-most common liver cancer [4], mass-forming intrahepatic cholangiocarcinoma presents as a homogeneous low-attenuation mass with irregular peripheral enhancement and periductal infiltrating cholangiocarcinoma characterized by growth along the dilated or narrowed bile duct without mass formation on CT [6]. In their previous repot of undifferentiated carcinoma of the liver, Nakasuka et al. [1] showed that multiple small nodules measuring 1–3 cm were found throughout the whole liver with no enhancement by contrast medium on dynamic CT. Maeda et al. [2] observed marked swelling of the liver and hepatic parenchyma with diffuse roughness on CT. In this case, the hepatic parenchyma had been almost completely replaced by innumerable minute nodules in the autopsy specimen. The two previous cases of tumors seemed to diffusely grow and spread, whereas our case was characterized by a huge hypovascular cystic mass with ring enhancement and partial solid component on the initial CT images. Taken together, these findings suggest that undifferentiated carcinoma of the liver can show at least two patterns of tumor growth: "diffuse type" or "solitary type". The solitary type can grow quickly and shows necrosis at the center of the tumor, making it difficult to distinguish from liver abscess.

Regarding the treatment and prognosis, only our case was successfully treated with radical surgery. We did not administer any additional post-operative chemotherapy because there was no evidence supporting a standard regimen for this type of disease. However, the patient has remained well without any recurrence for over three years since the operation. Nakasuka et al. [1] treated their patient with combined therapy of etoposide and cisplatin because multiple tumors were spread throughout the whole liver, and the tumor was well-controlled for eight months. Maeda et al. [2] failed to treat their patient with multiple tumors in the liver due to rapid disease progression; the patient ultimately died 16 days after presentation. These findings suggest that if a tumor is "diffuse type", chemotherapy should be considered. To establish a standard chemotherapy regimen for such tumors, the accumulation of similar cases is needed. If, however, a tumor is "solitary type", surgical resection might lead to a good prognosis, as in the present case. However, in general, undifferentiated carcinoma of the digestive system seems to have a poor prognosis [7–10]. Therefore, multimodal therapy should also be considered.

Table 1
Summary of previous reports of undifferentiated hepatocellular carcinoma.

Ref.	Year	Age (years)	Sex	Past medical history	CEA (ng/ml)	CA19-9 (U/ml)	AFP (ng/ml)	PIVKA- II (mAU/mL)	HCV	HBV	Tumor size (cm)	Solitary or multiple?	Treatment	Prognosis	
Nakasuka et al. [1]	1998	54	M	N.D.	2.9	40	7.9	N.D	–	–	<3	Multiple	Chemotherapy	8 month	Alive
Maeda et al. [2]	2017	56	M	Distal gastrectomy for duodenal ulcer	N.D.	N.D.	3.8	<0.06	–	–	Very small	Multiple	None	16 days	Dead
Our case	2018	45	M	Hepatitis B	0.5	4.4	N.E.	N.E.	–	+	11.5 × 9	Solitary	Radical surgery	3 years	Alive

N.D.; not documented, N.E.; not examined.

Fig. 5. The microscopic findings. Oval- and spindle-type tumor cells were diffusely shown (A) (HE, 400×). AE1/AE3 (B), vimentin (C), and G-CSF (D) were positive on an immunohistochemical study (200×).

We also performed an immunohistochemical study of G-CSF, as the white blood cell count was extremely high before the operation. G-CSF-producing tumors are diagnosed based on the presence of an elevated serum G-CSF level, a markedly increased leukocyte count, a decreased leukocyte count following tumor resection, and immunohistochemical confirmation of G-CSF in the tumor tissue [11]. We failed to examine the serum G-CSF level before the operation. However, an immunohistochemical study of G-CSF was

positive, and the white blood cell and leukocyte counts decreased to the normal range after the operation. While the present case might not meet the criteria for a G-CSF-producing tumor, this case still had characteristics of G-CSF-producing carcinoma. In general, G-CSF-producing HCC tend to grow rapidly, have a poor prognosis, and have a poorly differentiated type (76%) [12,13].

4. Conclusion

In conclusion, we herein report a case of undifferentiated carcinoma of the liver. This disease has markedly different clinical and biological features from common primary malignant tumor of the liver.

Conflicts of interest

The authors declare that they have no competing interests.

Funding

None.

Ethical approval

This case report is not research study. That is not applicable in this case report. The case report is exempt from ethical approval.

Consent

Informed broad consent and written informed consent for images were obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

All the authors contributed to diagnose and treat the patient. Masatsugu Hiraki contributed in drafting the manuscript. Atsushi Miyoshi and Kenji Kitahara edited the manuscript. Kenji Kitahara supervised and made the final approval of the manuscript. All authors read and approved the final manuscript.

Registration of research studies

This case report is not research study. That is not applicable in this case report.

Guarantor

Dr. Kenji Kitahara.

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