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Case Report

Granulocyte Colony-Stimulating Factor–Producing Cholangiocellular Carcinoma

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A 61-year-old female was admitted to our hospital with epigastric pain and fever. The laboratory data showed severe inflammatory reactions. Computed tomography revealed an irregular tumor in the left hepatic lobe and swelling of lymph nodes. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed high uptake by the tumor, with diffuse uptake in the spine. Based on the elevated leukocyte count and FDG-PET findings, the patient was diagnosed with a granulocyte colony-stimulating factor (G-CSF)-producing tumor (G-CSF, 213 pg/mL). We performed left trisegmentectomy of the liver, bile duct resection, and lymph node dissection. Histologically, the tumor was a poorly differentiated adenocarcinoma with some lymph nodes metastasis. Immunohistochemical staining of the tumor cells was positive for G-CSF. Therefore, the tumor was diagnosed as G-CSF–producing cholangiocellular carcinoma. The inflammatory reactions and serum G-CSF level transiently improved immediately after surgery. However, 1 month later, the leukocyte count and serum G-CSF level increased again, and recurrence was observed in the remnant liver. The patient died 3 months after the operation. G-CSF–producing cholangiocellular carcinoma is rare. This tumor progresses rapidly, and surgical treatment for advanced condition should be carefully selected.

Key words: Granulocyte colony-stimulating factor – Cholangiocellular carcinoma – FDG-PET – Immunohistochemistry – Leukocytosis

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Granulocyte colony-stimulating factor (G-CSF)-producing tumors were first reported in 1977.[1] G-CSF-producing cholangiocellular carcinomas (CCCs) are rare, with only 5 other reported cases. We herein report a surgical case of G-CSF–producing CCC with early recurrence and include bibliographic comments.

Case Report

A 61-year-old female was referred to our hospital with epigastric pain and fever. A physical examination revealed a temperature of 38.5°C with tenderness and a palpable, elastic, hard mass in the middle upper abdomen. No lymphadenopathy or hepatosplenomegaly was found. The laboratory data showed severe inflammatory reactions with a leukocyte count of 42,680/μL (93% segmented neutrophils, 2% stab neutrophils, 0% myelocytes, 0% eosinophils, 0% basophils, 2% monocytes, and 3% lymphocytes) and a serum C-reactive protein (CRP) level of 8.9 mg/dL. The serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (γ-GTP) were elevated to 66 U/L (normal range, 13–33 U/L), 67 U/L (normal range, 6–27 U/L), 797 U/L (normal range, 115–359 U/L), and 1253 U/L (normal range, 11–58 U/L), respectively. The levels of the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were within the normal ranges. Upper gastrointestinal endoscopy and colonoscopy did not reveal any pathology. Computed tomography (CT) showed an irregular and peripherally enhancing mass in the left hepatic lobe and swelling of the lymph nodes (Fig. 1). ^{18}F-fluorodeoxy-glucose positron emission tomography (FDG-PET) showed markedly high uptake by the tumor, with diffuse uptake in the spine (Fig. 2). Based on the elevated leukocyte count and FDG-PET findings, we suspected a diagnosis of a G-CSF-producing tumor. The serum level of G-CSF was elevated to 213 pg/mL (normal range, <39 pg/mL). We diagnosed the patient with a CCC-producing G-CSF and performed laparotomy. No peritoneal dissemination was found during exploratory laparotomy. Therefore, we performed left trisegmentectomy of the liver, bile duct resection, and lymph

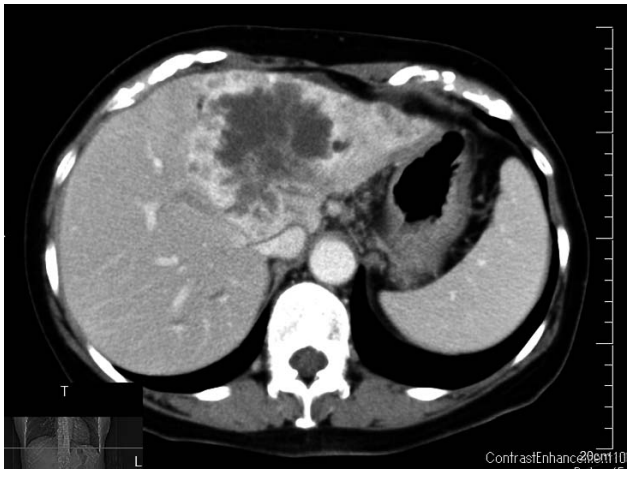

Fig. 1 CT showed an irregular and peripherally enhancing mass in the left hepatic lobe.

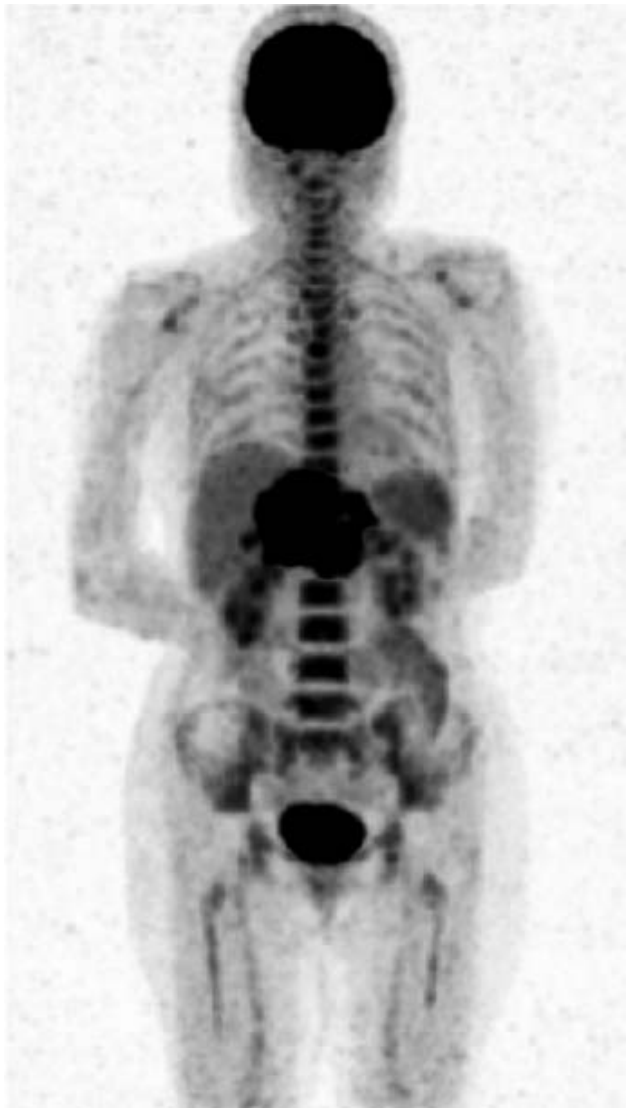

Fig. 2 FDG-PET showed markedly high uptake by the tumor, with diffuse uptake in the spine.

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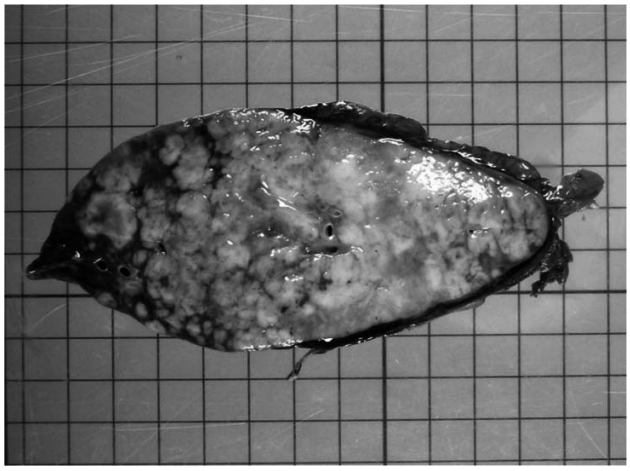

Fig. 3 The resected specimen measured 15 × 15 cm in size and showed a hard and solid tumor.

node dissection. The resected specimen measured 15 × 15 cm in size and showed a hard and solid tumor (Fig. 3). A microscopic examination revealed poorly differentiated adenocarcinoma with some lymph nodes metastasis (Fig. 4A). An immunohistochemical examination using anti–G-CSF monoclonal antibodies (Calbiochem, La Jolla, CA) demonstrated production of G-CSF by the tumor, as the cytoplasm was diffusely positive (Fig. 4B). Therefore, the tumor was diagnosed as G-CSF–producing CCC.

The leukocyte count decreased to within the normal range, the fever subsided, and the serum G-CSF level decreased to 37.2 pg/mL immediately after the operation. However, 1 month later, the leukocyte count and serum G-CSF level increased again, and recurrence was observed in the remnant liver. Three months after undergoing surgery, the patient died of multiple organ failure resulting from cancer metastasis.

Discussion

G-CSF, a hematopoietic growth factor, primarily influences the proliferation and differentiation of granulocytic precursors. In 1977, the production of G-CSF by malignant cells was first identified in lung cancer.[1] G-CSF–producing tumors often simultaneously produce cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor–α (TNF-α).[2] One report described a G-CSF–producing tumor that simultaneously produced cytokines including IL-1, IL-6, and TNF-α, causing chronic and progressive inflammation along with

Table 1 Reported cases of G-CSF–producing CCCs

Case No.	Author[Ref]	Year	Age, y	Sex	Symptoms	WBC[a]	G-CSF (pg/mL)	Tumor size	Operation	Histology	G-CSF in the tumor tissue	Prognosis
1	Tamai *et al* [4]	1995	78	Male	Fever, fatigue	23,700	129	10 cm	(-) (multiple liver tumors)	Poorly differentiated adenocarcinoma	ND	2 mo dead
2	Aizawa *et al* [5]	1997	69	Male	Fever, weight loss	13,700	82.5	ND	Hepatectomy	Squamous cell carcinoma	(+)	1 mo dead
3	Masuda *et al* [6]	2000	48	Male	Abdominal pain, fever	50,000	213	5 cm	(-) (multiple liver tumors)	Poorly differentiated adenocarcinoma	(+)	2 mo dead
4	Kakinoki *et al* [3]	2000	66	Female	Abdominal distension	28,200	99.2	13 cm	(-) (local advanced tumor)	Adenosquamous cell carcinoma	(+)	2 mo dead
5	Sohda *et al* [7]	2006	56	Male	Consciousness disturbance	118,000	264	5 cm	(-) (rupture of the tumor)	Poorly differentiated carcinoma	(+)	5 days dead
6	Our case	2013	61	Female	Epigastric pain, fever	42,680	213	15 cm	Left hepatic trisegmentectomy, bile duct resection, lymph node dissection	Poorly differentiated adenocarcinoma	(+)	3 mo dead

WBC, white blood cells; (-), no operation; (+), positive; ND, not described.
[a]Number of WBC per microliter.

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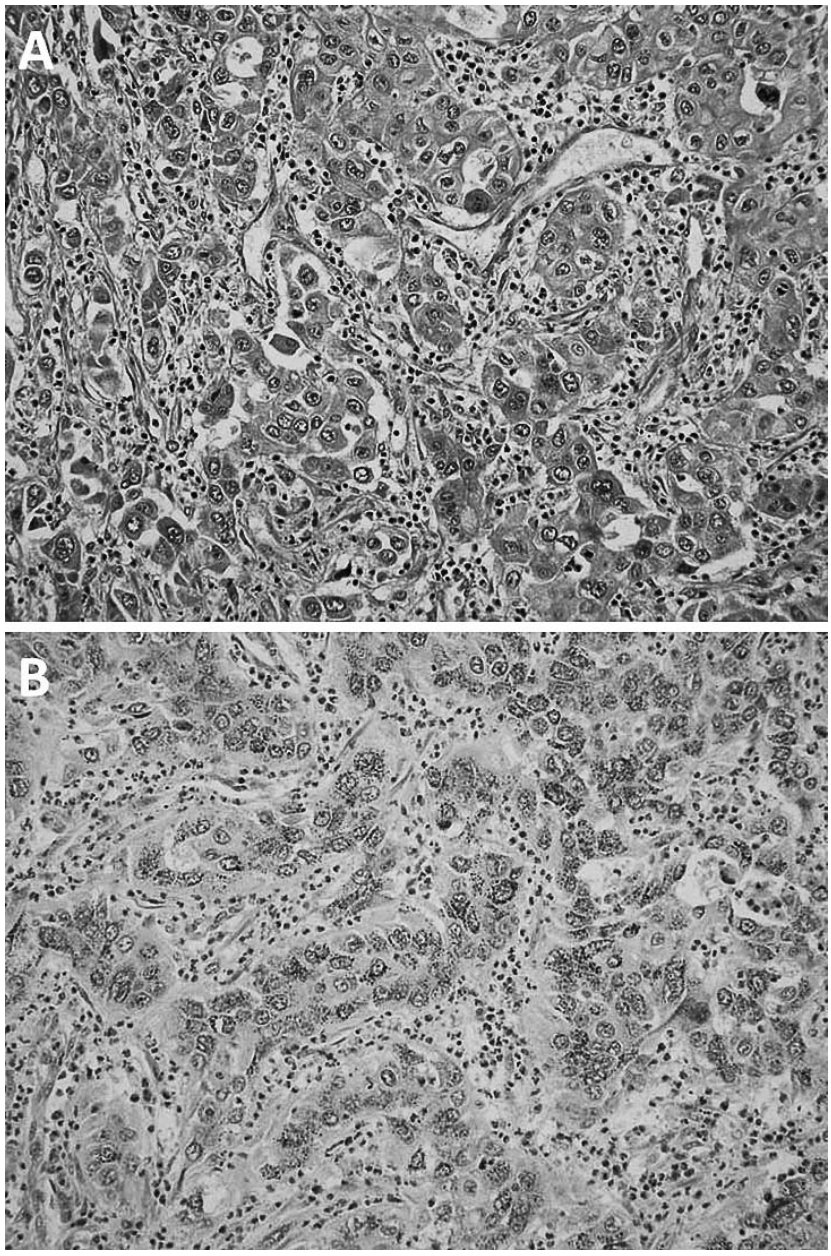

Fig. 4 (A) A microscopic examination showed poorly differentiated adenocarcinoma. H&E (×200). (B) An immunohistochemical examination showed a diffusely positive reaction for G-CSF antibodies in the cytoplasm of the tumor cells. H&E (×200).

tumor growth and exacerbation of symptoms of general wasting with cachexia, which were perceived to reflect worsening of the patient's prognosis.[3] There are few reports of G-CSF–producing CCC. Only 6 cases of G-CSF–producing CCC with leukocytosis have been reported, including our case (Table 1).[3–7] Among these cases, the tumors affected patients from 48 to 78 years of age (average age, 63 years) and included 4 men and 2 women. The most frequent symptom was fever. The serum G-CSF level did not correlate with the tumor size. Most of the G-CSF–producing CCCs were poorly differentiated adenocarcinomas. Four patients were inoperable; they died within 2 months. Two patients, including our case, received surgery; however, they died within 3 months.

G-CSF–producing tumors are diagnosed based on the presence of an elevated serum G-CSF level and immunohistochemical confirmation of the production of G-CSF in the tumor tissue. In our case, the serum G-CSF level was elevated, and an immunohistochemical examination showed the cy-

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toplasm of the tumor cells to be stained diffusely for G-CSF. Therefore, the tumor was diagnosed as G-CSF–producing CCC. FDG-PET can be used to assess the nature of a tumor. In our patient, FDG-PET showed markedly high uptake by the intrahepatic tumor, with diffuse uptake in the spine. Sugawara *et al*[8] described increased FDG uptake by bone marrow induced by increases in bone marrow metabolism and cellularity in response to G-CSF treatment. In our case, we believe that G-CSF produced by the CCC increased bone marrow metabolism, hence the diffuse FDG uptake present in the spine. FDG-PET is a useful method for diagnosing G-CSF–producing tumors.

G-CSF is thought to be an autocrine growth factor. G-CSF produced by tumor cells acts on the tumor, thus resulting in the upregulation of tumor progression. Therefore, G-CSF–producing tumors are generally associated with poor prognoses owing to rapid progression and metastasis.[9,10] The survival period after diagnosis of G-CSF–producing carcinoma is reported to be approximately 3 months.[11] All of the reported patients with G-CSF–producing CCC died within 3 months. Most of the patients with G-CSF–producing CCC could not be treated because of their poor condition and the progression of CCC. In our case, curative resection for advanced tumor with lymph node swelling was performed. Although we identified no tumors in the remnant liver intraoperatively, recurrence in the remnant liver developed 1 month postoperatively. The reason for early recurrence might be the existence of micrometastasis in the remnant liver preoperatively.

In conclusion, G-CSF–producing CCC progresses rapidly, and surgical treatment for advanced condition should be carefully selected.

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