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Usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography for assessment of tumorviability after resection of granulocyte-colony-stimulating-factor -Producing cholangiocarcinoma-a case report

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ABSTRACT

INTRODUCTION AND IMPORTANCE: Granulocyte colony-stimulating factor (G-CSF)-producing intrahepatic cholangiocarcinoma is rare. Surgical cases with postoperative clinical course have rarely been reported.
CASE PRESENTATION: A 63-year-old woman complained upper abdominal pain. Computed tomography (CT) showed intrahepatic mass measuring 9 × 9 × 9 cm in the left lateral segment. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed high uptake by the tumor, with diffuse uptake in the bone marrow. An extended left lobectomy was performed to achieve complete resection. Histopathological examination showed poorly differentiated adenocarcinoma with no lymph node metastasis. Immunohistochemical analysis revealed that tumor cells produced G-CSF. After chemotherapy with S-1 regimen at 10 months after the operation, CT and FDG-PET detected lymph node metastasis in the periduodenal area and left kidney metastasis, with no FDG uptake in the bone marrow. Serum G-CSF was normal. Combination chemotherapy with gemcitabine plus cisplatin was administered, and, 12 months after liver resection, metastases were enlarged and FDG uptake in the bone marrow was detected again. Serum G-CSF was elevated at 71.6 pg/mL. The patient was enrolled in a clinical trial of chemotherapy with another regimen and was alive at 19 months after liver resection.
CLINICAL DISCUSSION: Because of rapid progression, rapid diagnosis and resection are important. FDG uptake in the bone marrow is characteristic in G-CSF producing tumor. In this case, FDG uptake in the bone marrow reappeared after the enlargement of recurrent lesions, followed by tumor enlargement.
CONCLUSION: FDG-PET was useful for differential diagnosis and to assess tumor viability and determine the surgical indication.

1. Introduction

Granulocyte colony-stimulating factor (G-CSF)-producing tumors have been reported in various organs and generally have poor prognosis [1,2]. G-CSF-producing intrahepatic cholangiocarcinoma (ICC) is rare and case reports are limited.

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is reported to be useful for diagnosis of G-CSF-producing tumors. Here, we report a surgical case of G-CSF-producing ICC with FDG-PET, showing the change in multipoint reflecting tumor viability, performed preoperatively, postoperatively, and after enlargement of metastatic recurrence.

2. Presentation of case

A 63-year-old woman was referred to our hospital with the chief complaint of upper abdominal pain. She had a history of spinal canal stenosis, knee osteoarthritis, and hypertension. Contrast-enhanced computed tomography (CT) showed a large, intrahepatic mass measuring 9 × 9 × 9 cm in the left lateral segment, with small invasion of segment 4 of the liver (Fig. 1, arrow heads). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. This report has been prepared according to The SCARE 2020 Guideline [3].

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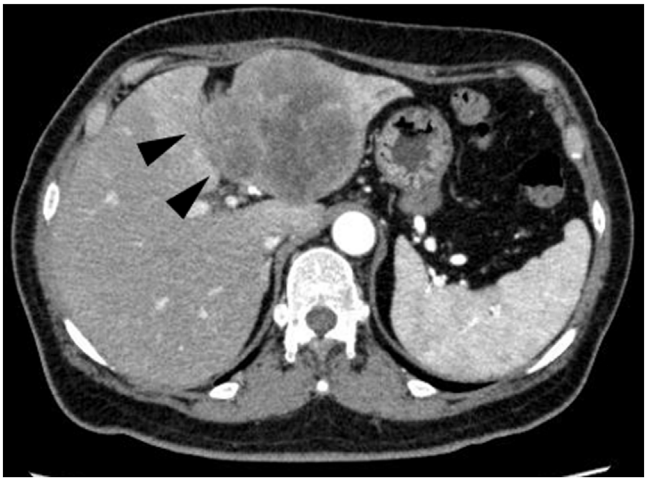

Fig. 1. Computed tomography scan showed an intrahepatic mass measuring 9 × 9 × 9 cm in the left lateral segment, with small invasion of segment 4 of the liver.

Physical examination revealed upper abdominal tenderness without fever or jaundice. Laboratory tests revealed an elevated white blood cell (WBC) count of 23,660/μL with a predominance of segmented neutrophils of 85.7% and elevated C-reactive protein (CRP) of 0.68 mg/dL. FDG-PET showed uptake by the mass lesion in the left lobe of the liver, with maximum standard uptake value (SUVmax) of 33.2. There was also diffuse uptake in the bone marrow with SUVmax of 9.6 in the second lumbar vertebra (L2), which showed that most FDG uptake was in the vertebra (Fig. 2). No other metastatic lesion was detected. Because of leukocytosis and diffuse FDG uptake in bone marrow, G-CSF-producing tumor was suspected.

No peritoneal dissemination was found by laparotomy. Peritoneal washing cytology was negative. Extended left lobectomy was performed to achieve complete resection. The resected specimen included a mass measuring 9 × 9 × 9 cm. Histopathological examination showed poorly differentiated adenocarcinoma with no lymph node metastasis (Fig. 3a). Immunohistochemical analysis revealed that tumor cells produced G-CSF (Fig. 3b) and the tumor was diagnosed as G-CSF-producing ICC. The resected margin was macroscopically and microscopically negative (R0). After the operation, the WBC count decreased to 15,490/μL on postoperative day (POD) 1, 9870/μL on POD3, and 7400/μL on POD5. The patient had an uneventful postoperative period and oral S-1 (80 mg/m2) was administered as adjuvant chemotherapy (Fig. 4).

Ten months after liver resection, contrast-enhanced CT and FDG-PET detected lymph node metastasis in the peri-duodenal area and a mass in the left kidney. FDG uptake in the bone marrow was not detected (Fig. 4a) . Serum G-CSF was normal at 35.0 pg/mL (upper reference limit, 39.0 pg/mL) and WBC count was also normal at 3960/μL. After diagnosis of postoperative recurrence, combination therapy with gemcitabine plus cisplatin was administered.

Twelve months after liver resection, although resection for metastatic regions was considered, lymph node metastasis in the peri-duodenal area and the mass in the left kidney were enlarged and we did not perform resection of metastatic lesions. FDG uptake in the bone marrow was detected with SUVmax of 6.0 in L2 (Fig. 4b). Serum G-CSF was elevated to 71.6 pg/mL.

The patient was enrolled in a clinical trial of chemotherapy with another regimen and was alive 19 months after liver resection.

3. Discussion

G-CSF is a regulator that increases neutrophil proliferation, differentiation, and mobilization from the bone marrow [4]. G-CSF-producing tumors were initially reported in lung cancer in 1977 [5]. Although subsequent reports of G-CSF-producing tumors in various organs have been published, resection for G-CSF-producing ICC is rare.

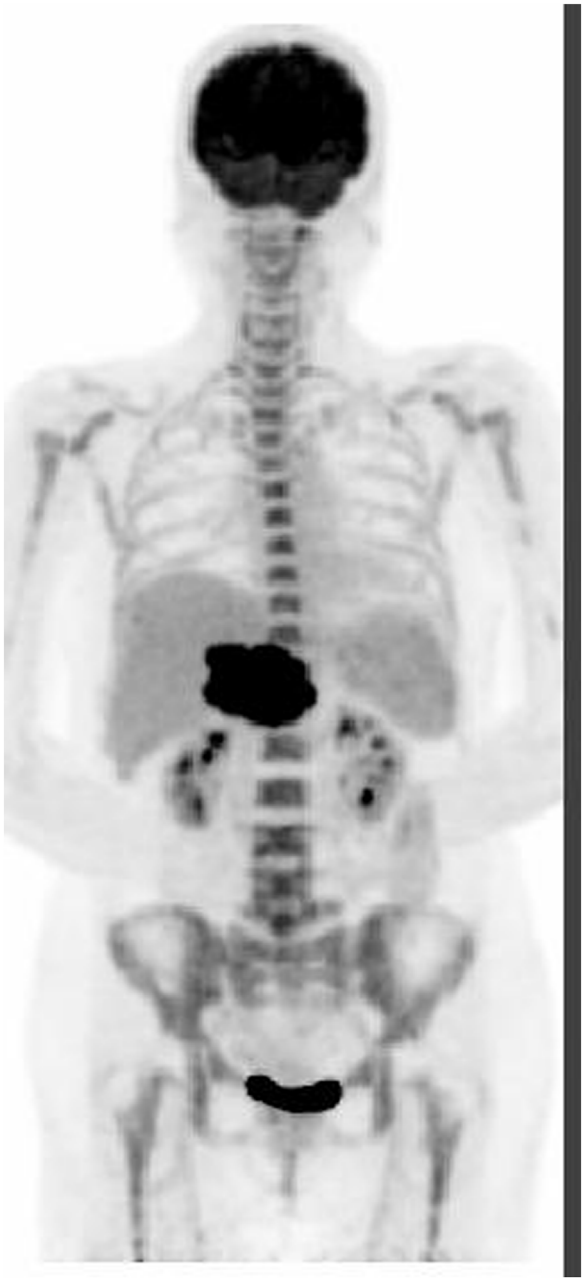

Fig. 2. Preoperative 18F-fluorodeoxyglucose positron emission tomography showed uptake by the mass in the liver with maximum standard uptake value (SUVmax) of 33.2, and diffuse uptake in the bone marrow with SUVmax of 9.6 in L2.

In general, G-CSF-producing tumors show aggressive growth and poor prognosis [1,2]. Some reports have mentioned the following mechanism of poor prognosis of G-CSF-producing tumors. G-CSF enhances the proliferation of carcinoma cells [2], stimulates angiogenesis and promotes tumor growth [6], and tumor-derived G-CSF increases the number of myeloid-derived suppressor cells, which are involved in tumor growth and chemoresistance [7].

To our knowledge, only 17 cases [8–23] of G-CSF-producing ICC, including our present case, have been reported (Table 1). The average age of the patients was 66.6 years (range, 48–83 years), excluding one woman whose age was described as being in the 70

Table 1
Characteristics of reported cases of granulocyte colony-stimulating factor-producing intrahepatic cholangiocarcinoma.

No.	Author/year	Age/Sex	Main clinical presentation	WBC (/μL)	G-CSF (pg/mL) [Normal value]	CRP (mg/dL)	Tumor size	Operation	Histological subtype	Chemotherapy	Follow- up	Outcome
1	Tamai[8]/1995	78/M	Fever up, fatigue	23,700	129 [<30]	17.24	10 cm	No (multiple liver metastasis)	Por	No	2 months	Dead
2	Aizawa[9]/1997	69/M	Epigastric pain	13,700	82.5 [unknown]	Unknown	Unknown	Hepatectomy (R2)	SCC	No	37 days after the operation	Dead
3	Masuda[10]/2000	48/M	Abdominal pain and swelling	50,000	213 [<9.8]	2.14	5 cm	No (multiple liver metastasis)	Por	No	2 months	Dead
4	Kakinoki[11]/2000	66/F	Abdominal distension	14,900	99.2 [<32.3]	13	13 cm	No (local advanced tumor)	Adenosq	No	2 months	Dead
5	Hayashi[12]/2001	55/M	Fever and vomitting	27,500	79 [<21]	17	5 cm	No (rapid progress)	Adenosq	No	64 days	Dead
6	Amano[13]/2005	70/M	Fever and upper abdominal pain	18,000	308 [<9.8]	9.5	Unknown	Palliative hepatectomy with subtotal gastrectomy	Combined HCC and ICC with sarcomatas change	No	34 days after the operation	Dead
7	Sohda[14]/2006	56/M	Fever and conciousness disturbance	74,300	264 [<27.5]	9.7	5 cm	No (rapid progress)	Por	No	5 days	Dead
8	Shinogima[15]/2006	68/F	erythematous eruption, pyrexia, general malaise, coughing and arthralgias	11,200	normal	13.1	6cm with galbladder invasion	Segmentectomy and cholecystectomy	Unknown	No	Unknown	Alive with no recurrance
9	Irie[16]/2011	83/M	Leukocytosis and kidney dysfunction	41,000	256 [unknown]	5.34	2 cm	No (multiple primary cancer)	Adenosq	No	38 days	Dead
10	Shimomura[17]/2013	64/M	Fatigue	43,300	170 [<18.1]	21.2	12 × 11 cm	Extended Left Hepatic Lobectomy	Adenocarcinoma with sarcomatous change	No	19 days after the operation	Dead
11	Takenaka[18]/2013	62/F	Fever and abdominal pain	11,900	Not performed	4.46	10 × 6 cm	No	Mod	Yes (GEM)	3 months	Dead
12	Suzumura[19]/2015	61/F	Epigastric pain and fever	42,680	213 [<39]	8.9	15 × 15 cm	Left hepatic trisegmentectomy, bile duct resection, lymph node dissection	Por	No	3 months after the operation (recurrence in 1 month)	Dead
13	Inoue[20]/2015	76/F	Upper abdominal pain	37,800	522 [<39]	17.1	Over 10 cm	No (lung and lymph node metastases)	Por	No	1 month	Dead
14	Kikuchi[21]/2016	70s/F	Weight loss and fever	19,100	109 [<39]	12.9	8 cm	Central bisegmentectomy with partial resection of duodenum	SCC	Yes (GEM + CDDP)	24 months after the operation	Alive with no recurrance
15	Ozawa[22]/2017	78/M	Fever, upper abdominal pain	14,190	333.4 [<39]	9.25	3 cm	No (rapid progress)	Por	Yes (S-1+radiation)	4 months and a half	Dead
16	Tsutsui[23]/2019	68/F	Fever, fatigue, right upper abdominal pain	22,700	58.2 [<39.2] (after reccurance)	4.95	7 × 5 cm	Laparoscopic hepatic posterior sectionectomy and cholecystectomy	Adenosq	No	3 months after the operation (recurrence suspicion in 1 month and a half)	Dead
17	Our case	63/F	Upper abdominal pain	23,660	71.6 [<39] (the highest after reccurance)	0.68	9 × 9 × 9 cm	Extended Left Hepatic Lobectomy	Por	Yes (S-1, GEM + CDDP)	19 months	Arrive with recurrance

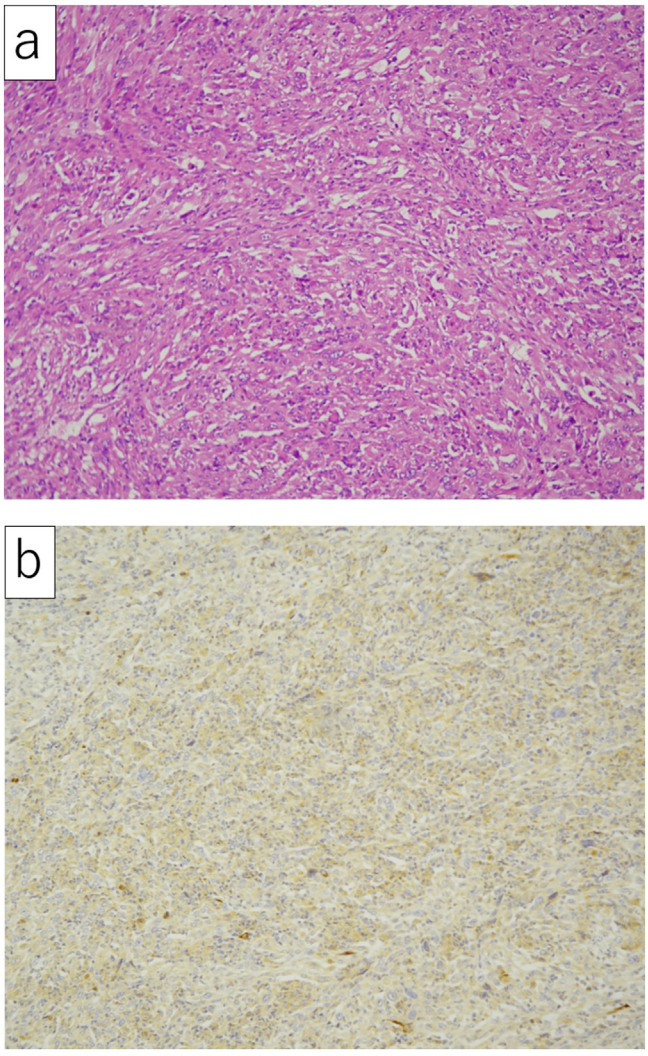

Fig. 3. (a) Histopathological examination showed poorly differentiated adenocarcinoma. Hematoxylin and eosin (×100). (b) Immunohistochemical examination showed a diffusely positive reaction for granulocyte colony-stimulating factor antibodies in the cytoplasm of the tumor cells.

s. Nine cases (52.9%) had fever and all except one, whose data were unknown, showed elevated WBC and CRP. Some cases were treated initially as liver abscess [8,17,23,22]. The life expectancy of G-CSF-producing ICC is within 3 months in most cases. Many cases could not be treated surgically because of the general condition of the patient or tumor progression [19]. The present case and the other that survived for 2 years after resection show that long-term survival is limited to cases that undergo curative resection. In general, hepatectomy contributes to better survival for ICC patients [24], even in those with lymph node swelling [25]. Curative resection might also be important for long-term survival in G-CSF-producing ICC. Rapid tumor progression and elevation of inflammation score with fever mean that rapid diagnosis, including differentiation from liver abscess, is needed for G-CSF-producing ICC.

The diagnostic criteria for G-CSF-producing tumors are as follows, [2]: 1) leukocytosis; 2) elevated G-CSF; 3) rapid return to normal leukocyte count following extirpation of the tumor; and 4) evidence of G-CSF production in the tumor. All four criteria were confirmed in our case. Although preoperative serum G-CSF was not tested in our case, G-CSF immunostaining was confirmed histopathologically and the diagnosis of G-CSF-producing ICC was made. After resection of the tumor, when metastases

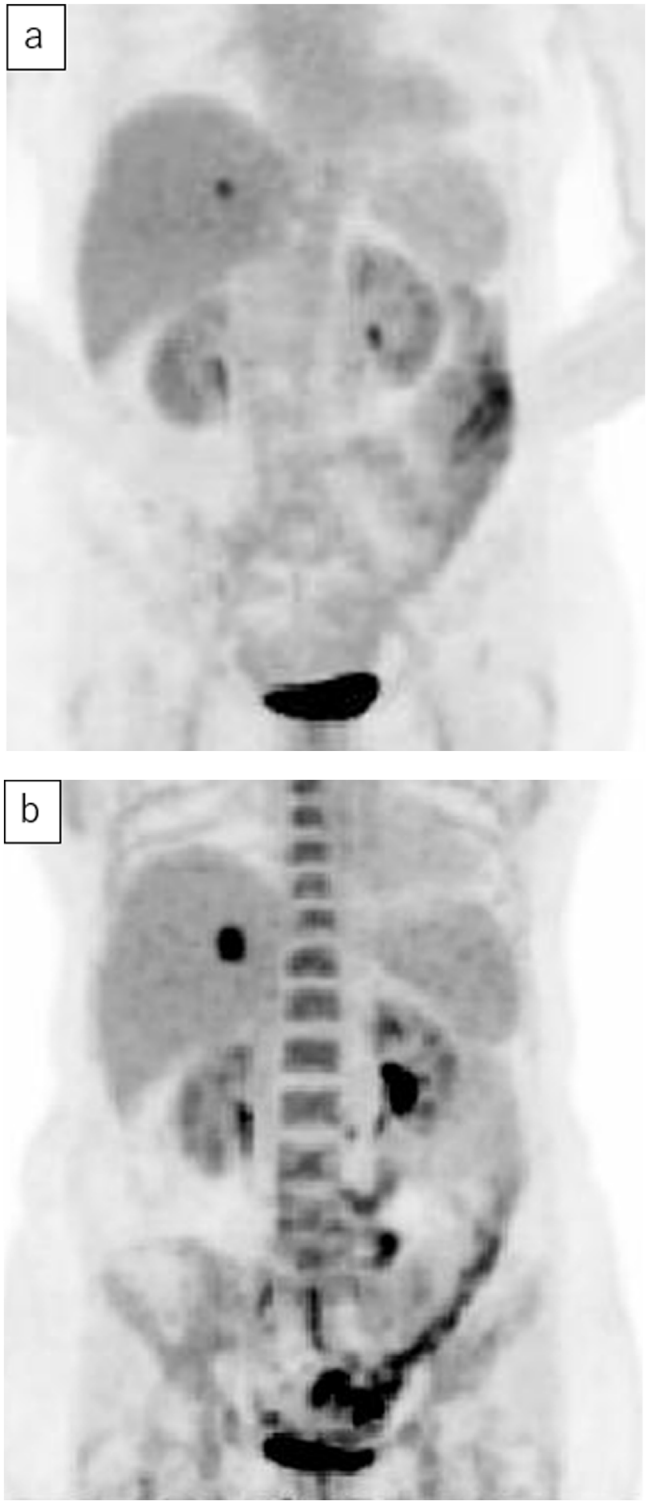

Fig. 4. (a) Postoperative 18F-fluorodeoxyglucose (FDG) positron emission tomography showed uptake by the mass in the lymph nodes in the peri-duodenal area and a mass in the left kidney, and no FDG uptake in the bone marrow. (b) FDG uptake in the bone marrow was detected after enlargement of metastatic lesions.

were detected, serum G-CSF was in the normal range, and after metastatic progression, serum G-CSF was elevated.

FDG-PET is useful for assessment of the nature of the tumor and to search for metastases. The hypermetabolic activity of FDG following G-CSF administration leads to hyperactive bone marrow and FDG uptake in normal bone marrow following G-CSF adminis-

tration. The hyperactive bone marrow after G-CSF administration lasts for up to 4 weeks [26]. G-CSF-producing tumors also show FDG uptake in the bone marrow, which is useful for their diagnosis [19]. In our case, FDG-PET showed uptake by the tumor with diffuse uptake in the bone marrow. After resection, FDG uptake in bone marrow disappeared instead of the recurrence. After the change of regimen, serum G-CSF was elevated and FDG uptake in the bone marrow reappeared, reflecting tumor viability.

Although surgical treatment for metastases has been associated with a good survival rate [24], we did not perform resection of metastatic lesions and changed the regimen. The reasons were as follows: 1) tumor progression was rapid, judging from increased FDG uptake and serum G-CSF; and 2) nephrectomy would have been needed for treatment of the metastatic lesions and postoperative chemotherapy could have been intolerable. The patient is receiving chemotherapy.

In this patient, FDG uptake in bone marrow was confirmed preoperatively and after enlargement of metastatic lesions. Postoperatively, PET-CT showed tumor recurrence in kidney and lymph nodes, without FDG uptake in bone marrow. We did not perform surgery for metastatic lesions because FDG uptake reappeared at 12 months after liver resection and it needs nephrectomy. At 10 months after liver resection there was no FDG uptake in bone marrow with metastasis; however, at 12 months we confirmed FDG uptake in bone marrow. We thought that the appearance of FDG uptake in bone marrow indicated rapid tumor progression.

4. Conclusion

We report a case of resection of G-CSF-producing ICC. Serum G-CSF and FDG-PET were useful for differential diagnosis and assessment of tumor viability.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

This is a case report and it did not require ethical approval from ethics committee. We have got permission from the patient to publish.

Consent

Written consent to publish this case report was obtained from the patient.

Author contribution

Shintaro Hashimoto, Yorihisa Sumida were responsible for study concept and performed the operation. Masato Araki, Kouki Wakata, Kiyoaki Hamada, Daisuke Niino collaborated in the patient's medical care. Yorihisa Sumida reviewed the manuscript. All authors approved the final article.

Registration of research studies

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