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

Shintaro Hashimoto a, Yorihisa Sumida a,*, Masato Araki a, Kouki Wakata a, Kiyokai Hamada b, Daisuke Niino b

a Department of Surgery, Sasebo City General Hospital, Sasebo, Nagasaki, Japan
b Department of Pathology, Sasebo City General Hospital, Sasebo, Nagasaki, Japan

ARTICLE INFO

Article history:
Received 1 February 2021
Received in revised form 3 February 2021
Accepted 3 February 2021
Available online 9 February 2021

Keywords:
Intrahepatic cholangiocarcinoma
Granulocyte colony-stimulating factor
$^{18}$F-fluorodeoxyglucose positron emission tomography
Case report

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 peri-duodenal 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.

© 2021 Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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.

$^{18}$F-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].
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, 9,870/μL on POD3, and 7,400/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.

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, fatigue, Epigastric pain | 23,700  | 129 (<30)                      | 17.24       | 10 cm      | No (multiple liver metastasis) | Por           | No        | 2 months | Dead    |
| 2   | Aizawa[9]/1997| 69/M    | Abdominal pain and swelling | 13,700  | 82.5 [unknown]                 | Unknown     | Unknown   | Hepatocotomy (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 vomiting | 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 sarcomatous change | No        | 34 days after the operation | Dead    |
| 7   | Sohda[14]/2006 | 56/M | Fever and consciousness disturbance | 74,300  | 264 (<27.5)                  | 9.7         | 5 cm       | No (rapid progress)              | Por           | No        | 5 days   | Dead    |
| 8   | Shinogima[15]/2006 | 68/F | Fever, Abdominal erythematous eruption, pyrexia, general malaise, coughing and arthralgia | 11,200  | normal                        | 13.1        | 6 cm with gallbladder invasion | Segmentectomy and cholecystectomy | Unknown       | No        | Unknown | Alive with no recurrence |
| 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  | Left hepatic resegmentectomy, bile duct resection, lymph node dissection | Por           | Yes (GEM) | 3 months | Dead    |
| 12  | Suzumura[19]/2015 | 61/F | Epigastric pain and fever | 42,680  | 213 (<39)                    | 8.9         | 15 × 15 cm | No (lung and lymph node metastases) | 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 | Central bipancreatico-duodenotomy | SCC           | Yes (GEM + CDDP) | 24 months after the operation | Alive with no recurrence |
| 14  | Kikuchi[21]/2016 | 70s/F | Weight loss and fever | 19,100  | 109 (<39)                    | 12.9        | 8 cm       | Combined HCC and ICC with sarcomatous change | Por           | No        | 1 month | Dead    |
| 15  | Ozawa[22]/2017 | 78/M | Fever, upper abdominal pain | 14,190  | 333.4 (<39)                  | 9.25        | 3 cm       | No (rapid progress)              | Adenosq       | No        | 4 months and a half | Dead    |
| 16  | Tsutsui[23]/2019 | 68/F | Fever, fatigue, right upper abdominal pain | 22,700  | 58.2 (<39.2)                | 4.95        | 7 × 5 cm   | Laparoscopic hepatic posterior sectionectomy and cholecystectomy | Adenosq       | Yes (S-1 + radiation) | 19 months | Dead    |
| 17  | Our case     | 63/F | Upper abdominal pain | 23,660  | 71.6 (<39)                   | 0.68        | 9 × 9 × 9 cm | Extended Left Hepatic Lobectomy | Por           | Yes (S-1, GEM + CDDP) | Alive with no recurrence | Dead    |
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 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-
uration. 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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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, Kiyohi Hamada, Daisuke Nino collaborated in the patient’s medical care. Yorihisa Sumida reviewed the manuscript. All authors approved the final article.

Registration of research studies

Not Applicable.

Guarantor

Yorihisa Sumida

Provenance and peer review

Not commissioned, externally peer-reviewed

Acknowledgement

We thank Cathel Kerr, BSc, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

References

[1] S. Vinzenz, J. Zindel, M. Zweifel, T. Rau, B. Cloor, A. Wochner, Granulocyte colony-stimulating factor producing anaplastic carcinoma of the pancreas: case report and review of the literature, Anticancer Res. 37 (2017) 223–228.
[2] M. Futagami, Y. Yokoyama, M. Wakui, R. Taniguchi, T. Higuchi, H. Mizumuma, A case of ovarian clear cell carcinoma simultaneously producing parathyroid hormone-related protein and granulocyte colony-stimulating factor, World J. Oncol. 1 (2010) 138–141.
[3] R.A. Agha, T. Franchi, C. Sohrab, G. Mathew, A. Kerwan, A. Thoma, et al., The SCARE 2020 guideline: updating consensus surgical Case Report (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230.
[4] J.L. Eyles, A.W. Roberts, D. Mercalf, J.P. Wicks, Granulocyte colony-stimulating factor and neutrophils—forgotten mediators of inflammatory disease, Nat. Clin. Pract. Rheumatol. 2 (2006) 500–510.
[5] S. Asano, A. Urabe, T. Okabe, N. Sato, Y. Kondo, Demonstration of granulopoietic factor(s) in the plasma of nude mice transplanted with a human lung cancer and in the tumor tissue, Blood 49 (1977) 845–852.
[6] T. Natori, M. Sata, M. Washida, Y. Hirata, R. Nagai, M. Makuuchi, G-CSF stimulates angiogenesis and promotes tumor growth: potential contribution of bone marrow-derived endothelial progenitor cells, Biochem. Biophys. Res. Commun. 297 (2002) 1058–1061.
[7] M. Kawano, S. Mabuchi, Y. Matsumoto, T. Sasano, R. Takahashi, H. Kuroda, et al., The significance of G-CSF expression and myeloid-derived suppressor cells in the chemoresistance of uterine cervical cancer, Sci. Rep. 5 (2015) 18217.
[8] O. Tamai, M. Matsumoto, T. Nakamoto, T. Miyaguni, M. Shiraishi, M. Yamada, et al., Cholangiocellular carcinoma with pyrexia and leukocytosis, Jpn J. Gastroenterol. Surg. 28 (5) (1995) 1100–1104.
[9] M. Aizawa, H. Koshiyama, D. Inoue, Y. Fukunaga, H. Katakami, M. Miki, et al., Postoperative aggravation of hypercalcemia-leukocytosis syndrome in a case of squamous cell type cholangiocarcinoma, Intern. Med. 36 (3) (1997) 372–373.
[10] J. Masuda, K. Omagari, T. Nomoto, H. Hazama, K. Ohba, K. Yamaguchi, et al., An autopsy case of cholangiocellular carcinoma producing granulocyte colony-stimulating factor, Nihon Shokakibyo Gakkai Zasshi 97 (3) (2000) 347–352.
[11] K. Kakinoki, Y. Takemori, Y. Noda, M. Hoso, An autopsy case of intrahepatic cholangiocarcinoma producing granulocyte-colony stimulating factor, Nihon Shokakibyo Gakkai Zasshi 97 (2000) 1165–1169.
[12] T. Hayashi, A. Mizuki, T. Yamaguchi, T. Hasegawa, T. Kunihiro, N. Tsukada, et al., Primary adenosquamous carcinoma of the liver which produces granulocyte-colony-stimulating factor and parathyroid hormone related protein: association with leukocytosis and hypercalcemia, Intern. Med. 40 (2001) 631–634.
[13] H. Amano, T. Tamoto, K. Emoto, H. Hino, T. Asahara, F. Shimamoto, Granulocyte colony-stimulating factor-producing combined hepatocellular/cholangiocellular carcinoma with sarcomatous change, J. Gastroenterol. 40 (2005) 1158.
[14] T. Sohda, H. Shiga, H. Nakane, H. Watanabe, M. Takeshita, S. Sakisaka, Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein, Int. J. Clin. Oncol. 11 (2006) 246–249.
[15] Y. Shinjojima, Y. Toma, T. Terui, Sweet syndrome associated with intrahepatic cholangiocarcinoma producing granulocyte colony-stimulating factor, Br. J. Dermatol. 155 (2006) 1103–1104.
[16] T. Irie, A. Takeda, R. Takada, Y. Saito, T. Fujinaga, S. Tanaka, et al., A case of granulocyte colony-stimulating factor-producing adenocarcinoma of the liver accompanied by an adenocarcinoma of the ascending colon and urothelial carcinoma of the urinary bladder, Nihon Shokakibyo Gakkai Zasshi 108 (2011) 259–266.
[17] O. Shimomura, K. Fukunaga, Y. Nakano, T. Nowata, A. Kobayashi, T. Oda, et al., A case report of the granulocyte colony-stimulating factor producing intrahepatic cholangiocarcinoma with sarcomatous change, Jpn. J. Gastroenterol. Surg. 46 (2013) 41–49.
[18] M. Takenaka, J. Akiba, T. Kawaguchi, T. Niiikei, T. Arinaga-Hino, M. Sata, et al., Intrahepatic cholangiocarcinoma with sarcomatous change producing granulocyte-colony stimulating factor, Pathol. Int. 63 (2013) 233–235.
[19] K. Suzumura, Y. Iimuro, T. Hirano, Y. Asano, N. Kuroda, T. Okada, et al., Granulocyte colony-stimulating factor-producing cholangiocellular carcinoma, Int. Surg. 100 (2015) 123–127.

[20] T. Inoue, F. Okumura, Y. Mizushima, Y. Nishi, H. Nishie, K. Anbe, et al., A case of granulocyte colony stimulating factor producing Intrahepatic cholangiocarcinoma, J. Jpn. Biliary Assoc. 29 (2015) 138–144.

[21] I. Kikuchi, T. Sato, T. Wakabayashi, T. Miura, M. Sageshima, A case of granulocyte colony-stimulating factor (G-CSF) producing squamous cell carcinoma arising from intrahepatic bile duct, J. Jpn. Biliary Assoc. 30 (2016) 251–258.

[22] N. Ozawa, S. Doi, T. Tsujikawa, M. Mabuchi, Y. Kajiyama, K. Sato, et al., Intrahepatic cholangiocarcinoma producing granulocyte colony-stimulating factor and parathyroid hormone-related protein, Nihon Shokakibyo Gakkai Zasshi 114 (2017) 1285–1292.

[23] Y. Tsutsui, M. Ninomiya, T. Honboh, N. Sadanaga, Y. Naito, S. Kato, et al., Granulocyte-colony-Stimulating factor producing intrahepatic cholangiocarcinoma mimicking tumor with infectious cyst, Jpn. J. Gastroenterol. Surg. 52 (2019) 637–645.

[24] Y.I. Yamashita, K. Shirabe, T. Beppu, S. Eguchi, A. Nanashima, M. Ohta, et al., Surgical management of recurrent intrahepatic cholangiocarcinoma: predictors, adjuvant chemotherapy, and surgical therapy for recurrence: a multi-institutional study by the Kyushu Study Group of Liver Surgery, Ann. Gastroenterol. Surg. 1 (2017) 136–142.

[25] T. Adachi, S. Eguchi, T. Beppu, S. Ueno, M. Shiraishi, K. Okuda, et al., Prognostic impact of preoperative lymph node enlargement in intrahepatic cholangiocarcinoma: a multi-institutional study by the kyushu study group of liver surgery, Ann. Surg. Oncol. 22 (2015) 2269–2278.

[26] Y. Sugawara, S.J. Fisher, K.R. Zasadny, P.V. Rison, L.H. Baker, R.L. Wahl, Preclinical and clinical studies of bone marrow uptake of fluorine-1-fluorodeoxyglucose with or without granulocyte colony-stimulating factor during chemotherapy, J. Clin. Oncol. 16 (1998) 173–180.