Int Surg 2018;**103:**548–551
DOI: 10.9738/INTSURG-D-16-00168.1

Case Report

Granulocyte-Colony Stimulating Factor Producing Extrahepatic Bile Duct Carcinoma: A Case Report

Masayuki Sho[1], Shoichi Kinoshita[1], Kinta Hatakeyama[2], Yasunori Enomoto[2], Takahiro Akahori[1], Minako Nagai[1], Satoshi Nishiwada[1], Kota Nakamura[1], Kohei Morita[2], Chiho Ohbayashi[2]

[1]*Departments of Surgery, Nara Medical University, Nara, Japan*

[2]*Diagnostic Pathology, Nara Medical University, Nara, Japan*

Granulocyte-colony stimulating factor (G-CSF) producing tumors are rare diseases and occur in various organs. However, due to the rarity of these tumors, the precise biologic characteristics and optimal therapeutic strategies are largely unknown. Previous studies have shown the extremely high malignant potential and aggressive clinical features of G-CSF producing tumors, regardless of the histologic type and tumor location. We present the case of a 59-year-old female who had large tumor in extrahepatic bile duct. She underwent surgery and adjuvant chemotherapy. Then, she also received gemcitabine and cisplatin combination chemotherapy for metastatic lesions. The therapy showed a certain effect and she survived for 17 months after surgery. To the best of our knowledge, this is the first report of multidisciplinary treatment with surgery and systemic chemotherapy for G-CSF producing extrahepatic bile duct cancer. This study highlights the potential of multidisciplinary treatment even for this lethal disease condition.

Key words: G-CSF – Extrahepatic bile duct cancer – Surgery – Chemotherapy – Multidisciplinary treatment

Granulocyte-colony stimulating factor (G-CSF) producing tumors are rare and have been reported to occur in a variety of organs including the liver, biliary tract, and pancreas.[1–6] Previous studies have shown the extremely high malignant potential and aggressive clinical features of G-CSF producing tumors, regardless of the histologic type and location of tumor.[7,8] However, due to the rarity

Corresponding author: Masayuki Sho, MD, Department of Surgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara, 634-8522, Japan.
Tel.: +81 744 22 3051; Fax: +81 744 24 6866; E-mail: m-sho@naramed-u.ac.jp

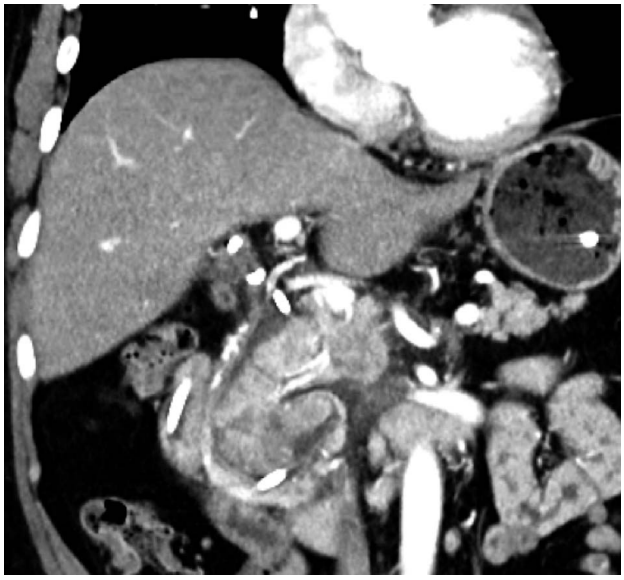

Fig. 1 Computed tomography demonstrated a large tumor in the distal common bile duct.

of these tumors, the precise biologic characteristics and optimal therapeutic strategies are largely unknown. Herein, we present the first operative case of G-CSF-producing extrahepatic bile duct cancer to provide the information of our multimodal treatment.

Case Report

A 59-year-old woman was admitted to our hospital for the treatment of obstructive jaundice and acute cholangitis. After endoscopic biliary drainage, she recovered from liver dysfunction and infection. However, leukocytosis persisted even after the resolution of cholangitis. Major serum tumor markers were within normal ranges. The serum concentration of G-CSF was 73.0 pg/mL (normal range, <39.0). Endoscopic retrograde cholangiography (ERC) showed defects in the dilated common bile duct. However, the tumor was too large to be entirely visualized by ERC. Furthermore, cytology of bile juice during ERC was negative. Computed tomography (CT) showed a large mass of 60 mm in the head of the pancreas and enlarged para-aortic lymph nodes (Fig. 1). Since other distant organ metastases were not detected, she eventually underwent pancreatoduodenectomy. The postoperative course was uneventful except for transient pancreatic fistula. After operation, the leukocytosis was resolved, and the serum concentration of G-CSF was normalized to 27.3 pg/mL.

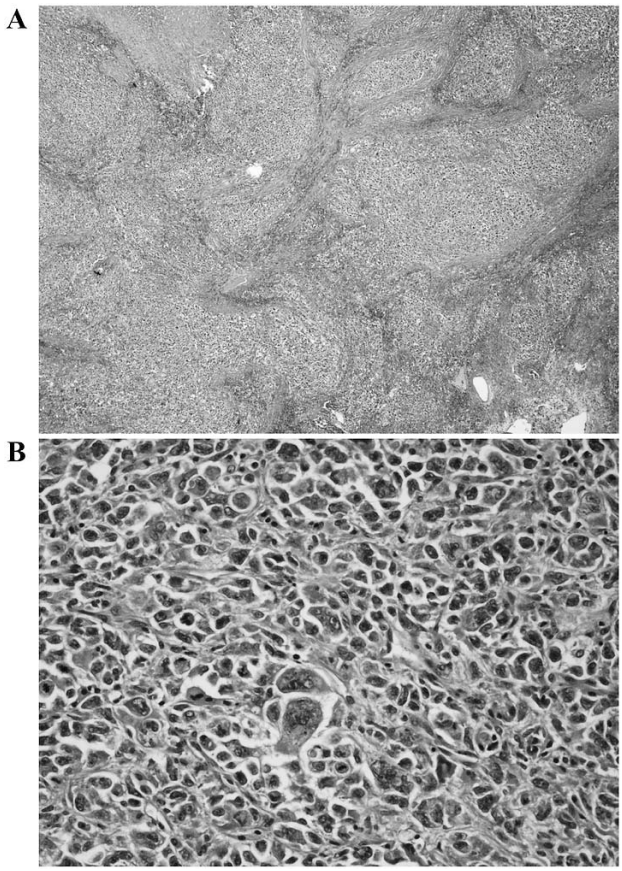

Fig. 2 Microscopically, spindle or polygonal tumor cells having enlarged pleomorphic nuclei proliferated in sheets or vague nests. Bizarre giant tumor cells are observed [hematoxylin and eosin stain original magnification, (A) ×40, (B) ×200].

Grossly, the lower portion of the common bile duct was markedly dilated, and a large polypoid tumor measuring 8 × 5 cm fills the lumen of dilated bile duct. The cut surface of the tumor showed yellowish-white tissue with invasive growth to the adventitia/subserosa. Microscopically, spindle or polygonal tumor cells having enlarged pleomorphic nuclei proliferated in sheets or vague nests without tubular formation. Desmoplastic reaction is associated in tumor tissue. Bizarre, giant tumor cells are frequently observed (Fig. 2). Immunohistochemically, these tumor cells were weakly positive for epithelial membrane antigen (EMA) and CA19–9, and negative for MUC5AC, MUC2, MUC1, CEA, and CK19. The tumor was diagnosed as undifferentiated carcinoma. In addition, tumor cells were also positively stained for G-CSF (Fig. 3).

She received adjuvant chemotherapy of gemcitabine (1,000 mg/m^2 *intravenously* for 30 minutes).

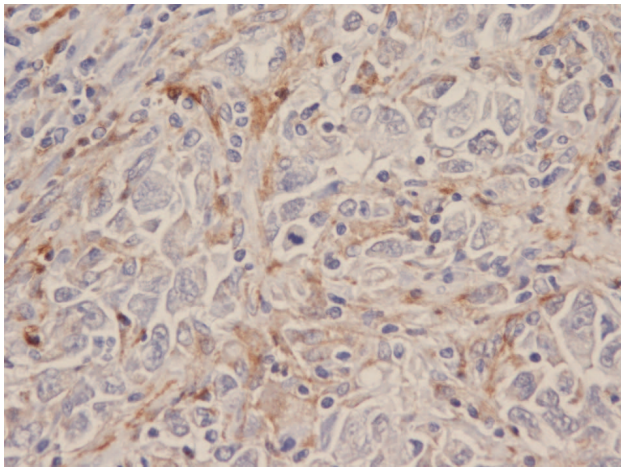

Fig. 3 Immunohistochemical staining showed that the tumor cells were positive for G-CSF.

After a total of 8 doses of gemcitabine, CT revealed metastases in the lung and distant lymph nodes. Then she received the combination of cisplatin (25 mg/m^2 *intravenously* for 90 minutes) and gemcitabine (1,000 mg/m^2). The therapy was effective especially for pulmonary metastasis leading to complete response. However, several paraaortic and mesenteric lymph nodes became enlarged thereafter. After 11 doses of cisplatin and gemcitabine therapy, chemotherapy was switched to the combination of oral S-1 (80 mg on alternate days) and gemcitabine (1,000 mg/m^2). Although a total of 8 doses of S-1 and gemcitabine therapy were given, her condition gradually worsened due to tumor enlargement. She died 17 months after surgery.

Discussion

Previous reports have shown that G-CSF producing tumors can occur in various organs and tissues including gastrointestinal tract. Most of them also demonstrate the aggressive clinical features of G-CSF tumors regardless of organs or histologic types. Even after curative-intent surgery, G-CSF tumors rapidly recur and spread widely, leading to a fatal condition of patient. In biliary tumors, some G-CSF producing gallbladder carcinoma and intrahepatic cholangiocarcinoma (ICC) have been reported. There are only a few reported cases of gallbladder carcinoma with favorable outcome after surgery.[3,4] Furthermore, a few reported ICC had an extremely poor prognosis of patients.[5,6] These patients died only several days after diagnosis or palliative surgery. Furthermore, to our knowledge, only one autopsy case of G-CSF producing extrahepatic bile duct carcinoma has been reported.[7] In that case, he did not receive any anticancer treatment such as surgery and chemotherapy, and he died at 28 days after admission. However, the underlying mechanisms in extremely high malignancy of G-CSF producing tumors remain largely unknown.

G-CSF is a cytokine known for its ability to stimulate migration of granulocyte precursor stem cells, leading to increased white blood cell counts. Besides this common function, G-CSF also has diverse effects in physiologic and pathologic conditions. G-CSF has been shown to enhance Ab-dependent cellular cytotoxicity and cytokine production in neutrophils.[9] Furthermore, it also induces surface expression of important effector molecules, such as CD14, CD32, and CD64. These effects may lead to favorable clinical outcomes in patients with an increased risk of infections, such as cancer and immunocompromised patients. In sharp contrast, G-CSF has inhibitory effects in immune response. Previous studies have demonstrated that G-CSF exerts immunosuppressive effects on monocytes, macrophages, and dendritic cells under various conditions.[10–12] In addition, G-CSF has also been shown to be a potent immune regulator of allogeneic T-cells.[13] Furthermore, a recent study has suggested that G-CSF is a cancer stem cell-specific growth factor.[14] These diverse functions of G-CSF may contribute to high malignancy of various cancers, although the precise function in the tumor environment is not elucidated. In fact, Morris *et al* have shown that G-CSF and G-CSF receptors are highly expressed in human gastrointestinal cancers.[15] They also demonstrated that G-CSF induces the proliferation and migration of gastrointestinal carcinoma cells, and expands a subpopulation of carcinoma cells expressing stem-like markers. Taken together, it is most likely that tumor-producing G-CSF plays a critical role and contributes to the nature of this lethal disease. However, further fundamental studies are clearly required to clarify the etiology of G-CSF producing tumors.

Biliary tract cancers are relatively rare malignancies especially in Western countries.[16] Although complete surgical resection offers the only chance for a cure, recurrence often develops. Furthermore, many patients are not candidates for surgery owing to the high incidence of distant metastases at the time of diagnosis. Chemotherapy may be considered for patients with unresectable biliary tract cancers. A phase III clinical trial for metastatic biliary tract cancers has shown a survival benefit.[17]

The study demonstrated that gemcitabine plus cisplatin treatment was statistically significantly superior to gemcitabine monotherapy. The median overall survivals in the former and latter treatment groups were 11.7 and 8.1 months, respectively. In our case, distant metastasis other than enlarged paraaortic lymph nodes was not detected preoperatively. Furthermore, there is no evidence of survival benefit with neoadjuvant treatment for biliary tract cancers. Therefore, we tried to perform curative-intent surgery. Although the role of adjuvant therapy is unclear, we employed adjuvant chemotherapy of gemcitabine. Because metastases in the lung and distant lymph nodes were found during the treatment, the patient received the combination of cisplatin and gemcitabine. The therapy turned out to be effective especially for pulmonary metastasis. As a result, the patient survived more than 1.5 years. Although the outcome was not entirely satisfactory, our clinical experience suggests a certain effect of combined aggressive treatment for G-CSF producing tumors.

To our knowledge, this is the first report of multimodal treatment with surgery and systemic chemotherapy for G-CSF producing extrahepatic bile duct cancer. Our data highlight the potential of multidisciplinary treatment even for this lethal disease condition. Thus, this study may provide new insights into the pathogenesis and treatment of G-CSF producing tumors.

Acknowledgments

The authors have nothing to disclose.

References

1. Araki K, Kishihara F, Takahashi K, Matsumata T, Shimura T, Suehiro T *et al*. Hepatocellular carcinoma producing a granulocyte colony-stimulating factor: report of a resected case with a literature review. *Liver Int* 2007; **27**(5):716–721
2. Kitade H, Yanagida H, Yamada M, Satoi S, Yoshioka K, Shikata N *et al*. Granulocyte-colony stimulating factor producing anaplastic carcinoma of the pancreas treated by distal pancreatectomy and chemotherapy: report of a case. *Surg Case Rep* 2015;**1**(1):46
3. Omura N, Abe S, Hirai K, Aoki T. A case of granulocyte-colony stimulating factor producing gallbladder cancer. *Am J Gastroenterol* 1999;**94**(1):273–275
4. Ikeda T, Ohgaki K, Miura M, Aishima S, Shimizu T, Maehara Y. Granulocyte-colony stimulating factor-producing gallbladder cancer without recurrence more than 2 years after resection: report of a case. *Surg Today* 2005;**35**(7):590–593
5. Amano H, Itamoto T, Emoto K, Hino H, Asahara T, Shimamoto F. Granulocyte colony-stimulating factor-producing combined hepatocellular/cholangiocellular carcinoma with sarcomatous change. *J Gastroenterol* 2005;**40**(12):1158–1159
6. Sohda T, Shiga H, Nakane H, Watanabe H, Takeshita M, Sakisaka S. Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein. *Int J Clin Oncol* 2006;**11**(3):246–249
7. Matsuyama S, Shimonishi T, Yoshimura H, Higaki K, Nasu K, Toyooka M *et al*. An autopsy case of granulocyte-colony-stimulating-factor-producing extrahepatic bile duct carcinoma. *World J Gastroenterol* 2008;**14**(18):2924–2927
8. Kawaguchi M, Asada Y, Terada T, Takehara A, Munemoto Y, Fujisawa K *et al*. Aggressive recurrence of gastric cancer as a granulocyte-colony-stimulating factor-producing tumor. *Int J Clin Oncol* 2010;**15**(2):191–195
9. Carulli G. Effects of recombinant human granulocyte colony-stimulating factor administration on neutrophil phenotype and functions. *Haematologica* 1997;**82**(5):606–616
10. Martins A, Han J, Kim SO. The multifaceted effects of granulocyte colony-stimulating factor in immunomodulation and potential roles in intestinal immune homeostasis. *IUBMB Life* 2010;**62**(8):611–617
11. Kim SO, Sheikh HI, Ha SD, Martins A, Reid G. G-CSF-mediated inhibition of JNK is a key mechanism for Lactobacillus rhamnosus-induced suppression of TNF production in macrophages. *Cell Microbiol* 2006;**8**(12):1958–1971
12. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia. *J Immunol* 2015;**195**(4):1341–1349
13. Franzke A, Piao W, Lauber J, Gatzlaff P, Konecke C, Hansen W *et al*. G-CSF as immune regulator in T cells expressing the G-CSF receptor: implications for transplantation and autoimmune diseases. *Blood* 2003;**102**(2):734–739
14. Agarwal S, Lakoma A, Chen Z, Hicks J, Metelitsa LS, Kim ES *et al*. G-CSF promotes neuroblastoma tumorigenicity and metastasis via STAT3-dependent cancer stem cell activation. *Cancer Res* 2015;**75**(12):2566–2579
15. Morris KT, Khan H, Ahmad A, Weston LL, Nofchissey RA, Pinchuk IV *et al*. G-CSF and G-CSFR are highly expressed in human gastric and colon cancers and promote carcinoma cell proliferation and migration. *Br J Cancer* 2014;**110**(5):1211–1220
16. Chan E, Berlin J. Biliary tract cancers: understudied and poorly understood. *J Clin Oncol* 2015;**33**(16):1845–1848
17. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**(14):1273–1281