Case and Review

Aggressive Recurrent Pancreatic Cancer Producing Granulocyte Colony-Stimulating Factor

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Abstract
Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein which stimulates the proliferation, differentiation, and functional activation of myeloid hematopoietic cells. G-CSF-producing pancreatic cancer is rare and its prognosis is strikingly poor. A 69-year-old woman with well-to-moderately differentiated ductal adenocarcinoma (pT3N0M0, stage IIA) underwent distal pancreatectomy and splenectomy. Postoperative adjuvant chemotherapy with S-1 was administered for 6 months. Eleven months after surgery, periodic blood examination revealed remarkable leukocytosis (19,120/µL) without fever, which worsened 3 weeks later (36,160/µL). Furthermore, laboratory data showed elevation of the fibrin degradation product-D dimer and
that the G-CSF level was high (406 pg/mL), as well as thrombopenia. Multiple liver and lung metastases were detected by contrast-enhanced computed tomography (CT). The patient was treated with gemcitabine plus nab-paclitaxel, and heparin, thrombomodulin alfa, and platelet transfusion were administered concurrently. Leukocytosis and thrombopenia were alleviated after 1 course of chemotherapy. However, remarkable leukocytosis (53,480/µL) recurred on day 1 of the third course of chemotherapy. Contrast-enhanced CT showed a significantly increased number of liver metastases and lung metastases. The patient chose not to receive second-line chemotherapy and died 1 month later at the affiliated hospital. Pancreatic cancer producing G-CSF shows very aggressive behavior. Leukocytosis without infection during routine observation should be considered as a warning of a rapidly growing recurrence.

Introduction

Granulocyte colony-stimulating factor (G-CSF) is one of the four human CSFs including macrophage CSF, granulocyte-macrophage CSF, and interleukin-3. G-CSF stimulates the proliferation, differentiation, and functional activation of myeloid hematopoietic cells [1, 2]. Until now, G-CSF-producing tumors from various organs have been reported. Among them, the most common primary tumor is large cell carcinoma of the lung [3]. In contrast, G-CSF-producing pancreatic cancer is rare [4–15], and its prognosis is strikingly poor. In the great majority of reported cases, leukocytosis and the pancreatic tumor were simultaneously recognized. Histologically, this disease usually shows an anaplastic, poorly differentiated, or adenosquamous phenotype.

Here we report a recurrent case of pancreatic cancer recurring as a G-CSF-producing tumor 11 months after a curative resection.

Case Presentation

A 69-year-old female with pancreatic cancer underwent distal pancreatectomy and splenectomy. Perioperative blood examination did not show remarkable elevation in leukocyte levels. Histological examination revealed a well-to-moderately differentiated ductal adenocarcinoma, leading to a diagnosis of T3N0M0 stage IIA, in accordance with the 8th edition of the TNM staging guidelines published by the American Joint Committee on Cancer [16]. The cancer cells were not immunoreactive for G-CSF (Fig. 1).

Postoperative adjuvant chemotherapy with S-1 (80 mg/day) was administered for 6 months. Monthly blood examination showed no particular change. Ten months after surgery, blood examination revealed a slight elevation of WBC (9,280/µL) without fever. Eleven months after surgery, blood examination revealed remarkable leukocytosis (19,120/µL), and a slight elevation of the C-reactive protein (CRP) level (0.64 mg/dL) without fever. Tumor markers were within normal range.

Enhanced CT showed multiple liver metastases (max. diameter of 5 cm) in the left lobe. Three weeks later, the patient was admitted to our hospital for chemotherapy. A blood test
performed on the day of admission revealed an extremely high level of leukocyte (38,480/µL) and fibrin degradation product-D dimer (135.3 µg/mL) and reduced platelet and hemoglobin levels (Table 1). She did not have any symptoms of infection. Enhanced CT showed enlargement of the liver metastases (max. diameter of 8 cm) and multiple newly developed lung metastases (Fig. 2). The serum G-CSF level was high (406 pg/mL).

Since disseminated intravascular coagulopathy caused by rapid tumor growth was suspected, gemcitabine plus nab-paclitaxel (GnP) was concurrently administered with heparin, thrombomodulin alfa, and platelet transfusion (Fig. 3). After 1 course of GnP treatment, leukocytosis and thrombopenia were alleviated. Enhanced CT showed intratumoral hypoperfusion in the liver metastases. There was no remarkable change in the lung metastases. The serum G-CSF level was sustained (426 pg/mL).

These chemotherapeutic effects continued for 2 courses of GnP therapy. Then, drastic leukocytosis (53,480/µL) recurred on the first day of the third course of chemotherapy. Enhanced CT showed a significantly increased number of liver metastases and lung metastases (Fig. 4). The patient was a homozygous carrier of the UGT1A1*6 allele. She refused second-line chemotherapy such as FOLFIRINOX. One month later (only 4 months after recurrence), she died of cancer at the affiliated hospital.

**Discussion**

G-CSF-producing carcinoma of the lung was first described by Asano et al. [17] in 1977. The original diagnostic criteria for G-CSF-producing cancer are the following: (1) extreme leukocytosis, (2) elevated G-CSF activity, (3) fall-off of WBC count after tumor resection or treatment, or (4) proof of G-CSF production in the tumor [17]. However, G-CSF-producing pancreatic cancer has rarely been described where G-CSF expression of the tumor was confirmed by immunohistochemical staining. Since G-CSF is secreted protein, immunohistochemical confirmation is sometimes difficult.

To date, only 12 cases have been reported in the English-language literature [4–15]. The patient characteristics, including those of our case, are shown in Table 2. The mean age at diagnosis was 64 years (range 46–89). The dominant gender was male (male-to-female ratio was 10:3). Patients with this disease showed fatigue, abdominal discomfort, and body weight loss. Most patients showed unspecific symptoms and were afebrile, but had remarkable leukocytosis (range 14,300–91,500/µL). The serum C-reactive protein level was also elevated in 8 cases (range 0.64–15.9 mg/dL). In a great majority of reported cases (11 of 13), leukocytosis and the pancreatic tumor were simultaneously recognized. Histologically, the anaplastic (6 of 13), poorly differentiated adenocarcinoma (3 of 13), and adenosquamous (2 of 13) phenotypes were predominant. Out of 10 cases where immunohistochemistry was used to test for the production of G-CSF within the tumor, 9 cases were positive. Surgical resection was performed in 6 cases, including our case. The patients’ prognoses were extremely poor, and the median survival starting from diagnosis was only 59 days. Leucocyte count at diagnosis seemed to be related to tumor burden and shorter survival expectancy.

In the present case, perioperative blood examination did not show obvious leukocytosis, but remarkable leukocytosis occurred 11 months after curative resection. Previously, there has been only 1 case (case 2 in Table 2) with a normal leukocyte count (5,800/µL) at the time
Of tumor detection and a subsequent leukocytosis (24,300/µL), which occurred 4 weeks after surgery. However, G-CSF was already elevated in the resected tumor [5], contrary to the observation in our case.

Previously reported G-CSF-producing pancreatic cancers were of predominantly atypical histological types, such as anaplastic carcinoma. In only 1 case (case 11 in Table 2), G-CSF was detected in a bizarre giant cell and spindle cell cytoplasm, also as in moderately differentiated adenocarcinoma cells [14]. In our case, the primary tumor was histologically diagnosed as a well-to-moderately differentiated adenocarcinoma. Unfortunately, we could not evaluate the histological type and the G-CSF expression of the recurrent tumor. We speculate that the recurrent tumor cells acquired G-CSF production capability in the metastasized liver microenvironment. A similar clinical course (rapid tumor growth after liver metastasis) has been reported in a case of esophagogastric junction cancer [18]. In that case, the perioperative leukocyte count was within the normal range and the primary tumor had a typical histology (well-to-moderately differentiated adenocarcinoma). The metastatic cells in the liver were histologically similar to the primary tumor cells. Leukocytosis was alleviated by resection of the liver metastasis. Interestingly, lung metastasis detected during the same period neither showed rapid growth nor did it produce G-CSF. Both the heterogeneity of tumor cells and the microenvironment of the metastasized organ may affect G-CSF production.

In conclusion, G-CSF-producing tumor can arise from a typical histological phenotype such as well-to-moderately differentiated adenocarcinoma. Leukocytosis without infection during routine observation should be considered as a warning of a rapidly growing recurrent tumor.

Statement of Ethics

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval No. 15-318). Written consent to participate in this study was substituted for providing a means of opting out on the website (https://www.hama-med.ac.jp/research/clinicalres/erc/disclosure-info/h29.html) according to the ethics guidelines for clinical studies of the Japanese Ministry of Health, Labour and Welfare.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yoshifumi Morita: design of the work, data acquisition, and drafting the work; Takanori Sakaguchi: design of the work, drafting the work; Shinya Ida: data acquisition, drafting the work; Ryuta Muraki: data acquisition, drafting the work; Ryo Kitajima: data acquisition, drafting the work; Satoru Furuhashi: data acquisition, drafting the work; Makoto Takeda: data acquisition, drafting the work; Hiroshi Kikuchi: drafting the work; Yoshihiro Hiramatsu: data acquisition, drafting the work; Hiroe Tsukui: pathological diagnosis, drafting the work; Hiroya Takeuchi: drafting the work. All authors read and approved the final manuscript.

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**Fig. 1.** a Hematoxylin-eosin staining revealed well-to-moderately differentiated adenocarcinoma cells with glandular organization (×100). b Immunohistochemical staining using anti-granulocyte colony-stimulating factor (G-CSF) mouse monoclonal antibody (Calbiochem®) showed that the tumor cells were negative for G-CSF expression.

**Fig. 2.** a Enhanced computed tomography revealed multiple liver metastases (arrow), with a maximum diameter of 8 cm, in the left lobe. b Multiple metastases (arrowhead) were detected in both lungs.
Fig. 3. Treatment course after recurrence. The dark blue line shows the WBC count (left axis). The light blue bars show the serum granulocyte colony-stimulating factor (G-CSF) concentration (right axis). GnP, gemcitabine plus nab-paclitaxel (white arrows); PTF, platelet transfusion (bold white arrows); CT, computed tomography (dotted arrows).

Fig. 4. a After 2 courses of gemcitabine plus nab-paclitaxel treatment, enhanced computed tomography showed a significantly increased number of liver metastases (arrows). b Significantly increased number of lung metastases (arrowheads).
Table 1. Results of blood examination at the day of admission

|          | Value       | (Normal range)     |
|----------|-------------|--------------------|
| WBC      | 38,480/μL   | (3,600–9,200)      |
| Neutrophils | 89%        | (40–73)            |
| Eosinophils | 0.5%      | (1–11)             |
| Basophils | 0%          | (0–2)              |
| Monocytes | 5%          | (4–10)             |
| Lymphocytes | 5.5%    | (18–49)            |
| RBC      | 289×10^4/μL | (385–500×10^4)     |
| Hb       | 9.5 g/dL    | (11.4–14.7)        |
| Ht       | 28.3%       | (35.4–49.5)        |
| PLT      | 6.4×10^4/μL | (15.3–35.2×10^4)   |
| CRP      | 3.29 mg/dL  | (<0.1)             |
| PCT      | 0.45 ng/mL  | (0.3–1.3)          |
| TBIL     | 1.3 g/dL    | (6.7–8.1)          |
| TP       | 6.3 g/dL    | (3.9–4.9)          |
| ALB      | 3.3 g/dL    | (1.1–15)           |
| ALT      | 25 U/mL     | (5–30)             |
| ALP      | 933 U/mL    | (117–356)          |
| BUN      | 13.8 g/dL   | (8.6–21.6)         |
| CRE      | 0.47 mg/dL  | (0.42–0.82)        |
| Na       | 141 mEq/mL  | (139–145)          |
| K        | 3.9 mEq/mL  | (3.6–4.8)          |
| Cl       | 103 mEq/mL  | (101–108)          |
| PT       | 95%         | (70–130)           |
| aPTT     | 75%         | (70–130)           |
| FBG      | 300 mg/dL   | (178–360)          |
| FDP-DD   | 135.3 μg/mL | (<1.0)             |
| CEA      | 1.3 ng/mL   | (1.1–4.4)          |
| CA19-9   | 23 U/mL     | (1–36)             |
| DUPAN-2  | 87 U/mL     | (<150)             |
| Span-1   | 15 U/mL     | (<30)              |
| G-CSF    | 406 pg/mL   | (<39)              |
### Table 2. Reported characteristics of patients with G-CSF-producing pancreatic cancer

| No. [Ref.] | Age, years | Sex | Onset | Fever | WBC, /μL | CRP, mg/dL | Serum G-CSF, pg/mL (normal value) | Pathology | IHC of G-CSF | Treatment | Survival from leukocytosis, days |
|------------|-----------|-----|-------|-------|---------|-----------|---------------------------------|-----------|-------------|-----------|-------------------------------|
| 1 [4]      | 72        | F   | S     | N.M.  | 61,000  | N.M.      | 225 (<60)                        | N.M.      | N.M.        | N.M.      | N.M.                          |
| 2 [5]      | 64        | M   | 4 weeks after surgery | 24,300 | N.M.   | 157 (<30) | Anaplastic                       | Negative  | Resection   | 56        |
| 3 [6]      | 83        | M   | S     | No    | 15,700  | N.M.      | 123 (6–21.9)                    | Adenosquamous | Positive | FAM therapy | 120     |
| 4 [7]      | 50        | M   | S     | N.M.  | 49,180  | N.M.      | 350 (5–1)                       | Poorly differentiated | Positive | BSC | 20        |
| 5 [8]      | 60        | M   | S     | Yes   | 28,900  | 15.16     | 77 (<30)                        | Poorly differentiated | Positive | BSC | 46        |
| 6 [9]      | 46        | M   | S     | No    | 14,300  | 4.6       | 155<sup>a</sup> (5.8–27.5)      | Anaplastic | N.M. | Resection | 120     |
| 7 [10]     | 63        | M   | S     | No    | 91,500  | N.M.      | 134 (<18.1)                     | Anaplastic | Positive | BSC | 11        |
| 8 [11]     | 74        | M   | S     | Yes   | 29,500  | 15.9      | 110<sup>b</sup> (<18.1)         | Poorly differentiated | Positive | Resection | 42        |
| 9 [12]     | 89        | F   | S     | No    | 53,400  | 11.98     | 690 (<18.1)                     | Adenosquamous | Positive | BSC | 62        |
| 10 [13]    | 59        | M   | S     | No    | 17,430  | 8.36      | 83 (6.0–21.9)                   | Anaplastic | Positive | Resection; adjuvant chemo (GEM) | 240     |
| 11 [14]    | 68        | M   | S     | Yes   | 17,500  | 13.2      | 355 (<39)                       | Anaplastic | Positive | Resection; adjuvant chemo (S-1) | 83      |
| 12 [15]    | 67        | M   | S     | No    | 25,200  | 8.7       | 5.6 (<N.M.>)                   | Anaplastic | Positive | Resection | 34      |
| Our case   | 69        | F   | 11 months after surgery | Yes   | 19,120  | 0.64      | 406 (<39)                      | Well-to-moderately differentiated | Not performed | Resection; adjuvant chemo (S-1) GnP | 120     |

G-CSF, granulocyte colony-stimulating factor; IHC, immunohistochemistry; S, synchronous; N.M., not mentioned; FAM, 5-fluorouracil, pirarubicin hydrochloride, mitomycin-C; GnP, gemcitabine plus nab-paclitaxel.<sup>a</sup> G-CSF was measured 3 months after surgery.<sup>b</sup> G-CSF was measured 1 week after surgery.