Case report

Aggressive G-CSF-producing gastric cancer complicated by lung and brain abscesses, mimicking metastases

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Abstract

A 57-year-old Japanese man had type II c gastric cancer with marked lymph node metastases associated with leukocytosis and elevated granulocyte colony-stimulating factor (G-CSF). Total gastrectomy and distal pancreatectomy with lymph node dissection were performed. Although the primary lesion was negative for G-CSF by histopathological immunostaining, a highly increased G-CSF m-RNA level, measured using reverse transcriptase-polymerase chain reaction in frozen sections, led to a diagnosis of G-CSF-producing gastric cancer. The leukocytes and G-CSF decreased immediately after surgery. He then had an intraabdominal recurrence, and was diagnosed with multiple tumors in his lung and brain, with abnormally elevated leukocytes and greatly increased G-CSF; he died 4 months after the surgery. Autopsy showed intraabdominal recurrence of cancer, with no metastases to the lung or brain, but with multiple brain and lung abscesses. We speculate that the excessively increased neutrophils induced by G-CSF infiltrated the lung and brain and formed abscesses, mimicking metastases.

Key words G-CSF · Gastric cancer · Abscess

Introduction

Gastric cancer that produces granulocyte colony-stimulating factor (G-CSF) is thought to be an extremely rare disease with a poor prognosis. Although more than 20 cases of G-CSF-producing gastric cancer have been reported, mainly from Japanese institutes [1], little is known about the clinical course related to leukocytosis, owing to its rarity. Recently, we encountered a patient with G-CSF-producing stomach cancer with marked lymph node metastases treated with surgery, but he had an intraabdominal recurrence and died 4

months after the surgery, with abnormally elevated leukocyte levels induced by G-CSF. Autopsy revealed lung and brain abscesses, which had been clinically evaluated as distant metastases.

Case report

The patient was a 57-year-old Japanese man who had no remarkable past or family history. He was referred to our hospital because of fever, malaise, and anorexia, and was consequently hospitalized. On physical examination, his temperature was 38.2°C, and there was no palpable abdominal mass. Blood biochemistry tests showed a high leukocyte level, of 34 000/mm³ (90% neutrophils). The tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 were not elevated, but the levels of G-CSF were high, at 107 pg/ml (5.78–27.5 pg/ml). Endoscopic examination showed type II c gastric cancer [2] in the posterior wall of the lower stomach, with extramural compression of the lesser curvature by lymph node metastasis. Stomach biopsy revealed the proliferation of large, multinucleated cells, which led to a diagnosis of undifferentiated carcinoma. Abdominal computed tomography (CT) showed a 7-cm lymph node lesion at the lesser curvature.

After admission, the patient developed a high fever (temperature of 39°C) and his sensation of general fatigue worsened. The leukocyte level rose to 67 000/mm³. A second endoscopy, on the eighteenth hospital day, revealed enlargement and ulceration of the mass on the lesser curvature, and an operation was performed on the twentieth day after admission. During surgery, the tumor was evaluated as T1 (submucosal invasion), N3 (metastasis to the posterior side of the common hepatic artery), H0 (without liver metastasis), and P0 (without peritoneal dissemination), stage IV [2]. Total gastrectomy plus distal pancreatectomy with lymph node dis-

Fig. 1. **A** Macroscopic findings of the resected specimen. A type II c cancer was present in the lower stomach (*black arrow*) and disintegrating lymph node metastasis was exposed to mucosa in the upper stomach. **B** Histopathological findings of the type II c cancer. The cancer invaded within the submucosal layer. **C** Most of the tumor showed medullary proliferation of pleomorphic tumor cells, with no specific differentiation

section were performed, and the degree of curability was B (relative curative resection), according to the *Japanese classification of gastric carcinoma* [2].

Macroscopically, a type II c cancer was present in the lower stomach, and disintegrating lymph node metastasis exposed to the mucosa was present in the upper stomach (Fig. 1A). Histopathologically, the primary II c lesion was within the submucosal layer (Fig. 1B), with marked lymphatic invasion. Lymph node metastases extended along the lesser curvature (No. 3) invading the gastric wall and pancreas, as well as along the common hepatic artery (No 8a,p) (pT1N3, stage IV) [2]. Most of the tumor showed medullary proliferation of pleomorphic tumor cells, with no specific differentiation (Fig. 1C), which led to a diagnosis of undifferentiated carcinoma. Although G-CSF immunostaining for gastric cancer and lymph node metastatic tissue was negative, the G-CSF mRNA level (in frozen sections) showed a high increase, to 233.94 compared with 1.00 for the control (common gastric cancer tissue), using a real-time reverse transcriptase — polymerase chain reaction (RT-PCR) method. After surgery, the fever subsided, and the leukocyte and G-CSF levels decreased to 13000/mm³ and 35.6pg/ml, respectively. He had an uneventful course, and he was subsequently discharged. Chemotherapy with cisplatin plus TS-1 (S-1) [3] was administered, on an outpatient basis.

Fig. 2. (Changes in WBC (*solid line*) and granulocyte-colony-stimulating factor (*G-CSF*; *dotted line*))

Two months after the surgery, the leukocyte and G-CSF levels increased again, to 81000/mm³ (neutrophils more than 90%) and 419pg/ml, respectively, and abdominal CT showed intraabdominal lymph node recurrence. Four months after the surgery, the leukocyte and G-CSF levels were markedly increased, to 169000/mm³ and 733pg/ml, respectively (Fig. 2). Chest X-ray revealed abnormal shadows in the left lung, raising suspicions of lung metastases (Fig. 3A). He then developed generalized seizures with a decreased level of con-

Fig. 3. **A** Chest X-ray showed abnormal shadows in the left lung, and metastases were suspected. **B** Lung tumors in the left superior lobe, and multiple white nodules in the bilateral inferior lobes, proved to be multiple abscesses, with marked infiltrations of neutrophils

Fig. 4. **A** Brain metastases (*white arrows*) were suspected on nonenhanced brain computed tomography (CT). **B** Multiple abscesses (*black arrow*) were recognized in the brain

sciousness, and nonenhanced head CT scans suggested brain metastases (Fig. 4A). The patient also developed small skin abscesses on his face and abdominal wall, without any evidence of infectious bacteria. The patient died of multiple organ failure with drug-resistant high fever and general seizures 4 months after the surgery.

Autopsy showed recurrence of undifferentiated carcinoma in the lymph nodes at the hepatic porta, around the abdominal aorta, and in the mediastinum. On histopathological examination, the lung tumors (including one that was 5 cm in size in the left superior lobe) and multiple white nodules in the bilateral inferior lobes, where metastases were suspected, proved to be multiple abscesses with marked infiltrations of neutrophils without cancer cells (Fig. 3B). Multiple abscesses, within 1 cm in size (which had caused the generalized seizures), were also recognized in the brain (Fig. 4B).

Discussion

G-CSF-producing tumors have been reported frequently in lung cancer [4], and sometimes in the digestive tract; for example, in the stomach, liver, gallbladder, and pancreas. Although more than 20 cases of G-CSF-producing gastric cancer, including ours, have been reported, mainly from Japanese institutes [1,5,6], little is known about the characteristic features associated with high levels of G-CSF and leukocytosis. The prognosis of G-CSF gastric cancer is extremely poor, and it was reported that many patients died approximately 2 to 6 months after diagnosis [1,5]. It is thought that, because these tumors are extremely malignant and grow very rapidly, they are already advanced at the time of detection, making the prognosis poor. The tumor in our patient was T1, and was highly malignant, with marked lymph node metastases of N3 and, rapid tumor enlargement after admission; the patient died 4 months after surgery in spite of receiving surgical resection and chemotherapy.

Although the resected specimens were not positive for G-CSF by immunostaining, the following findings were consistent with G-CSF-producing gastric cancer: a highly elevated, quantifiable G-CSF m-RNA level in the tumor frozen sections (determined by real-time RT-PCR); tumor resection that resulted in transient decreases in the G-CSF and leukocyte levels to within a near-normal range; and recurrence of cancer that was associated with a simultaneous increase in G-CSF and neutrophil levels. Because G-CSF protein stays in the cell for only a short period and is then released, its detection has been reported to be difficult in some cases [1,7,8]. Recently, real-time RT-PCR has become a widely used method of quantifying cytokine levels in tissues and cells with high accuracy and sensitivity [9]. This method was very helpful in clarifying the present case as a G-CSF-producing tumor.

In our patient, the leukocyte levels increased to extremely high levels, up to 169000/mm³, when the recurrence became marked and there was formation of lung and brain abscesses. Metastases to the lung and brain were strongly suspected, but histopathological examination at autopsy confirmed that there were no cancer cells in the lung or brain, and demonstrated only neutrophil infiltrates, mimicking abscesses. As for the previously reported differential diagnosis of abscesses and G-CSF-producing tumors, there was a report of G-CSF-producing glioblastoma mimicking brain abscess, proved by subtotal extirpation of the tumor [10].

With regard to whether or not markedly elevated G-CSF causes the formation of abscesses, bullous pyoderma gangrenosum was reported to occur after G-CSF administration in a patient with lung cancer and neutropenic complications during anti-cancer chemotherapy [11]. Perianal and apical tooth abscesses, respectively, manifested in two healthy donors who received G-CSF for stem-cell mobilization [12]. The formation of these abscesses indicates the possible adverse effects of G-CSF leading to neutrophil activation [13]. We speculate that the hypersecretion of G-CSF from the aggressive tumor in our patient resulted in neutrophil infiltrates forming abscesses in the skin, lung, and brain. Because no G-CSF-producing tumors have been reported to cause aseptic abscesses due to marked leukocytosis, as occurred in our patient, further studies of similar cases are necessary for the confirmation of this speculation.

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