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Case Report

A Case of G-CSF–Producing Histiocytic Sarcoma of the Stomach

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No reports have been published to date regarding primary gastric granulocyte colony–stimulating factor (G-CSF)–producing histiocytic sarcoma. We encountered a case of primary gastric histiocytic sarcoma that also fulfilled the criteria for a G-CSF–producing tumor. A 75-year-old man was diagnosed with gastric cancer with poorly differentiated adenocarcinoma. The patient's white blood cell count was elevated to 20,700/μL, and the G-CSF level was elevated to 380 pg/mL. A computed tomography scan showed hepatic infiltration; therefore, a preoperative diagnosis of T4 (liver) N2H0M0 cStage IV gastric cancer was made, and surgery was performed. No. 11d lymphatic metastasis was noted, resulting in invasion of the pancreatic tail, and combined resection of the liver, pancreas, and spleen was conducted with complete gastrectomy. The results of hematoxylin-eosin and immunohistochemical staining were subsequently assessed. On discharge, the G-CSF level had fallen to 22.7 pg/mL. Currently, the patient is still alive and has experienced no recurrence approximately 4 years after the operation.

Key words: Histiocytic sarcoma – Stomach – Granulocyte colony-stimulating factor (G-CSF)–producing tumor

Histiocyte-induced neoplasms can be categorized into two types—the macrophage system cell type and the dendritic cell type, although in 2008 the World Health Organization integrated all macrophage system cell–induced malignant neoplasms into the category of histiocytic sarcoma.[1] The primary extranodal sites for histiocytic sarcoma are the gastrointestinal tract, soft tissue, nasal cavity, and lungs.[2] There are few reports of gastric histiocytic sarcoma. According to our research, 3 cases of gastric histiocytic sarcoma have been reported in the online database PubMed. One case involved multi-

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focal histiocytic sarcoma of the gastrointestinal tract; this case was excluded because the histiocytic sarcoma was not specified as being primary to the stomach. The remaining cases were advanced, the treatment for which involved surgery, chemotherapy, and radiotherapy, although in most cases the sarcoma was resistant to treatment. The present case involved a primary gastric histiocytic sarcoma that also met the criteria for a granulocyte colony–stimulating factor (G-CSF)–producing tumor.[3] No reports of primary gastric G-CSF–producing histiocytic sarcoma have been published to date; therefore, this report is considered to be the first case report of this type of lesion.

Case Report

A 75-year-old man presented with a 1-month history of upper abdominal pain and lack of appetite. These symptoms were followed in due course by the development of a strange upper abdominal sensation and pain. The patient subsequently began to have difficulty taking food orally and came to the hospital for an examination. Gastroscopic examination showed a neoplasm in the stomach, and he was admitted to the hospital for a detailed examination and treatment because of his difficulty eating.

The patient's vital signs were normal, and superficial lymph nodes were impalpable. A blood test showed the following results: white blood cell count, 20,700/μL (range, 4000–8000/μL), and C-reactive protein concentration, 9.7 mg/dL (range, 0–0.3 mg/dL), with no clear evidence of infection. During a detailed examination, the level of G-CSF was measured and found to be high, at 380 pg/mL (range, 0–39.0 pg/mL). The levels of tumor markers were all within the standard ranges, with a carcinoembryonic antigen level of 2.5 ng/mL and a carbohydrate antigen 19-9 level of 5.7 U/mL.

A double-contrast examination showed a 10-cm–long elevated lesion between the gastric fundus and the greater curvature of the body of the stomach, which was diagnosed as a type 1 lesion based on direct observation (Fig. 1).[4]

A gastroscopic examination revealed a type 2 neoplasm between the point directly below the cardiac end and the greater curvature of the body of the stomach (Fig. 2).[4] The type of lesion differed on the endoscopic and upper gastrointestinal tract radiologic examinations. The mass was found to be an elevated lesion with an irregular surface and a depression in the center, which bled easily. The histologic findings of the biopsy specimen indicated

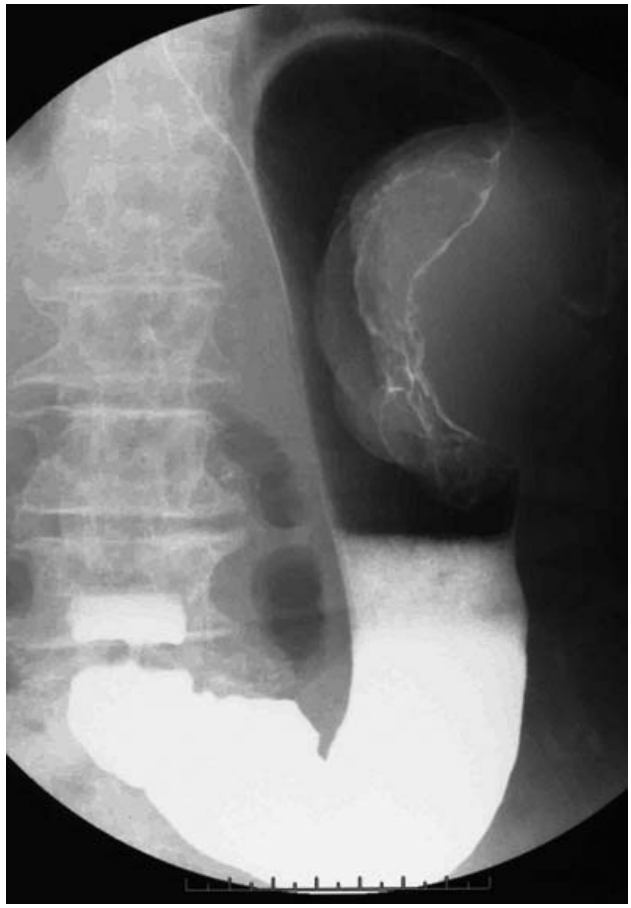

Fig. 1 Double-contrast examination. A 10-cm–long elevated lesion was found between the gastric fundus and the greater curvature of the body of the stomach and was diagnosed as a type 1 lesion based on direct observation.

poorly differentiated adenocarcinoma. An abdominal contrast computed tomography scan showed an irregular neoplasm with a low-contrast effect in the center of the greater curvature that was connected to and displaced the left hepatic lobe and was diagnosed as a lesion of hepatic infiltration. Furthermore, lymphatic tumentia with contrast effect was noted in No. 11d, diagnosed as being positive for metastasis. Other than these findings, no clear signs of metastasis were detected (Fig. 3).

Based on the above observations, the diagnosis was gastric cancer T4 (liver) N2H0M0 cStage IV. Surgery was subsequently performed because curative resection was deemed possible.

Upon opening the abdomen, hepatic infiltration and metastasis to the lymph nodes along the greater curvature and at the splenic hilum were noted.

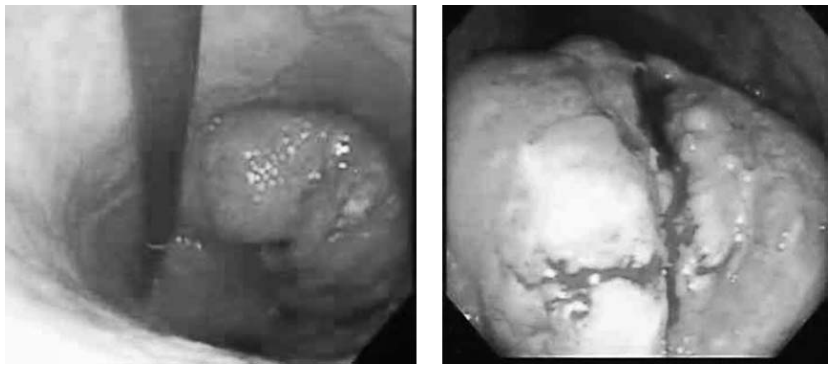

Fig. 2 A gastroscopic examination revealed a type 2 neoplasm between the point directly below the cardiac end and the greater curvature of the body of the stomach.

Surgical observation showed that the cancer had progressed to T4 (liver) N2P0H0M0 sStage IV. The lymph nodes at the splenic hilum had infiltrated the pancreatic tail, making it necessary to remove the pancreas, and combined resection of the liver, pancreas, and spleen was consequently performed with complete gastrectomy using gastric Roux-en-Y reconstruction.

The macroscopic examination revealed a type 2, 11-cm–diameter lesion centered on the gastric fundus and greater curvature of the body of the stomach, demonstrating metastasis to the lymph nodes along the greater curvature and at the splenic hilum (Fig. 4).

The histopathologic examination showed pleomorphic undifferentiated cancer with notable bizarre nuclei and multinucleated giant cells in addition to strong neutrophil invasion. Furthermore, massive continuous infiltration of the hepatic tissue was noted (Fig. 5). Lymph node metastasis to the lymph nodes along the greater curvature, splenic vein, and splenic hilum had also developed, demonstrating pathological lymph node metastasis (LN pN) disease (total 9 of 28).

Differentiating the lesions based on tissue morphology alone was difficult; therefore, additional immunostaining was performed, which showed findings of cytokeratin (CAM5.2, AE1/AE3)$^{-}$, vimentin^{+}, leukocyte common antigen (LCA^{+}), leading to the suspicion of a white blood cell neoplasm. Consequently, histiocytic marker findings of S100^{+} and CD68^{+} and a lymphocyte marker status of CD30^{-} led to a diagnosis of histiocytic sarcoma (Fig. 6).

The pathologic results indicated a final diagnosis of a Stage II 1E (liver) histiocytic sarcoma alimentary canal malignant lymphocyte neoplasm.[5]

Furthermore, after surgery the patient's G-CSF level fell to 22.7 pg/mL, demonstrating that the lesion met the criteria for a G-CSF–producing tumor.

The patient is currently being closely monitored with outpatient examinations. He remains alive and has experienced no episodes of recurrence for approximately 48 months since the operation.

Discussion

Histiocytic sarcoma is defined by the World Health Organization categorization in 2008 according to its

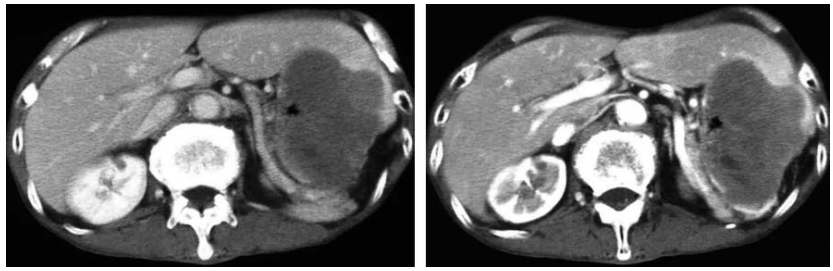

Fig. 3 Abdominal contrast computed tomography scan showed an irregular neoplasm with a low-contrast effect in the center of the greater curvature that was connected to and displaced the left hepatic lobe and was diagnosed as indicating hepatic infiltration. Furthermore, lymphatic tumentia with contrast effect was noted in No. 11d, diagnosed as positive for metastasis. Other than these findings, no clear signs of metastasis were found.

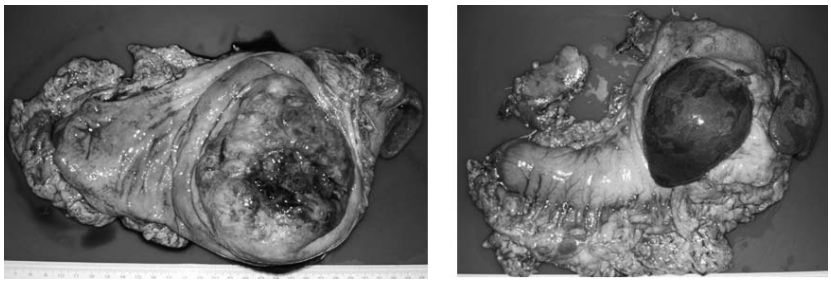

Fig. 4 A macroscopic examination revealed a type 2, 11-cm–diameter lesion centered on the gastric fundus and greater curvature of the body of the stomach, demonstrating metastasis to the lymph nodes along the greater curvature and at the splenic hilum.

type and immunity traits as a malignant neoplasm demonstrating mature histiocytic aspects.[1] However, the conditions related to acute myelomonocytic leukemia have been removed from this definition, which requires as its immunity trait the discovery of one or more histiocytic markers and no dendritic markers.

In the past, malignant histiocytosis was defined as a fatal condition caused by the proliferation of histiocytes in internal organs, lymph nodes, etc.[2] With recent developments in immunohistochemistry, however, it has become understood that most atypical histiocyte-type cells formerly considered to constitute malignant histiocytosis are in fact lymphocyte derived and are now redefined as cells of malignant lymphoma.[2] It has also become clear that histiocyte-induced neoplasms can result from the development of highly specific monoclonal antibodies within histiocytes. Of these tumors, those considered to originate within the cells of the macrophage system are now defined as belonging to histiocytic sarcoma. Histopathologically, the present case was one of undifferentiated cancer with bizarre nuclei and multinucleated giant cells, although immunostaining showed histiocytic markers of $S100^{+}$ and $CD68^{+}$ and a lymphocyte marker of $CD30^{-}$, leading to the diagnosis of histiocytic sarcoma. Histiocytic sarcoma is an extremely rare form of neoplasm, and few reports exist of cases in which it has been identified. The condition may occur at any time between infancy and old age, although most cases are detected in adults, with an average age of 46 years. The pathogenesis is unclear, with the main formation sites being extranodal, occurring in the intestinal tract, skin, and soft tissue, with approximately one third of cases occurring in each of these locations. Treatment includes surgery, radiation, and chemotherapy (with many institutions implementing CHOP in accordance with the criteria for lymphoma); however, resistance to treatment is high, and in many cases the cancer is advanced, thus resulting in a poor prognosis. Despite this background, the long-term prognosis is considered to be good if the lesion is localized or small. In the present case, the patient had an alimentary canal malignant lymphoma of Stage II 1E (liver), and although the lesion could not be considered small, it was surgically removed. The patient remains alive and has experienced no episodes of recurrence for approximately 3 years since the operation, thus suggesting the possibility of a good long-term prognosis in cases of histiocytic sarcoma. Furthermore, in the present case the tumor reflected localized metastasis to regional lymph nodes and the liver.

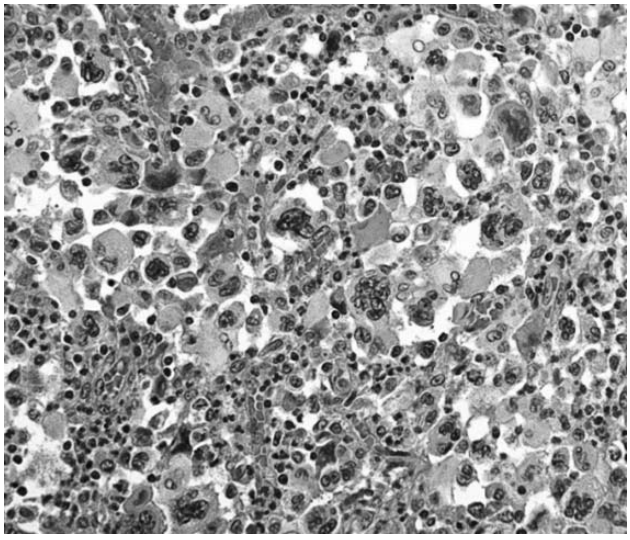

Fig. 5 A histopathologic examination showed pleomorphic undifferentiated cancer with notable bizarre nuclei and multinucleated giant cells in addition to strong neutrophil invasion. Furthermore, massive continuous infiltration of the hepatic tissue was noted. (H.E. stain ×200.)

A search of PubMed using the key words "histiocytic sarcoma, stomach" in English identified 4 case reports, including our case (Table 1).

Three of the four patients underwent surgery as treatment, whereas the remaining patient received adjuvant chemotherapy.[6]

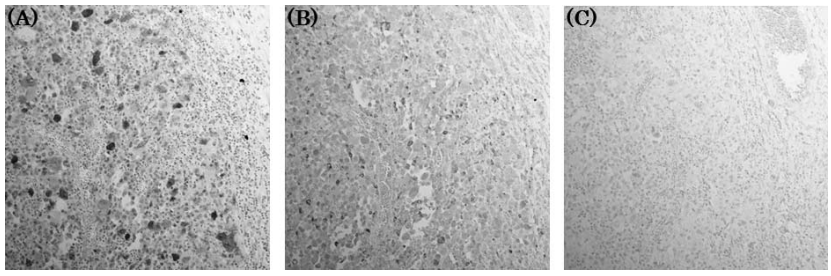

Fig. 6 Histiocytic marker findings of $S100^+$ and $CD68^+$ and a lymphocyte marker status of $CD30^-$ led to a diagnosis of histiocytic sarcoma.

Our case is rare in that the patient exhibited long-term survival compared with the other patients. Furthermore, in this case the patient presented with an elevated white blood cell count of 20,700/μL, and the G-CSF level was subsequently measured due to a high blood neutrophil count of 380 pg/mL, leading to suspicion of a G-CSF–producing tumor. In general, the following criteria are used as the diagnostic standard for detecting a G-CSF–producing tumor: (1) increased number of white blood cells, primarily mature neutrophils, with no other explanatory factors; (2) elevated serum G-CSF; (3) a reduction in the white blood cell count subsequent to tumor resection; and (4) the confirmation of G-CSF production on immunostaining.[7] However, immunostaining is not necessarily positive clinically in cases of G-CSF–producing tumors.[8,9] In the present case, the patient's G-CSF level fell to 22.9 pg/mL postoperatively, meaning that criteria 1 to 3 were fulfilled, and the lesion met the criteria for being a G-CSF–producing tumor.

It is known that G-CSF–producing tumors advance rapidly and have a poor prognosis. According to Sekawa *et al*, the high rate of malignancy of G-CSF–producing tumors is due to the actions of autocrine molecules that recognize G-CSF receptors within the tumor. These molecules promote neoplasm proliferation based on the fact that proliferated neutrophils induce the proliferation and metastasis of the neoplasm, and G-CSF inhibits macrophage and killer cells, reducing cellular immunity.[10,11] In the present case, the cancer was at Stage II, which is not particularly advanced compared with past cases of histiocytic sarcoma. However, the lesion was also considered to be a G-CSF–producing tumor; therefore, there is a possibility that it was more malignant than a regular histiocytic sarcoma. Hence, it will be necessary to closely watch the progress of the patient in the future. Three earlier reported cases of histiocytic sarcoma each involved an elevated white blood cell count. One patient exhibited an irregular white blood cell count, the origins of which were unclear. The case in question involved a histiocytic sarcoma of the spleen, with a white blood cell count of 22,100/μL. However, in that case the G-CSF level was not measured; therefore, it is unclear whether the tumor was a G-CSF–producing lesion.

No reports have been published to date of gastric histiocytic sarcoma that also met the criteria for a G-CSF–producing tumor, and the present case is considered to be extremely unusual. This case is also considered important because of its response to surgery, with the patient remaining alive and experiencing no recurrence for approximately 44 months after undergoing surgery. Because no effective chemotherapy or radiotherapy regimen has been established for histiocytic sarcoma, most institutions implement resection when possible, and, if impossible, apply radiotherapy and/or chemotherapy in accordance with the criteria for malignant lymphoma. The collection and evaluation of additional case stud-

Table 1 Results of the immunohistochemical study

Treatment	Meta	CD68	LCA	S100	CD45RO	CD31	CD1	Ki-67	CD30	Follow-up
Operation	None	+	+	+	+	ND	ND	ND	–	DOD, 7 mo
Operation plus chemotherapy	None	+	ND	ND	+	+	+	+	ND	ANED, 4 mo
None	Lymph node	+	+	–	+	+	ND	ND	ND	DOD, 5 mo
Operation	Lymph node	+	+	+	ND	ND	ND	ND	–	ANED, 44 mo

ANED, alive with no evidence of disease; DOD, died of disease; LCA, leukocyte common antigen; ND, not done.

ies are required to obtain further progress in elucidating this disease.

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