Case Report

Granulocyte colony-stimulating factor producing retroperitoneal leiomyosarcoma

Kyotaro Fukuta,1 Kei Daizumoto,1 Masayuki Takahashi,1 Hidehisa Mori,1 Yoichi Otomi,2 Hisanori Uehara,3 Tomoya Fukawa,1 Yasuyo Yamamoto,1 Kunihisa Yamaguchi1 and Hiro-omi Kanayama1

Departments of 1Urology and 2Radiology, Tokushima University Graduate School of Biomedical Sciences, and 3Division of Pathology, Tokushima University Hospital, Tokushima, Tokushima, Japan

Abbreviations & Acronyms
CT = computed tomography
CTCAE = Common Terminology Criteria for Adverse Events
G-CSF = granulocyte colony-stimulating factor
IL = interleukin
MMP-2 = metalloproteinase-2
VEGF = vascular endothelial growth factor
VEGFR-TKI = VEGF receptor tyrosine kinase inhibitor

Introduction: Granulocyte colony-stimulating factor-producing nonhematopoietic malignancies have poor clinical outcomes.

Case presentation: A 62-year-old woman complaining of fever and left lower quadrant pain was referred to our hospital. A left retroperitoneal tumor was suspected on computed tomography, and laboratory data showed leukocytosis and markedly elevated granulocyte colony-stimulating factor. She underwent left nephroureterectomy, partial colectomy, and psoas muscle resection. The histological examination showed a granulocyte colony-stimulating factor-producing retroperitoneal leiomyosarcoma. Three months after the operation, she developed lung and liver metastases and received the chemotherapy, including doxorubicin and ifosfamide. Eight months after the operation, these lesions had progressed, and a new bone metastasis appeared. Twelve months after the operation, she received pazopanib and radiation for bone metastases. However, the metastases progressed, and she died 17 months after the operation.

Conclusion: Since granulocyte colony-stimulating factor-producing retroperitoneal leiomyosarcoma had a very poor prognosis irrespective of intensive treatment including wide resection, effective systemic therapy should be required.

Key words: chemotherapy, G-CSF-producing tumor, immunohistochemical staining, leukocytosis, retroperitoneal leiomyosarcoma.

Keynote message

G-CSF-producing tumors have a very poor prognosis. This report may be the first report of a G-CSF-producing retroperitoneal leiomyosarcoma. When we see a patient with marked leukocytosis and no evidence of infectious or hematologic diseases, we should consider G-CSF-producing tumors.

Introduction

G-CSF-producing nonhematopoietic malignancies affect various organs and have poor clinical outcomes.1 In the urological field, most are urinary bladder cancers.2 G-CSF-producing retroperitoneal tumors are very rare and there appear to be no previous reports of leiomyosarcoma. The treatment strategy and prognosis of the G-CSF-producing retroperitoneal leiomyosarcoma has not been reported. Thus, a case of G-CSF-producing retroperitoneal leiomyosarcoma is presented.

Case presentation

A 62-year-old woman visited clinic due to fever and left lower quadrant pain for 2 months. Abdominal contrast-enhanced CT showed a 55-mm mass around the left ureter, descending colon, and iliopectineus muscle (Fig. 1a). A left retroperitoneal tumor was suspected, so she was referred to our hospital. Her clinical course is shown in Figure 2. Her laboratory data showed...
marked peripheral leukocytosis (leukocyte count 37 100/mm³, with 91.4% segmented forms) and elevated C-reactive protein (16.22 mg/dL). Since an unknown infectious disease was initially suspected, she was admitted to hospital 10 days before the planned surgery. She was started on antibiotic therapy (meropenem 2.0 g/day), but her laboratory data gradually worsened and her fever continued. So we suspected that the leukocytosis was caused by a tumor, especially a G-CSF-producing tumor, the serum G-CSF and IL-6 levels were examined before surgery. G-CSF was markedly elevated 428 pg/mL (Quantikine Human G-CSF Immunoassay; SRL, Inc., Tokyo, Japan: normal range <39 pg/mL). IL-6 was also elevated 27.9 pg/mL (chemiluminescence enzyme immunoassay; SRL, Inc.: normal range <4 pg/mL).

She underwent radical tumor resection with left nephroureterectomy, partial colectomy, and psoas muscle resection. The resected tumor invaded the left ureter and iliopsoas muscle, with no adhesions to descending colon and the surroundings (Fig. 3a). Her postoperative course was well without ileus continuing for a week, she was discharged on the 16th postoperative day. Immunohistochemical staining using anti-G-CSF antibody demonstrated G-CSF-secreting cells (Fig. 3b). Therefore, the diagnosis was a G-CSF-producing retroperitoneal leiomyosarcoma invading to the left ureter and iliopsoas muscle. The leukocyte count became normalized 10 days and G-CSF and IL-6 levels were normalized 1 month after the operation (G-CSF <19.5 pg/mL, IL-6 2.3 pg/mL). However, 3 months after the operation, both lung and liver metastases appeared (Fig. 1b). She received chemotherapy (doxorubicin 20 mg/m², ifosfamide 2 g/m²). During chemotherapy, she had ileus (CTCAE version 4.0 grade 3) and febrile neutropenia (CTCAE version 4.0 grade 3). Although the metastatic lesions had decreased in size, chemotherapy was discontinued due to these adverse events.
She was observed closely, but these lesions progressed, and a new bone metastasis appeared on CT 8 months after the operation (Fig. 1c). G-CSF and IL-6 levels were also elevated (G-CSF 111 pg/mL, IL-6 18.8 pg/mL). Reduced dose of chemotherapy (doxorubicin 14 mg/m², ifosfamide 1.4 g/m²) was restarted, but it was discontinued due to severe myelosuppression. Twelve months after the operation, pazopanib was administered and radiation therapy for the bone lesion...
was started. However, these metastases progressed gradually, and pazopanib was discontinued due to nausea. She died 17 months after the operation.

Discussion

G-CSF-producing malignancies are rare. In 1967, Robinson et al. first reported that elevated levels of G-CSF production from malignant tumors resulted in marked neutrocytosis. G-CSF produced by tumor cells acts on the tumor itself, causing rapid progression. Therefore, patients with G-CSF-producing tumors have a poor prognosis. Yasui et al. mentioned that 420 cases of G-CSF-producing tumors had been reported. G-CSF tumors were most commonly found in the lung, urinary tract, and stomach. G-CSF-producing retroperitoneal tumors are very rare, with only one reported case (liposarcoma: 1). To the best of our knowledge, this may be the first report of G-CSF-producing retroperitoneal liposarcoma.

The diagnostic criteria for G-CSF-producing tumors are as follows: (i) marked leukocytosis; (ii) increased serum G-CSF activity; (iii) the leukocytosis and G-CSF levels decrease with treatment; and (iv) proof of G-CSF production by the tumor. The present case matched all of the criteria. Particularly, in this case, immunohistochemical staining revealed that invading edge of the tumor to ilioptos muscle was positive and the center of the tumor was negative for G-CSF. This finding may explain that there may be dense correlation between actively invading tumor cells and G-CSF production. G-CSF produced by tumor cells acts on the tumor itself, causing rapid progression because it increases MMP-2 activity which promotes invading tumor cells.

G-CSF-producing tumors are more likely to recur. Therefore, the present patient was carefully followed even though radical resection had been achieved. Despite complete tumor resection, the present patient developed metastatic lesions 3 months after the operation. One of the reasons why the prognosis is very poor is considered to be due to the existence of VEGF, which promotes neovascularity. It is suggested that VEGF was shown to promote advanced tumor which expressed G-CSF. Katoh et al. reported that VEGF protects tumor cells from chemotherapy-induced apoptosis. Furmento et al. suggested that G-CSF increases not only MMP-2 activity but also VEGF secretion.

Treatment for G-CSF-producing tumors is controversial. Higaki et al. reported that the most effective treatment was surgical resection. The chemotherapy regimen has not yet been established. When the present patient developed metastatic lesions, chemotherapy was started. Based on the pathological findings, doxorubicin and ifosfamide were selected because of their appropriateness for various sarcomas. In fact, these drugs were effective for the metastatic lesions, but could not be continued due to the toxicity. Then, other regimens should be considered for disease progression as it demonstrated aggressive behavior. Pazopanib was given as second-line treatment, but the metastatic lesions had progressed. Had pazopanib been given in earlier phase, it may have been effective because it is a VEGFR-TKI. Other studies demonstrated that autocrine G-CSF receptors activate proliferation or invasion in several cancers. Tachibana et al. demonstrated that anti-G-CSF antibody suppressed the proliferation of G-CSF-producing tumors. In the future, anti-G-CSF antibody therapy may be effective as an alternative therapy for G-CSF-producing tumors.

Conclusion

In conclusion, when a patient with marked leukocytosis and no evidence of infectious or hematologic diseases presents, we should consider G-CSF-producing tumors. Since patients with G-CSF-producing tumors have a very poor prognosis, they should be carefully observed even after radical surgery.

Conflict of interest

The authors declare no conflict of interest.

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