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CASE REPORT

Isolated granulocytic sarcoma of the small intestine successfully treated with chemotherapy and bone marrow transplantation

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Abstract Isolated primary granulocytic sarcoma is a rare disease that presents as an extramedullary tumor of myeloid lineage cells. Most patients subsequently develop acute myelogenous leukemia (AML) within a short period, and their prognosis is poor. Herein, we report the case of a 33-year-old woman with a primary isolated granulocytic sarcoma which originated in the small intestine. After she recovered from surgery, she received intensive chemotherapy equivalent to that for AML, followed by allogeneic bone marrow transplantation from an HLA-matched, unrelated donor. Four years after the transplantation, she remains in complete remission without graft-versus-host disease or any other symptoms. This case illustrates the effectiveness of our therapeutic strategy for isolated granulocytic sarcoma, not only with surgical resection of the tumor and intensive chemotherapy equivalent to that for AML, but also with allogeneic bone marrow transplantation, performed while no sign of AML is observed.

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1 Introduction

Granulocytic sarcoma is a rare, malignant tumor, composed of granulocytic precursor cells occurring in extramedullary sites. It is known to occur concurrently with acute myelogenous leukemia (AML), comprising 3–8% of all patients with AML [1, 2]. On the other hand, granulocytic sarcoma can be found as an isolated lesion in non-leukemic patients, and progression to AML occurs in most cases. Isolated granulocytic sarcoma tends to have a predilection for the skin, lymph nodes, central nervous system, or reproductive organs [3, 4]. The rate at which the small intestine is a primary site of granulocytic sarcoma was reported to be approximately 10% [3, 4]. The difficulty in diagnosing granulocytic sarcoma has been reported, and 46–75% of isolated granulocytic sarcoma cases in non-leukemic patients were reported to be initially misdiagnosed, most frequently as large cell lymphoma [3–5]. The addition of immunochemical staining, such as myeloperoxidase or naphthol-ASD-chloroacetate esterase, is useful to confirm tumors as myelogenous in origin. Isolated granulocytic sarcoma predominantly progresses to M2, M4, and M5 FAB subtypes of AML [4, 6]. In the majority of granulocytic sarcoma cases occurring concurrently with or without AML, chromosomal abnormalities of t(8;21) and inv(16) were reported [3]. Cell surface markers such as CD56 (NK cell), CD2, CD4, and CD7 have been associated with it at a high rate [3]. Abnormal karyotypes such as t(8;21) or inv(16) are known to be indicative of a good prognosis in de novo AML, but not so in granulocytic sarcoma. The resistance to chemotherapy of patients with

granulocytic sarcoma may be explained by the characteristics of blast cells with a high incidence of CD56 expression. Optimal treatment for isolated granulocytic sarcoma has not yet been established, though the requirement of intensive chemotherapy is well recognized [3, 4, 6].

Herein, we report a case of isolated granulocytic sarcoma which occurred in the small intestine without any manifestation of other hematological disorders, and which was successfully treated by surgical resection of the tumor, conventional intensive chemotherapy, and allogeneic bone marrow transplantation.

2 Case report

A 33-year-old woman first visited the Department of Surgery at Tokyo Women's Medical University hospital with constipation, intermittent abdominal pain, and vomiting in March 2003. As shown in Fig. 1, a contrast imaging study of the small intestine with an ileus tube revealed a 10–15-cm long stenosis of the left part of the small intestine. She was diagnosed with ileus, and surgical resection with laparoscopy was performed immediately. There were two separated tumors encircling the small intestine: one being 5 × 6 cm and located 2.2 m from the terminal ileum, and the other 3 × 3 cm at 2.4 m from the terminal ileum.

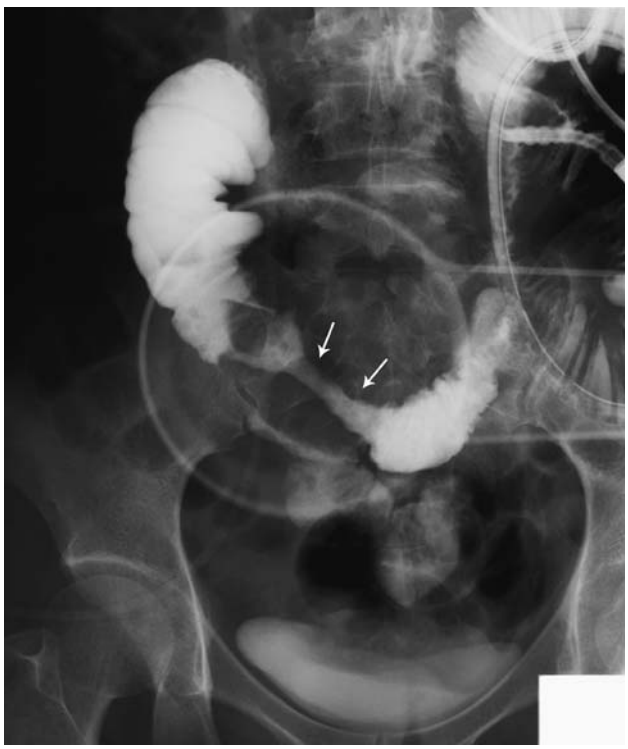

Fig. 1 A contrast study of the small intestine. *Arrows* indicate the area of stenosis

During the operation, multiple, enlarged mesenteric lymph nodes, including those surrounding the jejunal artery, were also observed. Approximately 40 cm of small intestine and several lymph nodes were removed simultaneously. Histopathologic examination of the specimens revealed the diffuse infiltration of medium to large-sized atypical cells with conspicuous nucleoli from the mucosa to the outside of the serosa. Cell infiltration was also observed in several lymph nodes surrounding the mass. Immunohistochemical staining showed that the infiltrating cells were positive for myeloperoxidase, CD34, and CD43, but were negative for CD20 (B-cell), CD3 (T-cell), CD56, CD68, non-specific esterase (monocyte), and leukocyte common antigen (Fig. 2). The diagnosis of granulocytic sarcoma was made from these findings. Chromosomal analysis could not be performed because leukemia was not suspected at the time of operation.

The patient was transferred to our Department of Hematology for additional treatment. On admission, her blood counts were as follows: hemoglobin, 12.0 g/dl; platelets, 315 × 10^9/l, and WBC, 6.8 × 10^9/l, with 61% neutrophils, 33% lymphocytes, 2% eosinophils, 1.5% basophils, and 2.5% monocytes. Morphological, immunocytochemical, and cytogenetical examination of a bone marrow specimen and peripheral blood smear did not demonstrate leukemic cells. Therefore, a diagnosis of isolated granulocytic sarcoma without bone marrow involvement was made. She was treated with induction therapy consisting of idarubicin (12 mg/m^2, days 1–3) and cytarabine (100 mg/m^2, days 1–7), followed by three courses of consolidation therapy including cytarabine, based on the Japan Adult Leukemia Study Group AML 97 protocol [7]. No serious complications were observed during the courses of chemotherapy.

Following chemotherapy, the patient underwent allogeneic bone marrow transplantation from an HLA-matched, unrelated male donor in October of 2003. The conditioning regimen consisted of oral busulfan of 4 mg/kg for 4 days and cyclophosphamide at 60 mg/kg for 2 days. She then received 7.21 × 10^9 bone marrow mononuclear cells. Cyclosporine A and short-term methotrexate were used as a prophylaxis for graft-versus-host disease (GVHD). Granulocyte-colony stimulating factor (300 μg/day) was given from day 6 until engraftment. No severe adverse event was observed, but there was grade 2 mucositis by NCI-CTCv3.0. She developed clinically-documented bacterial pneumonia during the neutropenic period that necessitated parenteral antibiotics, but it rapidly subsided after engraftment. Engraftment was achieved on day 22, and chimerism analysis of peripheral blood using XY-FISH demonstrated 100% donor cells. No symptom of acute GVHD was observed. A bone marrow biopsy performed on day 90 showed no morphological evidence of AML. At

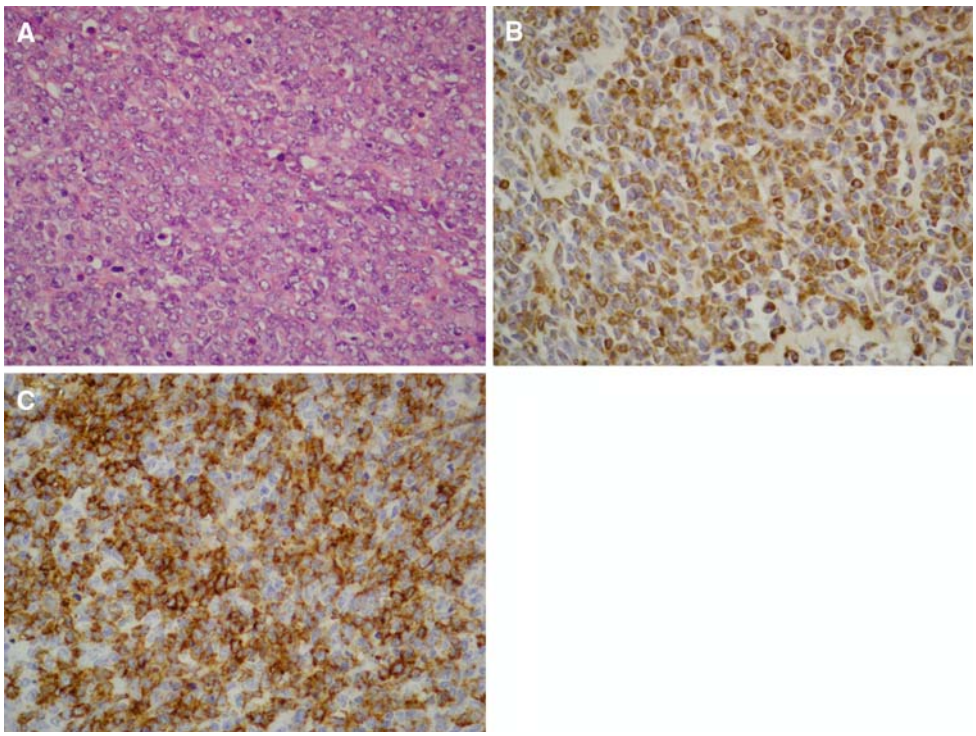

Fig. 2 Histology of the surgical specimen demonstrated diffuse infiltration of medium to large cells with conspicuous nucleoli. **a** HE staining, **b** immunohistochemical staining of CD34, and **c** myeloperoxidase staining

50 months after transplantation, she remains in complete remission and has no transplant-related complications such as chronic GVHD.

3 Discussion

It is well known that AML will develop in the majority of patients with isolated granulocytic sarcoma even if there is no evidence of bone marrow involvement at the initial diagnosis [3–5]. The period between the initial diagnosis and development of AML varied from 0.5 to 24 months (median 3–9 months) according to previous reports [3, 4, 6]. Once AML develops, the prognosis of patients with granulocytic sarcoma becomes poor; the median survival period was reported to be between 6 and 14 months [3, 6 8]. From the reports, it is recognized that granulocytic sarcoma patients should receive standard induction chemotherapy for AML during the non-leukemic period as soon as the diagnosis of isolated granulocytic sarcoma is made. Indeed, a much better prognosis was reported when patients received intensive chemotherapy before AML developed. Yamauchi et al. [4] reported that the non-leukemic rate was approximately 30% at 38 months from the diagnosis of granulocytic sarcoma, and systemic chemotherapy extended the non-leukemic period. Imrie et al. [6] reported that 41% of granulocytic sarcoma patients who received chemotherapy developed AML, and more than half of these patients were alive with a median follow-up time of 25 months at the time of publication. However, in their study, seven patients who received bone marrow transplantation were included. Furthermore, as leukemia relapse after chemotherapy of granulocytic sarcoma occurs after 2–3 years in most cases, the period of observation in Imrie's report may be too short to judge the effectiveness of chemotherapy. Even after intensive chemotherapy, extramedullar or bone marrow relapse occurred frequently, and once the relapse occurred, the leukemia was resistant to reinduction chemotherapy in most cases. Over the past 5 years, five isolated granulocytic sarcoma cases who received chemotherapy during the non-leukemic period have been presented at the Japan Society of Hematology [9–12]. Leukemia developed in two out of these five cases, and a second remission could not be achieved. The remaining three cases were reported shortly after diagnosis, and were still receiving chemotherapy with transplantations planned. These results indicate that intensive chemotherapy after the local resection or irradiation of granulocytic sarcoma is not sufficient to obtain a high leukemia-free survival rate. Based on previous reports, the presented case was assessed to have a 40–70% risk of AML progression [4, 6].

Stem cell transplantation is another recent treatment strategy for granulocytic sarcoma. According to previous reports, 12 patients received allogeneic or autologous stem cell transplantation 9.6 months (3–29 months) after the diagnosis of granulocytic sarcoma. Eleven out of the 12 patients were surviving disease-free at the time of the

publication [6, 13–19]. Their mean disease-free survival period was reported to be 27.3 months (12–48 months) after stem cell transplantation. The frequency and intensity of transplantation-related complications were reported to be minimal when stem cell transplantations were performed in the non-leukemic state. Our patient underwent allogeneic stem cell transplantation from an HLA-matched, unrelated donor, in addition to the surgical resection of granulocytic sarcoma and intensive chemotherapy, and remains disease-free after 50 months.

In conclusion, stem cell transplantation may be an attractive option for the treatment of granulocytic sarcoma, considering the excellent prognosis of the previously reported cases of stem cell transplantation following surgery of the tumor and intensive chemotherapy. Although the present report is confined to one patient, her long period of disease-free survival encourages continued efforts to improve therapies for patients with isolated granulocytic sarcoma. The accumulation of case studies is necessary to evaluate the usefulness of this treatment strategy.

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