Tohoku J. Exp. Med., 2021, **254**, 101-105

Durable Remission of Chemotherapy-Refractory Myeloid Sarcoma by Azacitidine

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Myeloid sarcoma is a rare disease entity of extramedullary myeloid neoplasm that can occur both as an initial isolated myeloid sarcoma without leukemic cell invasion in the peripheral blood and bone marrow, and as the secondary lesion of acute and chronic myeloid leukemias, myelodysplastic syndrome and chronic myeloproliferative neoplasms. Due to its rarity and its frequent emergence as the recurrent lesion after intensive systemic therapy, including allogeneic hematopoietic stem cell transplantation, the standard treatment has not been established for myeloid sarcoma. In this report, we presented an 84-year-old female patient with isolated myeloid sarcoma which progressed to myelodysplastic syndrome and systemic myeloid sarcoma despite various types of conventional anti-leukemic chemotherapies. However, the patient got a durable partial response by the monotherapy of azacitidine, a hypomethylating agent. She received thirteen courses of azacitidine therapy without progression. We discuss the possibility that hypomethylating agents are the novel effective and feasible therapeutic options for myeloid sarcoma, even in cases refractory to or relapsed after intensive systemic treatment. We also discuss the possible future development of hypomethylating agent-containing combinatory therapeutic strategy for myeloid sarcoma, given its direct anti-leukemic effect and immunomodulatory effect.

Keywords: azacytidine; hypomethylating agents; isolated myeloid sarcoma; myelodysplastic syndrome; myeloid sarcoma
Tohoku J. Exp. Med., 2021 June, **254** (2), 101-105.

Introduction

Myeloid sarcoma is one of the rare and aggressive entity of extramedullary myeloid neoplasms and is mostly accompanied by acute and chronic myelogenous leukemias, myelodysplastic syndrome, and chronic myeloproliferative neoplasms. Myeloid sarcoma can also occur as isolated tumor, i.e., isolated myeloid sarcoma, that emerges without any evidence of leukemic cell invasion in the peripheral blood and bone marrow (Yilmaz et al. 2013). Although conventional systemic chemotherapy for acute myeloid leukemia rather than local treatment such as resection and radiation therapy has been frequently applied to myeloid sarcoma on an empirical basis, there is no consensus about the treatment strategy for myeloid sarcoma, especially for isolated myeloid sarcoma due to insufficient evidence (Yilmaz et al. 2013; Almond et al. 2017). Here, we report a case of myeloid sarcoma with myelodysplastic syndrome who was refractory to various types of anti-leukemic chemotherapeutics and focal irradiation, but was successfully induced to durable remission using a hypomethylating agent, azacitidine.

Case Presentation

An 84-year-old female presented to our hospital complaining of a subcutaneous nodular lesion on the right side of her cheek (Fig. 1a) which was positively detected by 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (Fig. 2a). The histologic examination on the biopsied specimen of the nodule revealed the

Received February 12, 2021; revised and accepted April 20, 2021. Published online June 19, 2021; doi: 10.1620/tjem.254.101.
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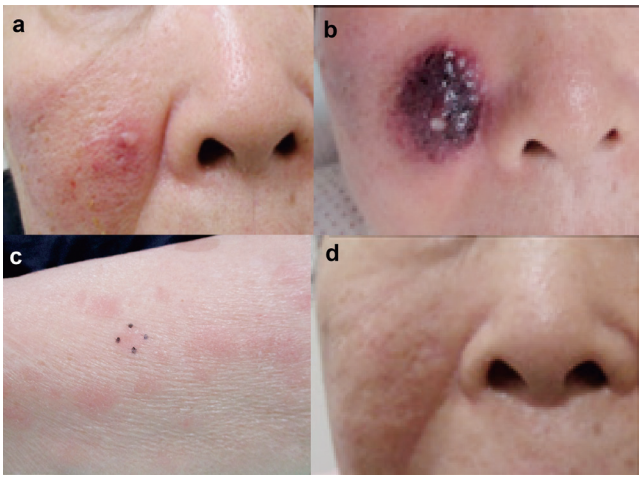

Fig. 1. Gross appearance of skin nodules.
a and b. Cheek nodule at diagnosis (a) and at progression before gemtuzumab ozogamicin monotherapy (b). c. Disseminated skin nodules of left upper arm before azacytidine therapy. d. Cheek nodule at remission induced by azacitidine.

dense infiltration of abnormal cells into the dermis (Fig. 2b, c). Those abnormal cells possessed irregular nuclei with high nucleus-to-cytoplasm ratios, and were positive for CD33, CD43, CD56, and HLA-DR, but were negative for CD3, CD4, CD8, CD34, CD117, or myeloperpxidase by immunohistochemical staining. Blood tests revealed a normal leukocyte count of 3.40×10^9/L (reference range: 3.30-8.60×10^9/L) with slightly decreased neutrophil proportion to 26.0% (reference range: 39.8-70.5%) without the presence of immature myeloid cell, a slight thrombocytopenia of 102×10^9 /L (reference range: 150-350×10^9/L) and normal hemoglobin level of 12.6 g/dL (reference range: 13.0-16.6 g/dL). Serological examination showed no clinically significant abnormality. Bone marrow examination showed the normocellular bone marrow with all nucleated cell count of 133×10^9/L, containing 2.0% of myeloblasts, without leukemic cell infiltration or dysplasia. Chromosomal analysis of bone marrow cells by G-banding showed normal karyotype. Based on these findings, the patient was diagnosed with isolated myeloid sarcoma. Series of systemic chemotherapies, including CAG regimens, consisted of conventional dosages of low-dose cytarabine, aclarubicin, and granulocyte colony-stimulating factor, dose-reduced conventional "7 + 3" therapy of cytarabine (80 mg/m^2 for 7 days) plus daunorubicin (40 mg/m^2 for 3 days), and dose-reduced combination therapy with cytarabine (160 mg/m^2 for 5 days) and mitoxantrone (5.6 mg/m^2 for 3 days), and focal radiotherapy failed to induce remission and the facial skin lesion progressed (Fig. 1b).

Four months later from the diagnosis of isolated myeloid sarcoma, the disease finally evolved to myelodysplastic syndrome with the emergence of leukemic blasts increased to 10.2% of all nucleated cells (Fig. 2d) and dysplasia with micromegakaryocytes and hypogranular neutrophils in bone marrow (Fig. 2e, f). Immunohistochemical staining showed the same phenotype with abnormal cells in the skin lesion. Chromosomal analysis of bone marrow cells by G-banding showed normal karyotype at this point. Although the salvage therapy with gemtuzumab ozogamycin monotherapy reduced leukemic cells to 2.4% of all nucleated cells in bone marrow, skin lesions were refractory to gemtuzumab ozogamycin and systemically disseminated (Fig. 1c).

Then, after eight months since the start of treatment, azacitidine monotherapy by conventional protocol (75 mg/m^2 for seven days, every 28 days) was initiated as the fifth-line systemic treatment, which mostly eradicated facial (Fig. 1d) and systemic skin lesions, including those infiltrated into back, upper arm and femur, and leukemic blasts in bone marrow, within the first cycle. Since then, although small skin lesions occasionally repeated to recur, continuous azacitidine therapy successfully prevented the regrowth of tumors for twelve months. Thus, the best response to azacitidine was considered to partial remission in this case. No major adverse event was observed. The patient received thirteen courses of azacitidine therapy, eventually relapsed as acute myeloid leukemia with myeloid sarcoma after twelve months of azacitidine therapy and died.

Discussion

The mechanism underlying the efficacy against myeloid sarcoma has remained to be clarified; however, the efficacy of hypomethylating agents for myeloid sarcoma in heavily pre-treated patients suggests their antitumor properties distinct from other conventional cytotoxic agents, and may include immunologic effects both on leukemic cells and immune cells (Lindblad et al. 2017; Nahas et al. 2019). Indeed, in addition to their primary cytotoxic activity for leukemic cells, hypomethylating agents have been shown to upregulate the expression of antigens including cancer testis antigens and minor histocompatibility molecules on leukemic cells, and, thereby, restore tumor-specific CD8 T cell responses against leukemic cells (Goodyear et al. 2010). In addition, hypomethylating agents are also potent in inducing cell surface expression of killer cell immunoglobulin-like receptors in natural killer cells (Santourlidis et al. 2002). Whereas, the precise reason for the insufficient effect of conventional chemotherapeutic agents remains unclear in our case. However, although dosages of cytarabine, daunorubicin, and mitoxantrone utilized in the salvage chemotherapies were reduced to 80% of standard dosages, these approaches were still intensive and this kind of dose modification according to patient's age was unlikely to impair therapeutic response. Rather, such a multi-refractory status may suggest the overall insensitivity to conventional genotoxic agents in our case.

As far as we searched English literature, eleven cases with myeloid sarcoma, including the present case, aged between 57 and 93 years, have been retrospectively reported to achieve remission with hypomethylating agents

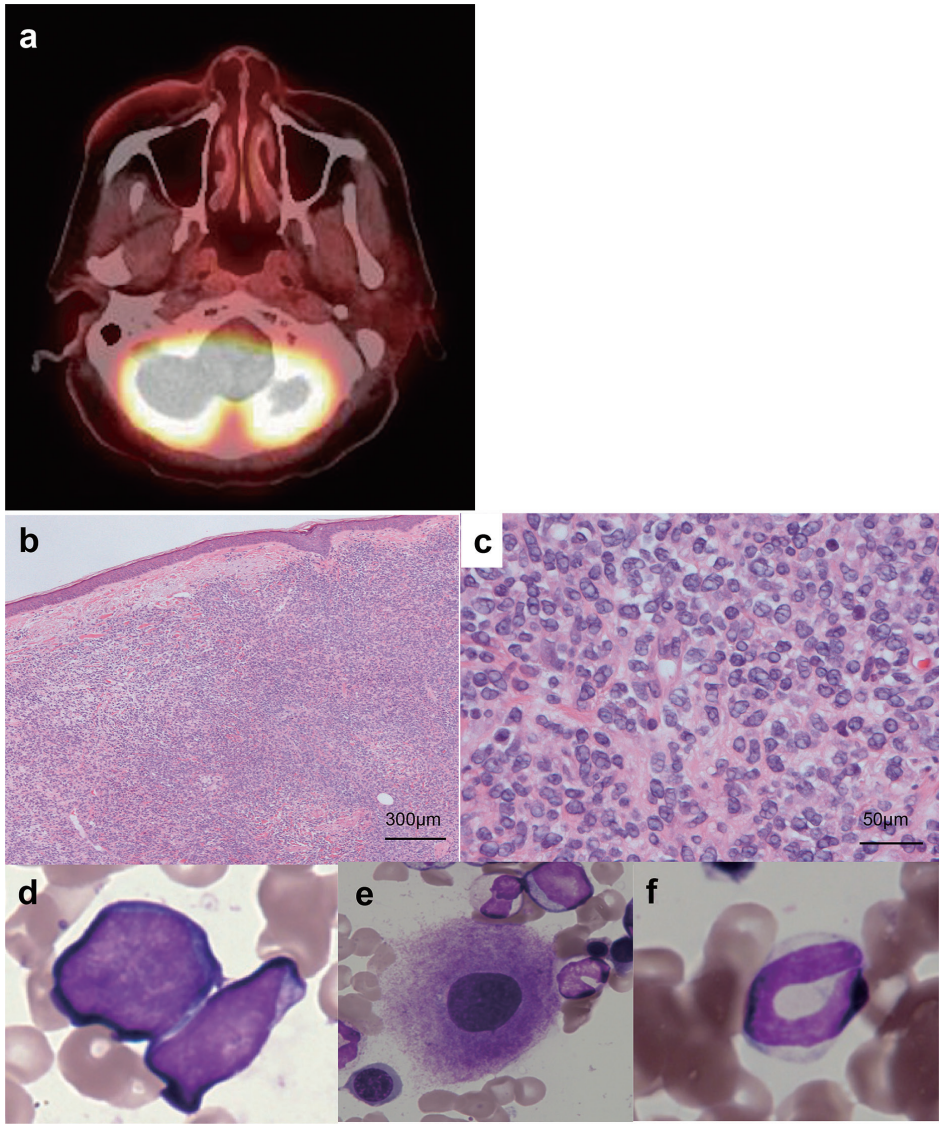

Fig. 2. 18F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography, histological and cytological findings.
a. FDG uptake on right side cheek. b and c. Lower (b: x 40) and higher (c: x 400) photomicrographs of histologic appearance of biopsied specimen at the initial diagnosis. Hematoxylin-eosin staining. d-f. leukemic blast cells (d), micromegakaryocyte (e) and hypogranular dysplastic neutrophil (f) in bone marrow at the evolution to myelodysplastic syndrome that was four months after the diagnosis of myeloid sarcoma. Wright-Giemsa staining.

(Table 1) (Singh et al. 2012; Serrao et al. 2013; Modi et al. 2015; Gornicec et al. 2017; Katagiri et al. 2017; Castelli et al. 2018; Evers et al. 2018; Minoia et al. 2019). Decitabine and azacitidine were used for 8 and 3 patients, respectively. Five patients were treatment-naïve, while six were either cases of relapse and/or refractory myeloid sarcoma after intensive systemic treatment, including allogeneic transplantation for three patients. In these eleven patients, five and six patients were reported to achieve complete remission and partial remission, respectively, and the median duration of response was 8 months (3-27 months). As the nature of the collection of published articles with successful treatment outcome, it should be noted that evidence about the efficacy of hypomethylating agents for myeloid sarcoma needs to be carefully addressed, and, are expected to be explored in prospective clinical trial. However, realistically, it would be difficult to conduct the clinical trial for myeloid sarcoma due to its rareness. Nonetheless, case series including ours suggest hypomethylating agents as one of treatment options for myeloid sarcoma, which is more feasible than other intensive systemic chemotherapies.

Only one patient was treated with hypomethylating agent in combination with donor lymphocyte infusion and two were treated in combination with focal radiation in our list of reported cases (Table 1), and, therefore, there is scare information about the combination therapy including hypomethylating agents for myeloid sarcoma. However, it would be also attractive to develop novel combinatory ther-

Table 1. Reported cases of myeloid sarcoma (MS) treated using hypomethylating agents (HMAs).

No.	Age/ Sex	Initial diagnosis	Prior treatment	Disease status at the start of HMA	Sites of MS	Type of HMA	Combined therapy	Cycles	Best response with HMAs	TTR (cycles)	DOR (M)	Relapse after HMA therapy	References
1	68/F	IMS	None	IMS	Vagina	DAC		4	PR	4	4+	–	Modi et al. 2015
2	71/F	IMS	None	MDS with MS	Breast	DAC	RT	22	CR	5	27	–	Minoia et al. 2019
3	73/M	MDS	None	MDS with MS	Ear	DAC		13	PR	4	14	+	Gornicec et al. 2017
4	93/F	AML	None	AML with MS	Skin	DAC		6	PR	2	8	+	Gornicec et al. 2017
5	68/M	IMS	Intensive CTx	AML with MS	Skin	DAC		3	CR	2	3+	–	Gornicec et al. 2017
6	69/F	AML	Intensive CTx, Allogeneic SCT	AML with MS	Skin	DAC		8	PR	6	8	+	Castelli et al. 2018
7	63/F	AML	Intensive CTx, Allogeneic SCT	Relapse as IMS	Pericardial lesion	DAC	DLI	6	PR	2	6+	–	Evers et al. 2018
8	57/M	AML	Intensive CTx, Allogeneic SCT	Relapse as IMS	LN	DAC		14	CR	4	26	–	Singh et al. 2012
9	62/M	CMMoL	None	CMMoL with MS	Skin	AZA	RT	6+	CR	4	6+	–	Serrao et al. 2013
10	71/F	IMS	Intensive CTx	MDS with MS	LN, Tonsil	AZA		20	CR	5	21+	–	Katagiri et al. 2017
11	84/F	IMS	Intensive CTx, RT	AML with MS	LN, Skin	AZA		13	PR	1	12	+	Our case

AZA, azacytidine; CTx, chemotherapy; DAC, decitabine; DLI, donor lymphocyte infusion; RT, radiotherapy; SCT, stem cell transplantation; F, female; M, male; LN, lymph node; CR, complete remission; PR, partial remission; AML, acute myeloid leukemia; CMMoL, chronic myelomonocytic leukemia; IMS, idiopathic myeloid sarcoma; MDS, myelodysplastic syndrome; TTR, time to response; DOR, duration of response.

apy containing hypomethylating agents for isolated myeloid sarcoma and myeloid sarcoma with myeloid neoplasms. One candidate is the addition of BCL2 inhibitor venetoclax to hypomethylating agents, since it has been reported that approximately 80% of myeloid sarcoma express BCL2 (Wang and Li 2016). Indeed, there was a report of a case with chemotherapy-refractory myeloid sarcoma who showed favorable response to venetoclax (Kanate et al. 2019). Considering the promising combinatory effect of venetoclax and azacitidine for treatment-naïve and relapsed/ refractory acute myeloid leukemia (Liu et al. 2020), the effect of this combination may be also expected for myeloid sarcoma. The other possible options may be the addition of immune check point inhibitor (CPI), such as those against PD-1, PD-L1 or CTLA4, to hypomethylating agents (Stahl and Goldberg 2019). It has been shown that hypomethylating agents enhance the expressions of PD-L1, PD-L2, PD-1 and CTLA4 in leukemic cells, while the overexpression of those genes associated with poor response to hypomethylating agents. In this scenario, the blockade of this pathway by the addition of CPI may potentially restores and enhances the sensitivity of leukemic cells to hypomethylating agent (Yang et al. 2014). The association between poor prognosis and PD-L1 expression of cells in tumor microenvironment has been reported with myeloid sarcoma, which also suggest the possible therapeutic targeting of the PD-1/ PD-L1 axis in myeloid sarcoma (Kawamoto et al. 2018). Indeed, the combination of hypomethylating agent and CPI has shown encouraging and durable clinical benefit in acute myeloid leukemia and myelodysplastic syndrome (Daver et al. 2018).

We experienced a case with multi-refractory isolated myeloid sarcoma who achieved durable remission with the help of azacitidine. The review of articles suggests that hypomethylating agents constitute a component of the novel therapeutic options for isolated myeloid sarcoma and myeloid sarcoma with myeloid neoplasms which are currently a hard-to-treat disease condition with poor outcome.

Acknowledgments

We would like to thank the patient's daughter, a legally acceptable representative, for giving permission with written informed consent for the use of the patient's picture and clinical data on February 10th, 2021.

Conflict of Interest

J.K. has received research funding and honoraria from Nippon Shinyaku Co., Ltd.

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