Clinical Case Report

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Successful 5-azacytidine treatment of myeloid sarcoma and leukemia cutis associated with myelodysplastic syndrome

A case report and literature review

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Abstract

Rationale: Myeloid sarcoma (MS) and leukemia cutis (LC) are extramedullary tumors comprising myeloid blasts. They can occur *de novo* or concurrently with hematological disorders, usually acute myeloid leukemia (AML). AML chemotherapy is generally the initial therapy for MS and LC, and hematopoietic stem cell transplantation (HSCT) can be considered as additional therapy. However, treatment for older patients who are unable to continue intensive chemotherapy is not currently standardized.

Patient concerns: A 71-year-old Japanese woman was diagnosed with multiple MSs associated with myelodysplastic syndrome (MDS), using bone marrow aspiration and lymph node biopsy.

Diagnoses: Additionally, LC was diagnosed by skin biopsy. Extramedullary MS and LC lesions were formed by massive infiltration of myeloblastic cells.

Interventions: Twenty courses of 5-azacytidine (5-Aza) were administrated as maintenance therapy after induction therapy with daunorubicin and cytarabine.

Outcomes: Myeloblasts decreased in the bone marrow and the LC disappeared after induction therapy. The MSs completely disappeared, except for the palatine tonsil lesion, after 5-Aza maintenance therapy. 5-Aza treatment provided long-term partial response for more than 21 months.

Lessons: 5-Aza was well tolerated and may be a good option for the treatment of MS and LC associated with MDS, especially in older patients who cannot receive HSCT.

Abbreviations: 5-Aza = 5-azacytidine, AML = acute myeloid leukemia, CXCR4 = chemokine receptor type 4, FDG = fluorodeoxyglucose, HSCT = hematopoietic stem cell transplantation, LC = leukemia cutis, MAGE antigens = melanoma-associated antigens, MDS = myelodysplastic syndrome, MS = myeloid sarcoma, PET-CT = positron emission tomography/computed tomography, RAEB = refractory anemia with excess blasts.

Keywords: 5-azacytidine, leukemia cutis, MDS, myeloid sarcoma, PET-CT

1. Introduction

Myeloid sarcoma (MS) is classified as a unique subtype of acute myeloid leukemia (AML) and forms as extramedullary lesions; however, MS can happen as solitary MS without leukemic presentation in the bone marrow (de novo MS) or concomitantly with myelodysplastic syndrome (MDS), myeloproliferative neoplasms, or chronic myelogenous leukemia.[1–4] MS lesions are extramedullary tumors composed of immature myeloid precursors and can occur in organs, such as the lymph nodes, intestine, testis, and bone.[5]

Leukemia cutis (LC) is another well-known manifestation of an extramedullary lesion of AML. LC is the infiltration of the epidermis, dermis, or subcutis by leukemia cells.[6] LC occurs most frequently in AML patients, although it has been reported in patients with chronic myeloid leukemia, MDS, and acute/chronic lymphocytic leukemia.[7]

The optimal treatments for MS and LC have not been established. Generally, AML chemotherapy is administered as the initial therapy, and hematopoietic stem cell transplantation (HSCT) or radiation therapy may also be considered. If MS persists after chemotherapy, further re-induction AML chemotherapy, including HSCT, radiation therapy, or participation in a clinical trial, will be considered.[6] However, HSCT and intensive chemotherapy are difficult for older patients, so it is necessary to consider further strategies.

5-azacytidine (5-Aza), a hypomethylating agent used in the treatment of all international prognostic scoring system risk MDS

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patients,[8,9] is well tolerated in older patients and improves quality of life as to fatigue, physical functioning, and so on. Furthermore, 5-Aza reduces the risk of leukemic transformation compared with supportive care in MDS,[10] and a recent study also suggested that 5-Aza improves outcomes in older patients with AML.[11] These recent results suggest that 5-Aza may be a therapeutic agent against MS with MDS and a good option in older patients.

The aim of this study is to confirm the therapeutic effects of 5-Aza against MS and LC with MDS in older patients for whom intensive chemotherapy including AML chemotherapy and HSCT is not an option. Herein we report a case of MS and LC complicated with MDS treated by 5-Aza.

2. Case report

We followed the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. We also included informed consent for the publication of the patient's radiological data.

A 71-year-old woman diagnosed with refractory anemia 5 years previously was admitted to our hospital with a sore throat. Physical examination showed enlargement of the tonsils and cervical lymph node swelling. Laboratory tests revealed the following data: white blood cell count, 14,480/μL; hemoglobin, 11.0 g/dL; and platelet count, 35 000/μL. A bone marrow aspiration showed 13.4% myeloblasts with multilineage dysplasia, and the patient was diagnosed with MDS refractory anemia with excess blasts 2 (MDS RAEB-2). The karyotype of the bone marrow cells was 46,XX. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) showed FDG uptake in the nasopharynx, tonsil, spleen, multiple lymph nodes, and bone marrow. Microscopic examination of the biopsy specimens from the cervical lymph node showed infiltration of medium-to-large-sized pathological cells in the interfollicular zone (Fig. 1). Immunohistochemical staining was positive for myeloperoxidase, cluster of differentiation (CD) 68, CD13, and CD33, partially positive for CD138 and CD41, and negative for CD3, CD20, and CD34. Moreover, CD56 and chemokine receptor type 4 (CXCR4) showed positive staining. These findings were consistent with MS with MDS RAEB-2. Prior to induction therapy, erythematous eruptions appeared rapidly on the extremities. These lesions were diagnosed as LC by skin biopsy.

We started daunorubicin (40 mg/m^2, days 1–3) and cytarabine (80 mg/m^2, days 1–5) as induction therapy. The LC lesions had clinically disappeared after induction therapy. In addition, the CT scan showed reduction of lymph node swelling and splenomegaly, and the myeloblasts had decreased to 7% in the bone marrow aspiration. 5-Aza was started (100 mg/body daily for 7 days every month) as maintenance therapy, owing to grade 3–4 neutropenia and thrombocytopenia that appeared following induction therapy. After AML induction therapy and 5 courses of 5-Aza therapy, ^{18}F-FDG PET-CT images showed remarkable reduction in FDG uptake in the nasopharynx, bilateral palatine tonsil, spleen, and multiple lymph nodes; however, aggravations were observed in the right paratracheal and left external iliac lymph nodes. In addition, myeloblast counts reached <5% in the bone marrow and became independent of blood transfusion. Unanticipated events were not seen. After 9 courses of 5-Aza therapy, the uptake of the lymph nodes improved, except for the palatine tonsil (Fig. 2). In total, she received AML induction therapy and 20 courses of 5-Aza therapy, and has achieved long-term partial response (more than 21 months) after 5-Aza maintenance therapy.

3. Discussion

Most MS patients have a single involved site; only 13% of patients have been shown to have multiple lesions.[5,12] The most

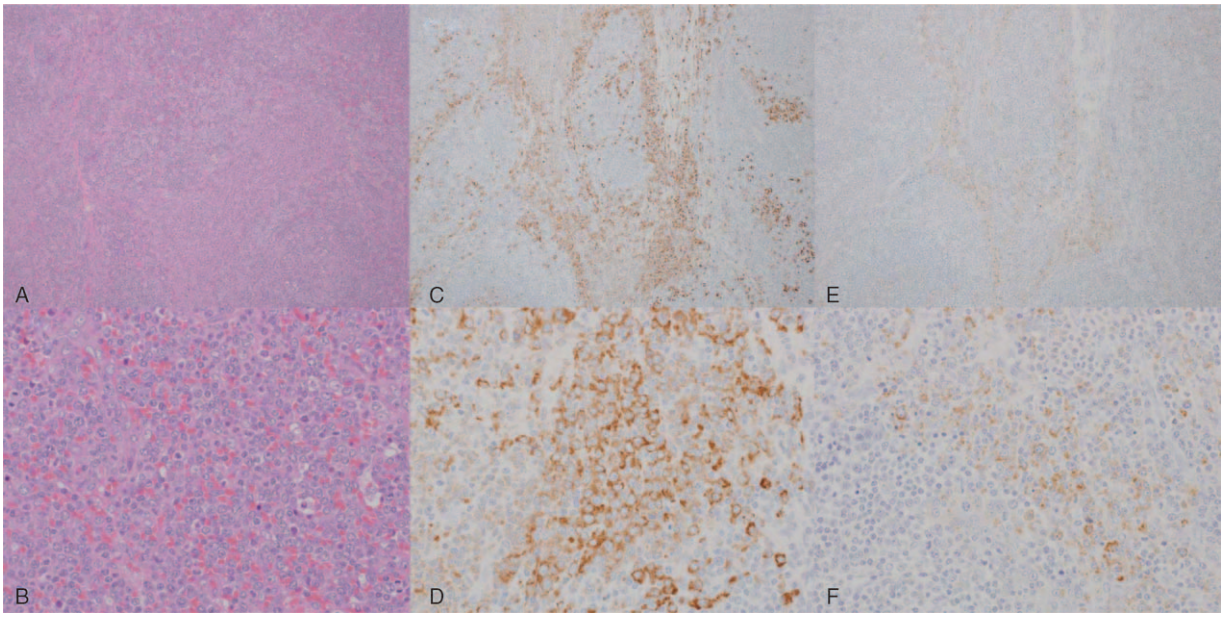

Figure 1. Microscopic and immunohistochemical analyses of the cervical lymph node. Microscopic examination of biopsy specimens from the cervical lymph node (hematoxylin and eosin stain, original magnification A: ×100, B: ×400) showed infiltration of medium-to-large-sized myeloblasts in the intrafollicular zone. These blasts were positive for myeloperoxidase (original magnification C: ×100, D: ×400) and cluster of differentiation 68 (original magnification, E: ×100, F: ×400). These findings were compatible with a diagnosis of myeloid sarcoma.

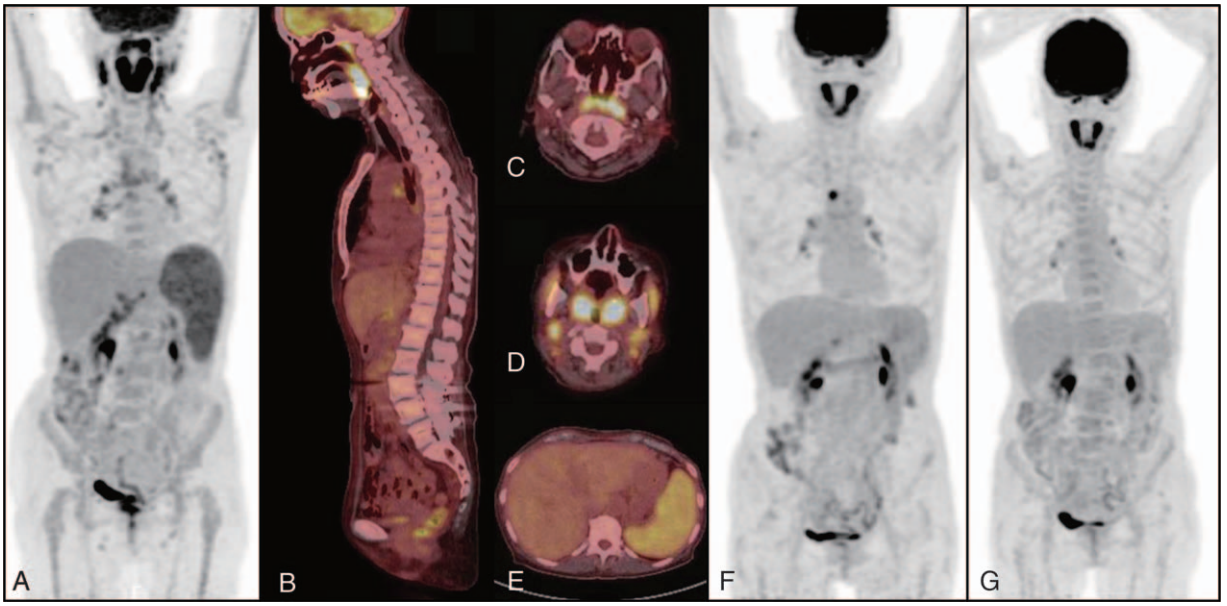

Figure 2. PET-CT imaging. Whole-body maximum intensity projection PET-CT images showed increased FDG uptake in the bone marrow (A, B), and strong FDG uptake in the nasopharynx (SUV_{max} 8.0) (C), palatine tonsil (SUV_{max} 14.6) (D), and spleen (SUV_{max} 5.2) (E). Moderate uptake was also observed in multiple lymph nodes, including the cervical, supraclavicular, axillary, mediastinal, pulmonary hilar, hilar (porta hepatis), and inguinal nodes (A). These findings were suggestive of malignancy and hyper-cellular marrow. (F) PET-CT after 5 courses of 5-Aza therapy. (G) PET-CT after 9 courses of 5-Aza therapy. 5-Aza = 5-azacytidine, FDG = fluorodeoxyglucose, PET-CT = positron emission tomography-computed tomography, SUV = standardized uptake value.

common sites of MS lesion formation are the skin (22.1–28.2%) and lymph nodes (16.3–55.0%), whereas involvement in the tonsil (1.0–3.1%), laryngopharynx (5.3%), and spleen (1.0–13.0%) are rare. In our case, there were multiple MS lesions formed.

The standard therapy for MS and LC is intensive AML chemotherapy with consideration of HSCT[6]; however, these therapies strongly suppress hematopoiesis in older patients. Our patient also developed severe anemia and thrombocytopenia with the administration of induction therapy; therefore, 5-Aza therapy was started as maintenance therapy. The 5-Aza maintenance therapy successfully suppressed the recurrence of MS and LC. Our case suggests that 5-Aza is a good option for MS therapy in older patients who are unable to receive HSCT or intensive therapy.

Thus far, 5-Aza has been reported to improve overall survival in high-risk MDS patients (based on an international prognosis scoring system rating of intermediate-2 or high risk) and those with French-American-British Classification-defined RAEB or RAEB in transformation. In these patients, overall survival is 24.5 months in the 5-Aza group, compared with 15.0 months in the conventional care group (best supportive care, low dose cytarabine, or intensive chemotherapy).[13] Moreover, the efficiency of 5-Aza was also confirmed in AML patients with $>$ 30% myeloblasts who were $\geq$65 years old. Additionally, 5-Aza prolongs median overall survival; patients who received 5-Aza had a survival of 10.4 months, compared to 6.5 months in patients who received conventional care regimens (standard induction chemotherapy, low dose cytarabine, or supportive care only).[11] The median time to AML transformation was 15.0 months in the 5-Aza group, compared with 10.1 months in the best supportive care group, and this was significant.[13] However, there are only a few reports on 5-Aza treatment in patients with MS. Therefore, the clinical evidence of 5-Aza against MS is still insufficient.

5-Aza belongs to a group of hypomethylating agents that normalize gene expression by suppressing DNA methylation; however, the mechanism of action is not completely understood. In addition to this therapeutic effect, 5-Aza is reported to have the ability to modulate immune response. 5-Aza augments graft versus leukemia effects without increasing graft versus host disease after allogenic stem cell transplantation in AML patients.[14] In this report, administration of 5-Aza increased regulatory T cells and induced cytotoxic CD8 T cells against several tumor antigens, such as melanoma-associated antigens (MAGE antigens), B melanoma antigen 1, and Wilm's tumor antigen 1. Similarly, 5-Aza and valproate have been shown to upregulate MAGE antigens in AML and myeloma cell lines.[15] Because MAGE antigens represent attractive targets for immunotherapy, AML and high-risk MDS patients with circulating MAGE cytotoxic T lymphocytes achieved a higher overall response rate after 5-Aza/valproate therapy. Thus, there is a possibility that 5-Aza has immunotherapeutic effects in addition to its effects as a hypomethylating agent, which could explain why the blastomas disappeared in our case.

It is rare for multiple MSs and LC associated with MDS not to transform into acute leukemia in the bone marrow. It has recently been determined that cell surface markers form extramedullary lesions through their homing mechanism. Particularly, CD56, cutaneous lymphocyte-associated antigen, intercellular adhesion molecule-1, and lymphocyte function-associated antigen 1 have been hypothesized to be associated with the homing of blasts.[6,16–18] Moreover, homing markers affect prognosis, and CXCR4 expression was recently reported to be a poor prognostic factor in de novo MS or MS with concomitant AML.[12] In our case, the MS lesion was CXCR4-positive, and the patient belonged to the poor prognosis group. However, the 5-Aza maintenance therapy successfully suppressed disease progression.

In conclusion, standard treatment for MS and LC needs further research, especially in elderly patients. 5-Aza may be a good option in the treatment of MS and LC associated with MDS.

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