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Case Report

Extramedullary Disease with Bone Marrow Necrosis at Disease Onset in A Case of Mixed Phenotypic Acute Leukemia with BCR::ABL1 Fusion Gene: a Case Report and Review of the Literature

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Abstract

Mixed phenotype acute leukemia (MPAL) is an uncommon acute leukemia, representing only 2–5% of acute leukemia cases. Extramedullary disease (EMD) is typically seen during a relapse or with disease progression. When EMD occurs in acute myeloid leukemia, it is called myeloid sarcoma. However, to the best of our knowledge, there are no reports of EMD in MPAL patients at the initial diagnosis. We provide the first case, which shows EMD associated with bone marrow necrosis of MPAL with minor BCR/ABL (BCR::ABL1 fusion gene) at disease onset. A 50-year-old Japanese man presented to a hematologist with a month-long history of immobility due to severe lumbar pain. Bone marrow aspirations were unsuccessful. Computed tomography revealed a mass in the left iliopsoas muscle and hepatosplenomegaly. He was diagnosed with MPAL associated with minor BCR/ABL, and EMD was confirmed by the analysis of blast phenotype in peripheral blood and necrotic bone marrow, as well as the biopsied mass in the iliopsoas muscle. He was first treated with cytarabine, then treatment was switched to a combination of steroids and dasatinib after the final diagnosis. The blast in peripheral blood disappeared, and the mass in the left iliopsoas shrunk one month after dasatinib treatment. Later bone marrow biopsy findings confirmed initial bone marrow necrosis. Although EMD associated with bone marrow necrosis at disease onset of MPAL with minor BCR/ABL is rare, our case underscores that no type of leukemia should be excluded from the differential diagnosis of bone marrow necrosis and EMD.

Introduction

Mixed phenotype acute leukemia (MPAL) is an uncommon acute leukemia, representing approximately 2–5% of acute leukemia cases.[1–4] The blast cells of MPAL express multilineage immunophenotypic markers and may have a shared B/T/myeloid phenotype.[1–4] Extramedullary disease (EMD) is typically seen during a relapse or with disease progression. When EMD occurs in cases of acute myeloid leukemia (AML), it is called myeloid sarcoma. However, to the best of our knowledge, there are no reports on EMD in MPAL patients at the initial diagnosis. Also, co-occurrence of EMD associated with bone marrow necrosis is rare. Here, we provide the first case report of EMD with bone marrow necrosis of MPAL with minor BCR/ABL at the initial diagnosis. The CARE checklist has been applied.

Case presentation

This study was performed in accordance with the ethical standards of our institutional and national research committee, and

Keywords: Extramedullary disease; Bone marrow necrosis; Mixed phenotype acute leukemia; Minor BCR::ABL1 fusion gene.

Abbreviations: MPAL, mixed phenotype acute leukemia; EMD, extramedullary disease; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; CML, chronic myeloid leukemia; MPO, myeloperoxidase; TdT, terminal deoxynucleotidyl transferase; BCR/ABL, BCR::ABL1 fusion gene; CD, cluster of differentiation; HLA-DR, human leukocyte antigen-DR isotype; GP-A, glycophorin A.

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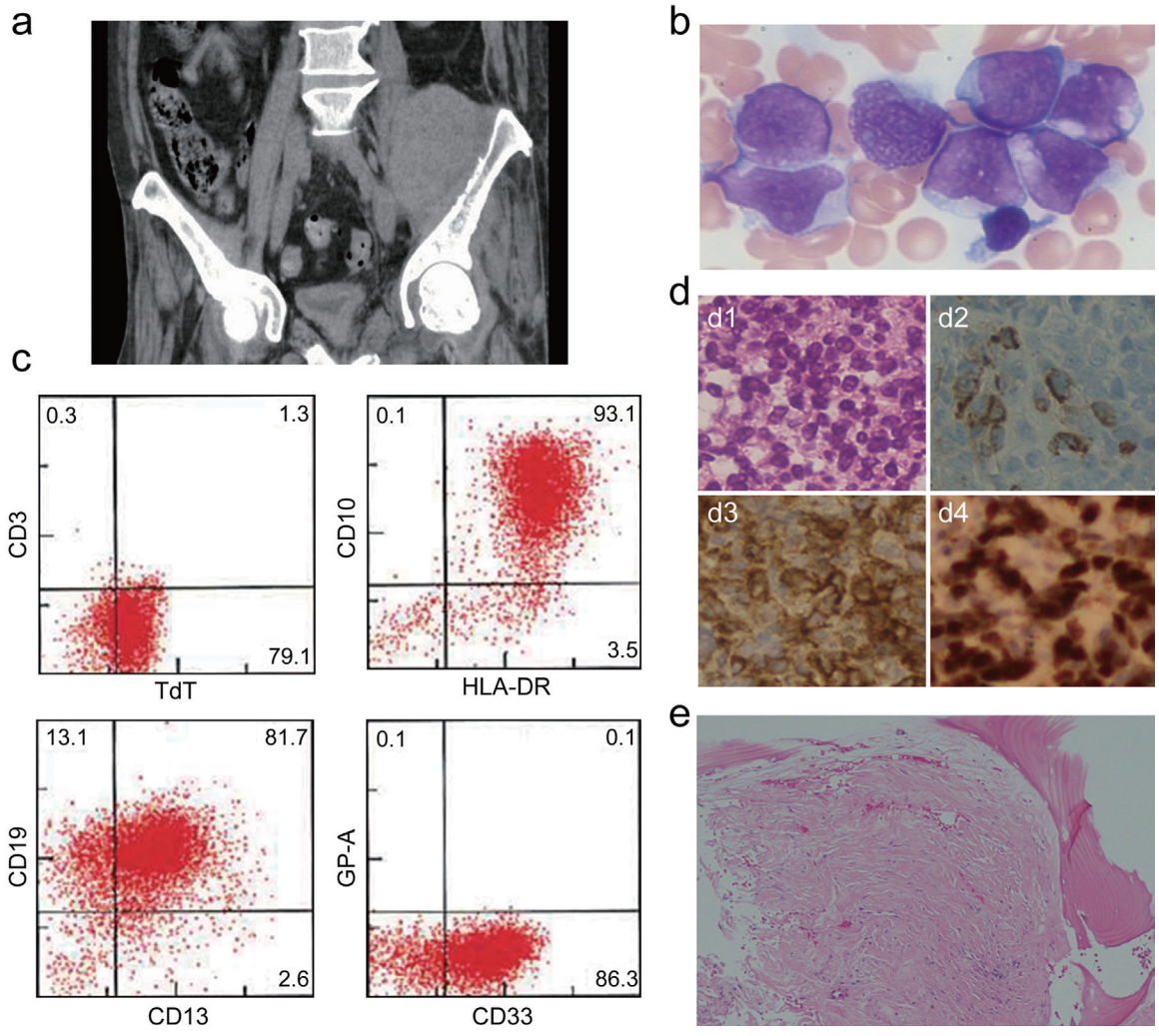

Fig. 1. (a) Computed tomography image of a mass in the left iliopsoas muscle is shown. (b) May–Giemsa staining (×1,000 magnification) of the blasts in peripheral blood. (c) The results of flow cytometry analysis (CD3 × TdT, CD10 × HLA-DR, CD19 × CD13, GP-A × CD33) show mixed phenotype. (d) Pathology and immunostaining of the biopsied tissue (a mass in the left iliopsoas muscle) are shown with hematoxylin and eosin staining (d1) anti-MPO staining (d2), anti-CD33 staining (d3) and anti-TdT staining (d4). (e) Hematoxylin and eosin staining of bone marrow biopsy after treatment showing pre-existing bone marrow necrosis. CD, cluster of differentiation; TdT, terminal deoxynucleotidyl transferase; HLA-DR, Human leukocyte antigen-DR isotype; GP-A, glycophorin A

with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A 50-year-old Japanese man with immobility due to severe lumbar pain and remittent fever (max. 38.2°C) for nearly two months was referred to us with leukocytosis (39,400/μL), thrombocytopenia (18 K/μL), high serum C-reactive protein (CRP; 23.6 mg/dL), lactate dehydrogenase (LDH; 1,241 U/L), and ferritin (6,547 ng/mL) associated with high plasma fibrinogen/fibrin degradation products (FDP; 158 μg/mL) presented to a hematologist. He complained of having difficulty moving his left leg. Physical examination revealed a mass in the left iliopsoas muscle, which was also confirmed by computed tomography (Fig. 1a). In addition, computed tomography revealed hepatosplenomegaly. Blood examination revealed leukocytosis (white blood cell count: 39.4 × 10^9/L) with blasts (61%, Fig. 1b), anemia (hemoglobin: 9.6 g/dL), and thrombocytopenia (platelet count: 0.18 × 10^9/L). The blast cells in peripheral blood were positive for minor BCR/ABL (BCR::ABL1 fusion gene), and expressed CD10+ CD19+ CD13+ CD33+ CD34+ HLA-DR+ by flow cytometry analysis. Terminal deoxynucleotidyl transferase (TdT) and myeloperoxidase (MPO) also tested positive (Fig. 1c). At disease onset, repeat bone marrow aspirations at 3 trials were all dry taps with a few MPO-positive blasts. Needle aspiration of the mass in the left iliopsoas muscle showed involvement of MPO and TdT-positive blast cells (Fig. 1d). Though he was started on cytarabine therapy (100 mg/m^2) for 2 days, treatment was switched to a combination of steroids and dasatinib after the final diagnosis of MPAL with minor BCR/ABL, and with EMD. During the treatment, severe pancytopenia persisted, requiring blood transfusions and antibiotics for febrile neutropenia. Since a fourth bone marrow aspiration trial was again unsuccessful, a bone marrow biopsy was performed. The biopsy strongly suggested the preexistence of bone marrow necrosis at the initial presentation (Fig. 1e). The patient eventually recovered from the cytopenia, and the blood transfusions were stopped. At one month after dasatinib treatment, the mass in the left iliopsoas muscle had started to shrink. He has

Table 1. Summary of EMD in MPAL cases

Case	Age(yrs.)/ gender	Site(s) of EMD	MPO+ myeloid sarcoma	BCR/ABL status	Bone marrow necrosis	Reference
1	32/F	Pleural fluid, multiple lymph nodes (lymphoma-like)	not available	negative	negative	10
2	49/F	Submandibular gland (lymphoma-like)	positive	major BCR/ABL	negative	13
3	61/F	Pleura, multiple lymph nodes (lymphoma-like)	positive	negative	negative	14
4	58/F	Thyroid, multiple bones	positive	negative	negative	15
5	69/M	Multiple GI tracts, lungs (lymphoma-like)	negative	major BCR/ABL	negative	16
6	50/M	Iliopsoas muscle	positive	minor BCR/ABL	positive	present case

Cases of EMD in MPAL were from the literature survey and present case. M; male, F; female, EMD, Extramedullary disease; MPAL, Mixed phenotype acute leukemia; MPO, myeloperoxidase; GI, gastrointestinal; M, male; F, female.

repeatedly been treated with an intensive chemotherapy regimen consisting of hyper-CVAD/MA (cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and cytarabine) plus dasatinib treatment with response.

Discussion

Differentiation of minor BCR/ABL positive acute leukemia between de novo acute lymphoid leukemia (ALL) and chronic myeloid leukemia (CML) blast crisis is often difficult. Also, there is one type of BCR/ABL positive AML, in which the B-cell marker CD19 on blasts was demonstrated,[5] causing an MPAL EMD in AML or in CML (termed myeloid sarcoma) which is usually seen during a relapse or disease progression. It could develop as single or multiple lesions. EMD occurring in ALL or in MPAL could be misdiagnosed as lymphoma. Recently, EMD of ALL was reported after chimeric antigen receptor-T cell therapy or blinatumomab treatment,[6,7] but EMD of ALL at initial diagnosis is extremely rare,[8,9] particularly in cases of MPAL with minor BCR/ABL like our case. The case described by Means, *et al*. had no leukemic features, but an anterior mediastinal mass and pericardial/pleural involvement that was initially diagnosed as primary mediastinal lymphoma. Flow cytometry on pleural fluid confirmed MPAL without BCR/ABL.[10] Here, we experienced a very rare co-occurrence of MPO-positive EMD in the muscle associated with probable bone marrow necrosis at disease onset in MPAL with minor BCR/ABL associated with positive B-cell (including TdT-positive) markers at the initial diagnosis. The patient had no history of CML.

Pelvic muscle involvement in our case was thought unusual, because EMD in leukemia often involves lymph nodes, skin, and bones, but rarely occurs as intramuscular lesions. When there is such an occurrence, most cases predominantly involve the extraocular and the extremity muscles.[11] In addition, EMD as myeloid sarcoma associated with cases of minor BCR/ABL leukemia was limited, having previously been described in a case after allogeneic bone marrow transplantation for CML.[12] Cho *et al*. described a therapy related MPAL with BCR/ABL with EMD.[13] With the literature survey, EMD in 6 MPAL cases including our case are summarized in Table 1.[10,13–16] Initially, 4 out of 5 EMD cases were thought to be lymphoma-like, probably because of multiple EMD lesions or from specific site(s). However, MPO-positive myeloid sarcoma was counted in 3 out of 5 cases (one case MPO-negative and one case not confirmed). Of 6 MPAL cases, BCR/ABL-positive were counted in 3 cases (major 2, minor 1). In addition, none except our case showed bone marrow necrosis simultaneously at disease onset.

Bone marrow necrosis is a rare clinicopathologic entity, which could be related to acute leukemia.[17] The mechanism of bone marrow necrosis might be ischemia due to hematological malignancy, disseminated intravascular coagulation, and autoimmune mechanisms.[18] Case reports on bone marrow necrosis in cases of minor BCR/ABL acute leukemia were very limited. Sato *et al*. reported a case of a 16-year-old patient with minor BCR/ABL-positive ALL preceded by knee joint pain due to bone marrow necrosis).[19] Our patient initially presented with high serum CRP, LDH, ferritin, and plasma FDP. We wondered about the causes of these abnormal laboratory data at the onset of MPAL. Later, we found that these markers, as well as his symptoms, such as bone pain and fever fit the clinical features of bone marrow necrosis.[18] Unfortunately, we initially did not perform a bone marrow biopsy because of severe thrombocytopenia. This highlighted an important lesson for us: whenever bone marrow aspirations are unsuccessful, a bone marrow biopsy is inevitable in order to obtain a correct diagnosis. Lastly, it remains unknown if the bone marrow failure due to marrow necrosis resulted in the development of EMD in this case. Since bone marrow necrosis in AML or ALL is suggestive of poor prognosis,[20] hematopoietic stem cell transplantation (HSCT) would be recommended for eligible patients. However, as the patient was not eligible for HSCT, he will require careful monitoring for disease progression with treatment.

Conclusions

We report the first case of MPO-positive EMD with bone marrow necrosis in an MPAL adult patient with a minor BCR/ABL fusion gene at the initial diagnosis. Although co-occurrence of EMD and bone marrow necrosis of MPAL with minor BCR/ABL is rare, our case underscores that no type of leukemia should be excluded from the differential diagnosis of patients suffering from bone marrow necrosis and EMD.

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None.

Conflict of interest

There are no conflict of interests related to this publication.

Author contributions

Conceptualization, methodology, investigation, data curation, visualization, writing, reviewing and editing (YS); Investigation, supervision, writing, reviewing and editing (TM); Investigation, data curation, visualization, writing and reviewing (SM); Investigation, writing and reviewing (YK, MK, KS); Investigation, data curation, visualization, writing, reviewing and editing (SI).

Ethical Statement

This study was performed in accordance with the ethical standards of our institutional and national research committee, and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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