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CASE REPORT

Effective treatment of relapsed/refractory CD19-positive B/T-type mixed-phenotype acute leukemia with blinatumomab: A case report

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Abstract

A 26-year-old man was diagnosed with B/T-type mixed-phenotype acute leukemia (MPAL-B/T) based on blasts being positive for CD19, cytoplasmic CD3, and cyCD79a, but negative for myeloperoxidase. Acute lymphoblastic leukemia-based chemotherapy was started, but the leukemia was refractory. He underwent cord blood transplantation with the conditioning regimen of total body irradiation plus cyclophosphamide and cytarabine with granulocyte-colony stimulating factor priming. Prophylaxis for graft versus host disease was performed with short-term methotrexate and cyclosporin. The leukemia relapsed in bone marrow 20 months later. At that time, he was treated with inotuzumab ozogamicin because the blasts expressed CD22 (75.4%), but this was ineffective. He was next administered blinatumomab with dexamethasone pretreatment, resulting in a complete remission (CR). He subsequently underwent human leukocyte antigen-haploidentical peripheral blood stem cell transplantation. He has still maintained a CR for 12 months. Blinatumomab might be a promising treatment and a bridge to stem cell transplantation even in relapsed/refractory CD19-expressing MPAL-B/T.

KEYWORDS
blinatumomab, CD19, HLA-haploidentical peripheral blood stem cell transplantation, mixed-phenotype acute leukemia with B/T cell lineages (MPAL-B/T)

1 | INTRODUCTION

Mixed-phenotype acute leukemia (MPAL) is classified as an acute leukemia of ambiguous differentiation [1, 2] and is characterized by the presence of two or more differentiation lineages. It accounts for 1.6%–2.4% of all acute leukemias [3–5]. The disease concept of MPAL was established through advances in flow cytometry, which showed that B/myeloid lineages account for 58% of MPAL cases, followed by T/myeloid lineages (36%), with other combinations are extremely rare [3].

Survival rates of patients with MPAL are generally higher with acute lymphoblastic leukemia (ALL)-type therapy than with acute myelogenous leukemia-type therapy [6]. However, no treatment has been established for relapsed/refractory (R/R) MPAL, the prognosis of which is dismal [6].

Blinatumomab is a bispecific T-cell engager antibody construct that simultaneously binds to CD3-positive cytotoxic T-cells and CD19-positive ALL blasts. Treatment with blinatumomab has improved the outcomes in patients with R/R B-ALL [7, 8]. In this report, we describe a case of R/R MPAL with B/T lineages, in which the patient relapsed after

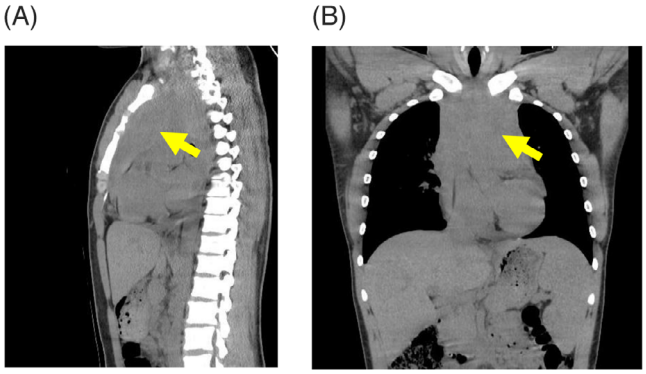

FIGURE 1 Imaging of the anterior mediastinal tumor. Computed tomography shows a large tumor (arrow) in the anterior mediastinum (A: sagittal image; B: coronal image).

cord blood transplantation (CBT) and was treated with blinatumomab, resulting in complete remission (CR). Human leukocyte antigen (HLA)-haploidentical peripheral blood stem cell transplantation (PBSCT) was subsequently performed, and the patient has maintained CR for 12 months.

2 | CASE PRESENTATION

A 26-year-old man was admitted to our hospital with leukocytosis. At admission, hemogram revealed a white blood cell count of 28.3 × 10^9/L (blasts 93.0%), accompanied by anemia and thrombocytopenia. Computed tomography showed a large tumor in the anterior mediastinum (Figure 1). Bone marrow examination revealed marked hypercellularity with 93.0% blasts (Figure 2A). Flow cytometry showed that the leukemic blasts were positive for CD7, CD10, CD19, CD34, cytoplasmic (cy)CD3, cyCD79a, and terminal deoxynucleotidyl transferase, but negative for CD3 and myeloperoxidase (Figure 2B). Cytogenetic analysis demonstrated a normal karyotype. *BCR::ABL1* or KMT2A gene rearrangement was not found. In addition, no T-cell receptor or immunoglobulin chain rearrangement was observed. Based on these results, the patient was diagnosed with MPAL, B/T (MPAL-B/T), according to the diagnostic criteria for MPAL [1].

He was treated with ALL-type therapy, but CR was not achieved. He received an HLA 2 locus mismatched CBT, following the conditioning regimen of total body irradiation (12 Gy) plus cyclophosphamide (60 mg/kg × 2) and cytarabine (2 g/m^2 × 4) with granulocyte-colony stimulating factor priming at 7 months after disease onset, resulting in CR. Prophylaxis for graft versus host disease (GVHD) was performed with short-term methotrexate and cyclosporin. The patient developed Grade II acute GVHD (skin stage 3, gut stage 1) on Day 28, which resolved by treatment with prednisolone.

At 20 months after CBT, leukemia relapsed in bone marrow with 84.8% blasts. The blasts showed a similar MPAL-B/T phenotype (Figure 2C). The chimerism test showed mixed chimerism with 80.3% of the recipient type. He was first treated with one cycle of inotuzumab ozogamicin (Day 1: 0.8 mg/m^2; Day 8, 15: 0.5 mg/m^2) because the blasts expressed CD22 (75.4%). Thereafter, bone marrow resulted in an almost dry tap due to 82.4% of remaining blasts. Flow cytometry revealed high expression of CD19 (87.3%) and cyCD3 (84.9%), but decreased CD22 expression (11.9%) compared with baseline.

We next administered blinatumomab (one cycle: Day 1–7: 9 μg; Day 8–28: 28 μg) in view of the high CD19 expression on blasts, and some reported cases of CD19 expressed MPAL being successfully treated with blinatumomab [9]. $CD45^{high}CD3^+$ cells (30.2%) were found in peripheral blood immediately before the start of blinatumomab treatment. He achieved CR after one cycle of blinatumomab with dexamethasone pretreatment (10 mg/m^2 for 5 days). No toxicities related to the administration of blinatumomab emerged.

It was difficult to find a suitable HLA-matched donor or cord blood during his CR. We, therefore, opted for HLA-haploidentical PBSCT from his sibling. After three cycles of blinatumomab treatment (at 27 months after the CBT), HLA-haploidentical PBSCT was performed with the following conditioning regimen: 30 mg/m^2 fludarabine for 5 days, 3.2 mg/kg busulfan for 4 days, 4 Gy total body irradiation, and post-transplantation cyclophosphamide (50 mg/kg for 2 days). A total of 3.24 × 10^6/kg CD34+ cells were infused. Prophylaxis for GVHD was performed with tacrolimus and mycophenolate mofetil. On Day 18 after transplantation, engraftment was confirmed. Acute GVHD did not occur. As of this writing, he has maintained CR for 12 months with mild chronic GVHD.

3 | DISCUSSION

MPAL usually harbors chromosomal abnormalities, such as the Philadelphia chromosome or 11q23 rearrangement (*KMT2A* mutation) [1, 2]. Our case showed no chromosomal abnormalities at the time of initial diagnosis. A normal karyotype is reported in 13% of MPAL cases [3]. Genetic analyses have revealed various genetic abnormalities in MPAL, such as *TP53*, *WT1*, *RUNX1*, *KMT2D*, and *FLT3* mutations [10, 11]. Mi et al. reported that genomic analysis of MPAL-B/T showed that its features are more similar to T-cell ALL than to B-cell ALL, especially early T-cell precursor ALL [10]. Our patient had a mediastinal tumor, which is usually found in T-cell ALL and is extremely rare in MPAL. Although we did not perform a genetic analysis of our patient, genetic factors may have contributed to the formation of the mediastinal tumor if his genetic pattern was similar to that of T-cell lineage leukemia.

The treatment of R/R MPAL remains challenging. It has been reported that the patients with R/R CD19-positive MPAL-B/myeloid improved with blinatumomab [9, 12–14]. One patient with relapsed CD19-positive MPAL-B/T achieved CR with blinatumomab, but declined the further treatment, relapsed 1 month later, died of sepsis [12].

Our patient was administrated blinatumomab, resulting in CR. Although we did not examine the T lineage in the chimerism test between the recipient and donor, many $CD45^{high}CD3^+$ cells (30.2%),

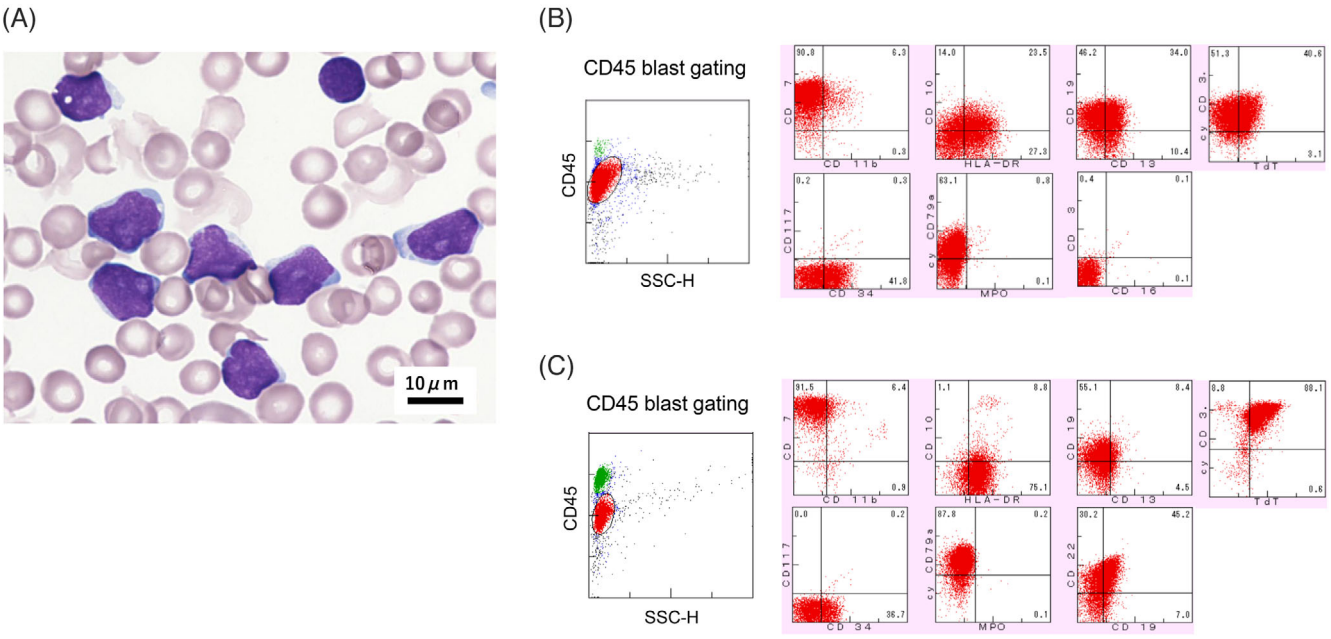

FIGURE 2 Bone marrow examination. (A) At the initial diagnosis, a bone marrow smear showed the presence of blasts with a high nuclear–cytoplasmic ratio, scant agranular cytoplasm, and prominent nucleoli (May–Grünwald–Giemsa stain: ×1000). (B) Flow cytometric analysis of bone marrow at diagnosis revealed that the blasts were positive for CD7, CD10, CD19, CD34, cytoplasmic (cy)CD3, cyCD79a, and terminal deoxynucleotidyl transferase (TdT), but negative for CD3 and myeloperoxidase. (C) At the relapse in bone marrow, blasts in the marrow showed a similar phenotype with positivity for CD7, CD19, CD22, CD34, cyCD3, cyCD79a, and TdT.

which were considered normal T cell, were found in peripheral blood. These residual T cells, which might be derived from cord blood, were activated by the administration of blinatumomab. This result suggested that blinatumomab treatment might be promising even in R/R CD19-expressing MPAL-B/T. A clinical trial of blinatumomab treatment for MPAL is ongoing and results regarding the efficacy are awaited (https://clinicaltrials.gov/study/NCT04827745).

4 | CONCLUSION

Our case suggests that blinatumomab might be a promising treatment and a bridge to stem cell transplantation even in R/R CD19-expressing MPAL-B/T.

AUTHOR CONTRIBUTIONS

Masanori Aoki, Maho Ishikawa, and Yasuhiro Ebihara designed the study; Masanori Aoki and Yoshitada Taji performed the laboratory examinations; Tsugumi Sato and Hidekazu Kayano performed the pathological examinations; Maho Ishikawa and Naoki Takahashi were responsible for the patient care; and Masanori Aoki and Yasuhiro Ebihara wrote the manuscript.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING INFORMATION

There are no funding sources to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

Because this is a case report, ethics committee approval is not required for this study, in accordance with the national ethical guidelines in Japan.

PATIENT CONSENT STATEMENT

The patient was informed of this case study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCE

There were no data from other sources.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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REFERENCES

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
2. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703–19.
3. Matutes E, Pickl WF, van't Veer M, Morilla R, Swansbury J, Strobl H, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Blood. 2011;117(11):3163–71.
4. Weinberg OK, Arber DA. Mixed-phenotype acute leukemia: historical overview and a new definition. Leukemia. 2010;24(11):1844–51.
5. Lingzhi Y, Nana P, Mingqing Z, Aining S, Yongquan X, Changgeng R, et al. Clinical, immunophenotypic, cytogenetic, and molecular genetic features in 117 adult patients with mixed-phenotype acute leukemia defined by WHO-2008 classification. Haematologica. 2012;97(11):1708–12.
6. Wolach O, Stone RM. How I treat mixed-phenotype acute leukemia. Blood. 2015;125(16):2477–85.
7. Goebeler M-E, Bargou R. Blinatumomab: a CD19/CD3 bispecific T cell engager (BiTE) with unique anti-tumor efficacy. Leuk Lymphoma. 2016;57(5):1021–32.
8. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera J-M, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376(9):836–847.
9. El Chaer F, Ali OM, Sausville EA, Law JY, Lee ST, Duong VH, et al. Treatment of CD19-positive mixed phenotype acute leukemia with blinatumomab. Am J Hematol. 2019;94(1):E7–E8.
10. Mi X, Griffin G, Lee W, Patel S, Ohgami R, Ok CY, et al. Genomic and clinical characterization of B/T mixed phenotype acute leukemia reveals recurrent features and T-ALL like mutations. Am J Hematol. 2018;93(11):1358–67.
11. Hennawi M, Pakasticali N, Tashkandi H, Hussaini M. Genomic landscape of mixed-phenotype acute leukemia. Int J Mol Sci. 2022;23(19):11259.
12. Abdo Y, Gibson GD, Jain SP, Milner CP, Hilal T. Treatment of relapsed B/T-cell mixed phenotype acute leukemia with blinatumomab. Cureus. 2023;15(6):e40661.
13. Bartram J, Balasch-Carulla M, Bhojaraja S, Adams S, Cheng D, Inglott S, et al. Blinatumomab for paediatric mixed phenotype acute leukaemia. Br J Haematol. 2021;195(2):289–92.
14. Adriana P, Hélène L-W, Sandrine H, Gilles S, Xavier T, Pierre S. Efficiency of blinatumomab in a t(8;21) acute myeloid leukemia expressing CD19. Haematologica. 2019;104(10):e487–88.

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