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SHORT REPORT

Overcoming post-transplant graft failure and adenovirus infection in a patient with *FLT3*-TKD-mutated mixed-phenotype acute leukemia: A case report

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Abstract

Mixed-phenotype acute leukemia (MPAL) with *FLT3*-TKD mutations is a rare and challenging subtype of leukemia. Effective management strategies are crucial for improving patient outcomes. A 31-year-old man with *FLT3*-TKD-mutated MPAL achieved hematological remission through the JALSG ALL202-O protocol and gilteritinib, followed by cord blood transplantation (CBT). Post-transplant complications included adenovirus-induced hemorrhagic cystitis, managed with bladder irrigation and ribavirin, and engraftment failure, necessitating a second CBT on Day 35. Subsequent adenoviral conjunctivitis resolved with vidarabine. The patient achieved neutrophil engraftment by Day 76 and was discharged on Day 173 without relapse. This case highlights the importance of vigilant supportive care and tailored therapy in managing MPAL with *FLT3* mutations, especially in the context of post-transplant complications.

KEYWORDS
acute leukemia of ambiguous lineage, cord blood transplantation, *FLT3*-TKD, mixed-phenotype acute leukemia

1 | INTRODUCTION

Mixed-phenotype acute leukemia (MPAL) is a rare subtype of acute leukemia, classified as acute leukemia of ambiguous lineage (ALAL), characterized by blasts of multilineage origin (bilineage) or a blast expressing markers specific to several lineages (biphenotypic) [1]. MPAL can be further categorized into types with specific genetic abnormalities, such as *BCR-ABL1* fusion gene or *KMT2A* gene rearrangements, and types without these specific abnormalities. *FMS-like tyrosine kinase 3* (*FLT3*) mutations represent crucial genetic alterations in acute leukemia, primarily known as *FLT3*-ITD and *FLT3*-TKD mutations. The recent advent of FLT3 inhibitors has significantly impacted the treatment paradigm for acute myeloid leukemia (AML) [2]. In a genomic analysis of MPAL cases, *FLT3* mutations were detected in 16% (five out of 31 cases) [3]. However, the breakdown of *FLT3* mutation types and the clinical outcomes were not reported in this study. In addition, previous case reports have depicted clinical courses exclusively

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in *FLT3*-ITD-mutated MPAL cases [4–7], leaving the clinical course of *FLT3*-TKD mutation cases unreported.

Cord blood transplantation (CBT) is a promising curative therapy for MPAL, particularly in cases where bone marrow or peripheral blood stem cell donors are not available. However, CBT carries a higher risk of graft failure compared to other donor sources, leading to an increased risk of infectious complications [8]. Herein, we report a case of MPAL with *FLT3*-TKD mutation undergoing CBT. Notably, the patient adeptly navigates post-transplant graft failure and disseminated adenovirus infection. The clinical course offers invaluable insights for enhancing transplant management practices.

2 | CASE PRESENTATION

2.1 | Diagnosis and pretransplant course

A 31-year-old man was admitted to Yokohama Municipal Citizen's Hospital due to loss of consciousness. The initial blood count revealed a white blood cell count of 147,000/μL (blasts: 95.0%) with anemia (hemoglobin: 3.3 g/dL) and thrombocytopenia (platelet count 9000/μL), and an elevated lactate dehydrogenase level of 1391 U/L. Bone marrow examination revealed a predominance of two distinct blasts, constituting 87.3% of the cellularity: one is lymphoblast characterized by a high nuclear-to-cytoplasmic (N/C) ratio of 90%–100% with some nuclear indentations, and the other resembling monocytes with a finer chromatin pattern and an N/C ratio of 70%–80% (Figure 1A). Flow cytometry identified two blast populations: The first population expressed CD10+, CD19+, CD20−, CD22−, CD79a dim, and TdT−; the second expressed MPO dim, CD13+, CD33+, and CD14+ (Figure 1B). Cytogenetic analysis revealed the presence of 46,XY,add(19)(p13) in the 20 cells. *FLT3*-TKD mutation was detected as indicated in Table 1. Based on these findings, the patient was diagnosed with MPAL, B/myeloid [1].

The patient received induction chemotherapy according to the Japan Adult Leukemia Study Group ALL202-O protocol, consisting of cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase [9]. The bone marrow examination conducted on Day 30 following the initiation of induction chemotherapy showed a blast percentage of less than 5%, and no abnormal expressions were observed via flow cytometry, corresponding to a state of complete remission (CR). Cytogenetic analysis indicated a normal karyotype. As consolidation therapy, the patient expressed a preference for hematopoietic stem cell transplantation. With no eligible human leukocyte antigen (HLA)-identical or haploidentical donors, cord blood was selected as an alternative. However, desiring several weeks of convalescence at home before undergoing CBT, the patient commenced a regimen of oral gilteritinib (80 mg/day orally) to sustain remission.

2.2 | Post-transplant course (graft failure and salvage transplantation)

Following a 25-day regimen of gilteritinib, CBT was performed (Table 2 and Figure 2). The conditioning regimen included cytarabine (4 g/m^2), cyclophosphamide (120 mg/kg), and total body irradiation (TBI) at 12 Gy. Ensuing bone marrow examination prior to initiating the conditioning regimen confirmed the persistence of CR. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus (TAC) and mycophenolate mofetil (MMF). Antiviral prophylaxis consisted of acyclovir (500 mg/day intravenously [i.v.]) and letermovir (480 mg/day orally). On Day 20, bone marrow examination revealed a hypoplastic marrow, indicative of engraftment failure, as confirmed by recipient pattern in a short tandem repeat analysis. A salvage CBT was performed on Day 35 after first CBT. The conditioning regimen consisted of fludarabine (60 mg/m^2), cyclophosphamide (2 g/m^2), and TBI (2 Gy), based on a previous report [10]. On Day 59, a bone marrow smear revealed hypocellular marrow with 20.4% histiocytes and hemophagocytosis, leading to a diagnosis of hemophagocytic syndrome (HPS). Blood and urine cultures and serological tests revealed no bacterial or fungal infections. Viral infections including COVID-19, Epstein–Barr virus, cytomegalovirus, influenza virus, hepatitis B or C virus, herpes simplex virus, varicella-zoster virus, measles virus, human

TABLE 1 Results of gene mutation analysis in the present case.

Method	Mutation	Results
PCR followed by capillary electrophoresis	*FLT3*-TKD mutation	**VAF: 0.63**
	FLT3-ITD mutation	VAF: <0.05
Qualitative PCR	*FLT3*-TKD mutation	**Positive**
	FLT3-ITD mutation	Negative
	NPM1 mutation	Negative
	CEBPA mutation	Negative
	DNMT3A mutation	Negative
	IDH1 mutation	Negative
	IDH2 mutation	Negative
Quantitative PCR	Major *BCR-ABL1*	BDL
	Minor *BCR-ABL1*	BDL
	KMT2A-AFF1	BDL
	KMT2A-AFDN	BDL
	KMT2A-MLLT3	BDL
	KMT2A-MLLT1	BDL
	Major *BCR-ABL1*	BDL
	Minor *BCR-ABL1*	BDL
	PML-RARA	BDL
	RUNX1-RUNX1T1	BDL
	CBFB-MYH11	BDL
	DEK-NUP214	BDL
	NUP98-HOXA9	BDL
	ETV6-RUNX1	BDL
	TCF3-PBX1	BDL
	STIL-TAL1	BDL

Abbreviations: BDL, below the detection limit; PCR, polymerase chain reaction; VAF, variant allele frequency.
All analyses were conducted using bone marrow samples.

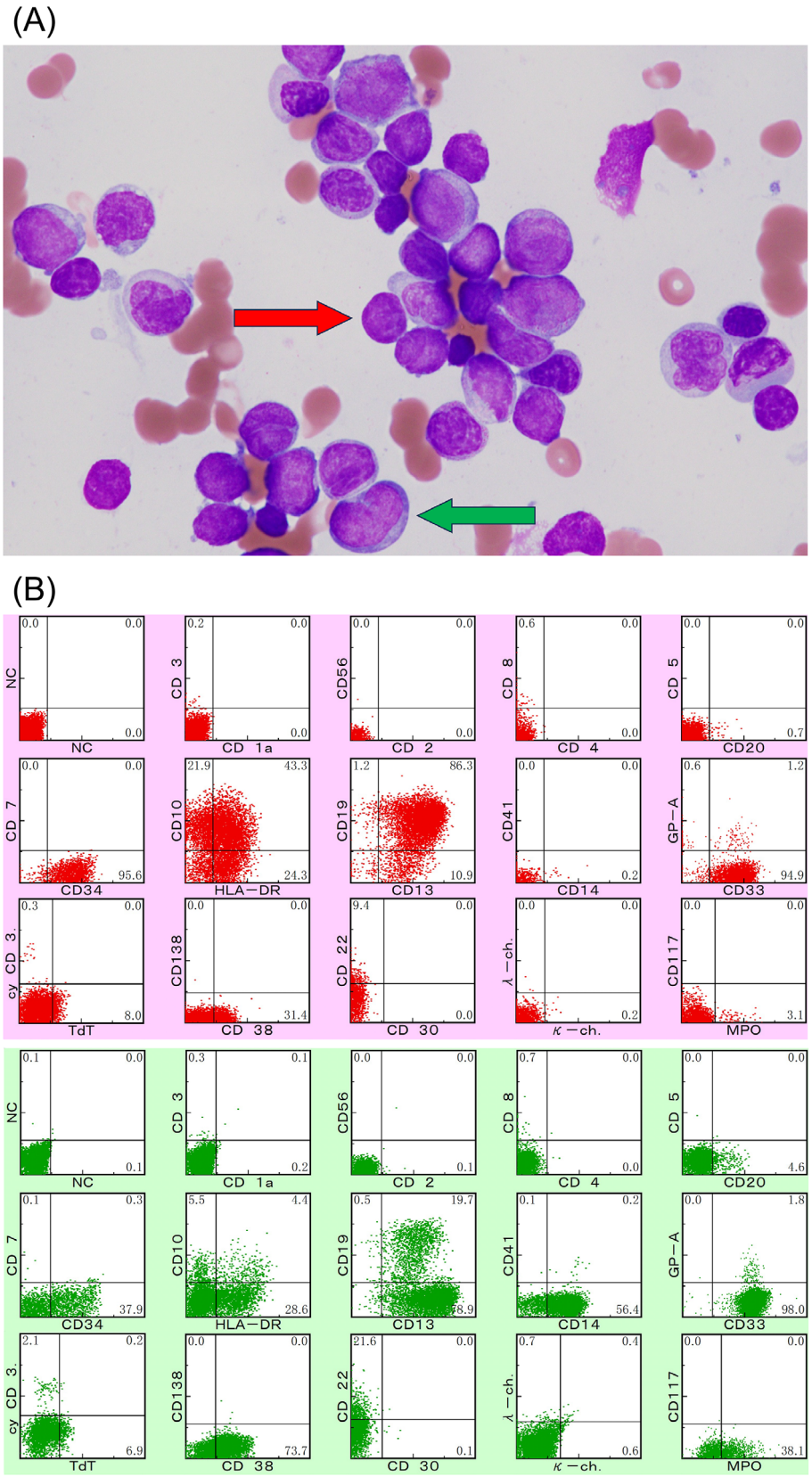

FIGURE 1 Results of bone marrow smear and flow cytometry analysis. (A) May–Giemsa staining of bone marrow smears shows two predominant blast populations: lymphoblasts with high nuclear-to-cytoplasmic ratios and slight nuclear indentations (red arrow), and myelomonocytic blasts with lower nuclear-to-cytoplasmic ratios and a finer chromatin pattern (green arrow). (B) Flow cytometric plots demonstrating the immunophenotypic profiles of the two distinct blast populations. The top panel (red) highlights the lymphoid blast population with dim CD79a expression and positivity for CD10 and CD19. The bottom panel (green) illustrates the myeloid blast population with dim myeloperoxidase expression and positivity for CD13, CD33, and CD14.

TABLE 2 Transplant modalities and outcomes in the present case.

	First CBT	Salvage CBT
Modalities		
Graft source		
TNC (/kg)	2.17×10^7	2.33×10^7
CD34 (/kg)	0.83×10^5	0.48×10^5
CFU-GM (/kg)	2.56×10^4	0.90×10^4
HLA compatibility	4/6	4/6
DSA	None	None
Conditioning regimen	Cytarabine (4 g/m^2)	Fludarabine (60 mg/m^2)
	Cyclophosphamide (120 mg/kg)	Cyclophosphamide (2 g/m^2)
	TBI (12 Gy)	TBI (2 Gy)
GVHD prophylaxis	Tacrolimus	Tacrolimus
	Mycophenolate mofetil	Mycophenolate mofetil
Outcomes		
Neutrophil engraftment	Failure	Day 76 after first CBT
Acute GVHD	None	Grade II (Gut stage 1)
Infection		
Bacteremia	None	None
CMV viremia/disease	None	None
Other virus infection	Adenovirus	Adenovirus
Fungal infection	None	None
Other complications	None	HPS, SOS

Abbreviations: CBT, cord blood transplantation; CFU-GM, colony forming unit-granulocyte macrophage; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HPS, hemophagocytic syndrome; SOS, sinusoidal obstruction syndrome; TBI, total body irradiation.

herpesvirus 6, and human immunodeficiency virus were excluded through antigen antibody testing and polymerase chain reaction (PCR) analysis. The patient was administered intravenous dexamethasone palmitate (10 mg/day). Donor chimerism was corroborated using sex chromosome fluorescence in situ hybridization (XX 97.2%). Neutrophil engraftment was achieved on Day 76. Platelet engraftment was achieved on Day 140. Due to suspicion of either upper gastrointestinal GVHD or adrenal insufficiency, the patient began receiving hydrocortisone (10 mg/day) on Day 157. The patient was discharged on Day 173 after first CBT. Thirteen months after first CBT, the patient still exhibited donor chimerism as evidenced by bone marrow examination and exhibited no apparent signs of extensive chronic GVHD.

2.3 | Post-transplant course (adenovirus infection)

Subsequent to the emergence of hematuria on Day 15 after first CBT, the patient was diagnosed with adenovirus-mediated hemorrhagic cystitis by urine PCR. This necessitated an alteration in the therapeutic approach from acyclovir to an intravenous administration of ganciclovir (500 mg/day) and vidarabine (500 mg/day), as delineated in Figure 2. Bladder irrigation commenced on Day 24. Due to worsening hematuria and suspected drug-induced bone marrow suppression, the antiviral regimen was changed from ganciclovir and vidarabine to acyclovir and ribavirin (1200 mg/day orally) on Day 29. The peak plasma adenovirus DNA level escalated to 1.1×10^6 copies/mL on Day 68. By Day 73, an amelioration in hematuria warranted the cessation of bladder irrigation. On Day 117, adenoviral conjunctivitis was diagnosed, accompanied by bloody tears, resulting in the administration of vidarabine (500 mg/day i.v.). The subsequent absence of detectable plasma adenovirus DNA precipitated the discontinuation of vidarabine therapy on Day 154 after first CBT.

3 | DISCUSSION

To thoroughly investigate this unique case, we sought out reports of ALAL with *FLT3* mutation by conducting a search in PubMed with terms ("acute leukemia of ambiguous lineage" or "ALAL" or "mixed-phenotype acute leukemia" or "MPAL" or "acute undifferentiated leukemias" or "AUL") and ("FLT3" or "FMS-like receptor tyrosine kinase 3"). Pediatric patients were excluded from the study. The lineage assignment of ALAL was based on a previous report [1]. Table 3 displays a literature review of eight cases of ALAL with *FLT3* mutation including our own case [4–7]. The median age was 55 years (range: 36–78 years), with four patients (50.0%) being male. FLT3 inhibitors were used in two cases (25.0%) with gilteritinib, three (37.5%) with sorafenib, and five (62.5%) with midostaurin. Allogeneic hematopoietic stem cell transplantation

TABLE 3 Literature review on acute leukemia of ambiguous lineage with *FLT3* mutation.

Reference	Age/sex	Subtype of ALAL	Karyotype	*FLT3* mutation	Concomitant mutations	Chemotherapy	Response	HSCT	Donor source	Conditioning regimen	Post-transplant FLT3i	Interval from HSCT to FLT3i	Outcome
Present case	31/M	MPAL, B/myeloid	46,XY, add(19)(p13)	TKD	*WT1*	• JALSG ALL 202-O protocol • Gilteritinib	CR	Yes	CB	CA+CY+TBI	No use	–	Alive 12 months postdiagnosis
4	55/F	MPAL, T/myeloid	Normal	ITD	*U2AF1*	• DFCI protocol • FLAG-IDA • Midostaurin • Midostaurin+CA	CR	Yes	MUD	FLU+BU+TBI	Sorafenib	3 months	Alive 13 months postdiagnosis
	78/F	MPAL, T/myeloid	46,XX, del16(q22)	ITD	*RUNX1* *U2AF1*	• DFCI protocol • Sorafenib	CR	No	–	–	–	–	Alive 14 months postdiagnosis
5	36/F	MPAL, T/myeloid	12p deletion	ITD	None	• Midostaurin+CA+DNR+PSL • Midostaurin+CA+Clo	CR	Yes	CB	RIC	No use	–	Alive 28 months postinduction therapy
	65/M	MPAL, B/myeloid	Normal	ITD	*ASXL1* *RUNX1*	• Midostaurin+CA+DNR+VCR • Midostaurin+CA	CRi	Yes	MUD	MAC	No use	–	Alive 31 months postinduction therapy
	45/M	MPAL, B/myeloid	Normal	ITD	*DNMT3A* *RUNX1*	• CA+DNR+VCR+PSL • Midostaurin+CA	CR	Yes	MRD	MAC	Sorafenib	4 months	Alive 11 months postinduction therapy
6	55/F	MPAL, B/myeloid	47,XX,+6	ITD	*RUNX1* *WT1*	• Hyper-CVAD+Midostaurin • Hyper-CVAD • Gilteritinib • Gilteritinib+AZA	NA	No	–	–	–	–	Alive under Gilteritinib+AZA
7	65/M	ALAL, NOS	NA	ITD	*WT1*	• FLAG-IDA+Midostaurin	CR	Yes	NA	NA	NA	NA	Death due to TRM post-HSCT

Abbreviations: ALAL, acute leukemia of ambiguous lineage; AZA, azacitidine; BU, busulfan; CA, cytarabine; CB, cord blood; Clo, clofarabine; CR, complete remission; CRi, complete remission with incomplete blood count recovery; CY, cyclophosphamide; DFCI, Dana–Farber Cancer Institute; DNR, daunorubicin; F, female; FLAG-IDA, fludarabine, cytarabine, granulocyte colony-stimulating factor, idarubicin; FLT3i, FLT3 inhibitor; FLU, fludarabine; HSCT, hematopoietic stem cell transplantation; Hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ITD, internal tandem duplication; JALSG, Japan Adult Leukemia Study Group; M, male; MAC, myeloablative conditioning; MPAL, mixed-phenotype acute leukemia; MRD, matched related donor; MUD, matched unrelated donor; NA, not available; PSL, prednisolone; RIC, reduced intensity conditioning; TBI, total body irradiation; TKD, tyrosine kinase domain; TRM, transplant-related mortality; VCR, vincristine.

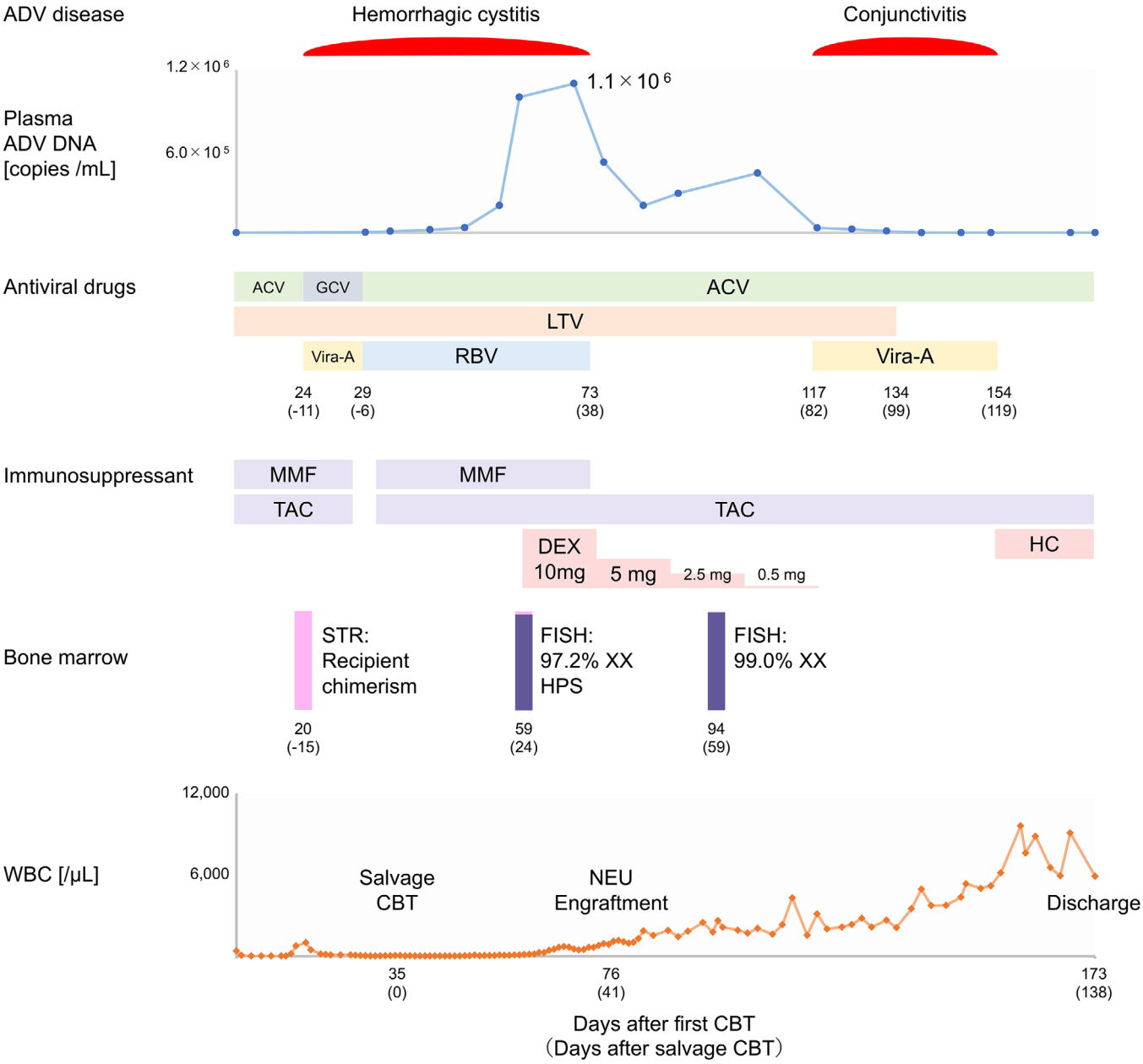

FIGURE 2 Clinical course of the present case. ACV, acyclovir; ADV, adenovirus; CBT, cord blood transplantation; DEX, dexamethasone palmitate; FISH, fluorescence in situ hybridization; GCV, ganciclovir; HC, hydrocortisone; LTV, letermovir; MMF, mycophenolate mofetil; NEU, neutrophil; RBV, ribavirin; STR, short tandem repeat; TAC, tacrolimus; Vira-A, vidarabine; WBC, white blood cell.

was performed in six cases (75.0%). Among them, two patients used FLT3 inhibitors as post-transplant maintenance therapy. All patients except for one [7] were reported to be alive at the time of reporting. FLT3 inhibitors have improved the prognosis of *FLT3*-mutated AML [2]. In our literature review of ALAL cases, favorable outcomes were documented; however, further validation through the accumulation of additional cases with *FLT3* mutations is essential. The present case is the only one with an *FLT3*-TKD mutation that could be found in the literature review, which underscores its novelty. *FLT3*-TKD mutations in AML are considered to have a more favorable prognosis than *FLT3*-ITD mutations [11]. In the present case, the patient maintained CR after induction chemotherapy, exemplifying a valuable clinical course in a rare disease. However, the significance of *FLT3*-TKD mutations in MPAL requires further validation.

As of April 2024, in Japan, gilteritinib and quizartinib are approved for leukemia treatment as FLT3 inhibitors. Among these, only gilteritinib, a type I inhibitor, is considered effective for *FLT3*-TKD mutations [2]. According to a recent randomized trial, post-transplant gilteritinib administration for *FLT3*-ITD-mutated AML extended relapse-free survival, although statistical significance could not be reached [12]. As cases with MPAL were not included in this study, the indication for maintenance therapy in this subtype remains unclear. In the

present case, due to the decreased performance status resulting from post-transplant complications including adenovirus infection, initiation of maintenance therapy could not be started promptly. Further accumulation of cases is essential to establish optimal strategies for post-transplant maintenance therapy in MPAL.

Several large-scale studies have reported outcomes of allogeneic transplantation for MPAL; however, cases receiving CBT are extremely rare [13]. In this case, owing to the unavailability of related donors, cord blood was chosen because of its capacity for the most rapid preparation from unrelated donors. However, the CBT for the present case necessitated salvage CBT due to graft failure. The patient did not have risk factors for engraftment failure, such as a low transfused cell count or the presence of donor-specific anti-HLA antibodies. One potential explanation for graft failure could be attributed to HPS, as it has been reported as one of the factors contributing to engraftment failure in CBT [14]. Additionally, adenovirus has been documented as a trigger for HPS in pediatric cases [15]. In the present case, with the exclusion of other infections, malignancies, and autoimmune diseases, adenovirus-induced HPS remains a plausible consideration. Over time, engraftment rates for CBT in AML have improved, and a reduction in nonrelapse mortality has been reported, contributing to improved outcomes [16]. Accumulation of further evidence on CBT for MPAL is anticipated to reduce complications, such as engraftment failure.

According to a literature review of adenoviral infections after allogeneic transplantation, the most common site of infection was disseminated (50%), followed by hepatic infection (8%), and hemorrhagic cystitis (8%). Cidofovir was administered in 40.9% of the cases, with a reported mortality rate of 34.4%. Ribavirin was administered as monotherapy in 15.9% of the cases, with a mortality rate of 57.1%. The choice of antiviral drug did not have a statistically significant impact on mortality [17]. Cidofovir is not approved in Japan, and in the present case, we referred to previous case reports and selected ganciclovir, ribavirin, and vidarabine [18, 19]. Although the potentially fatal consequences of disseminated infection before engraftment are concerning, diligent supportive therapy, including bladder irrigation, successfully controlled the situation. We anticipate that future reports detailing successful treatments for adenoviral cystitis will accumulate and pave the way for more refined strategies.

In conclusion, the successful management of *FLT3*-TKD mutation-positive MPAL with an FLT3 inhibitor and CBT illustrates an ideal course of treatment for this rare subtype. Although the present patient experienced disseminated adenovirus infection prior to engraftment, they made a remarkable recovery with the integration of intensive supportive care. Continued accumulation of cases and evidence will further refine therapeutic strategies to benefit similar patients.

AUTHOR CONTRIBUTIONS

Yusuke Takada and Shuhei Kurosawa drafted the manuscript. Toshimitsu Ueki, Yuho Najima, and Tomonori Nakazato critically revised the manuscript. Satoshi Wakita and Hiroki Yamaguchi supported the diagnostic process. All the authors provided patient care and approved the final version of the manuscript.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

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INFORMED CONSENT

The patient provided written informed consent for the publication of this article.

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

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