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【 CASE REPORT 】

Successful Cord Blood Transplantation for Myeloid/Natural Killer Precursor Acute Leukemia: A Case Report and Literature Review

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Abstract:

A 21-year-old man was diagnosed with myeloid/natural killer precursor leukemia (MNKPL) with bone marrow infiltration of blasts of cyCD3^{+}, CD7^{+}, CD33^{+}, CD34^{dim}, CD56$^{+/-}$, HLA-DR^{+}, cyMPO^{+}, and TdT^{-} immunophenotypes. Although hyper-hyperfractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone therapy was unsuccessful, induction treatment with idarubicin and cytarabine resulted in complete remission (CR). The patient subsequently underwent cord blood transplantation with a myeloablative conditioning regimen, which resulted in durable CR and complete donor chimerism. He had been in good health without relapse for over nine months since transplantation. Timely allogeneic hematopoietic stem cell transplantation using an available donor source may be a promising treatment strategy for MNKPL.

Key words: myeloid/natural killer precursor acute leukemia, allogeneic hematopoietic stem cell transplantation, cord blood transplantation

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Introduction

Myeloid/natural killer (NK) precursor acute leukemia (MNKPL) is a rare type of acute leukemia characterized by immature lymphoblastoid morphology with negative myeloperoxidase reactivity, azurophilic granules, and an immunophenotype suggesting a commitment to both NK and myeloid cell lineages. Although the clinicopathological features of MNKPL have not been fully elucidated because of its rarity, it is frequently refractory to chemotherapy and is associated with a poor prognosis. Furthermore, standard and optimal treatment strategies for MNKPL have not been established.

We herein report a case of MNKPL that was successfully treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) after achieving complete remission (CR) and review the literature on reported cases of MNKPL in which allo-HSCT was performed.

Case Report

A 21-year-old man with a fever and visual disturbance for several days presented to our department with pancytopenia. The patient had a good general health status and a mild fever. An ophthalmological examination revealed slight retinal hemorrhaging. A complete blood test revealed severe neutropenia with the emergence of blasts (white blood cell count of 600/μL, with 14% neutrophils, 68% lymphocytes, and 18% blasts) and anemia (hemoglobin 6.5 g/dL), with mild thrombocytopenia (13.4×10^{4}/μL). Coagulation tests revealed a slight elevation in fibrin degenerative products (5.3 μg/mL)

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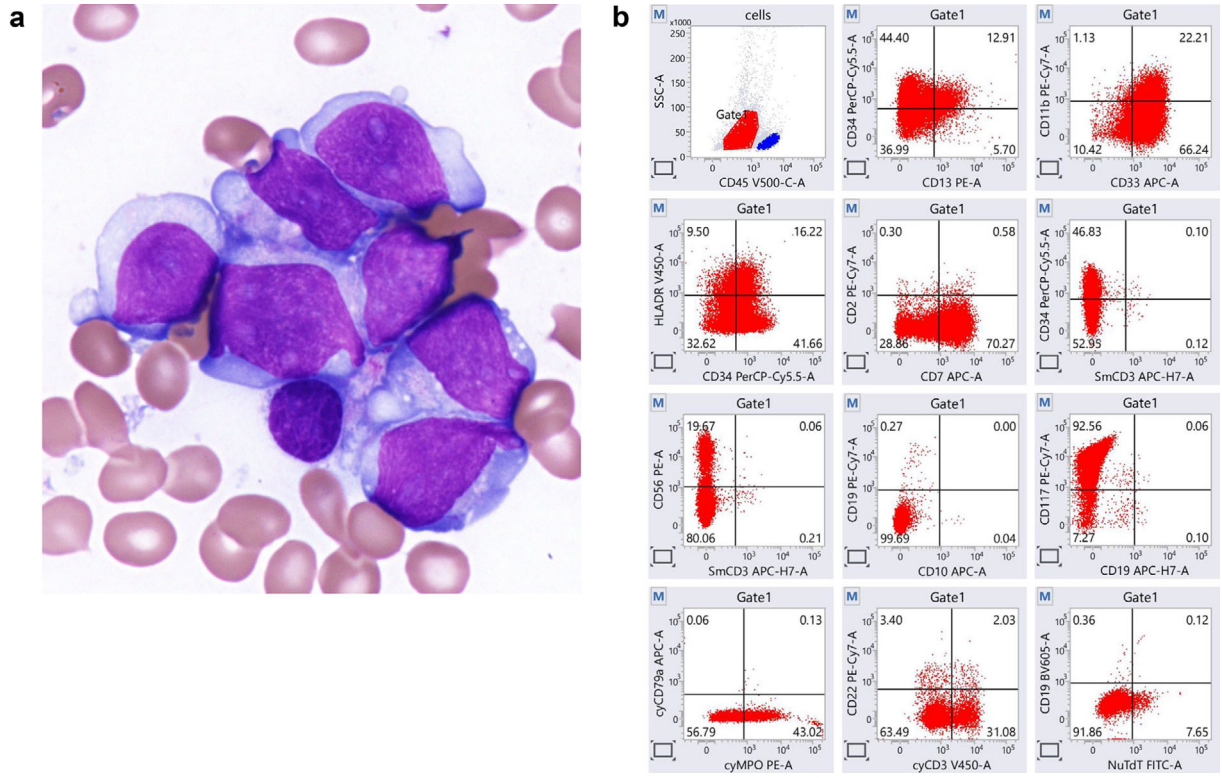

Figure 1. Leukemic blasts of bone marrow at the diagnosis. (a) Morphological findings of leukemic blasts (May-Giemsa staining, ×40). (b) Flow cytometry findings with CD45-gating. The population with dimly expressed CD45 cells (red dots) is a leukemic blast population.

with a normal concentration of fibrinogen (392 mg/dL). Biochemical tests revealed normal lactic dehydrogenase levels (163 IU/L) and a normal liver and renal function. A high WT1 mRNA level in the peripheral blood was observed (1.6 $\times 10^5$ copies/μg RNA).

Computed tomography revealed no apparent infection foci, extramedullary lesions, or lymphadenopathies. Bone marrow aspiration revealed massive infiltration of large blasts with a fine chromatin meshwork, conspicuous nucleoli, and relatively large cytoplasm with minimal azurophilic granules (Fig. 1a). They tested negative for myeloperoxidase (MPO) staining, and a flow cytometry analysis revealed a slightly CD45-positive cell population showing universal positivity for CD33 and CD117. They also revealed immunophenotypes of $CD13^{dim}$, $CD34^{dim}$, $HLA\text{-}DR^{+/-}$, $CD7^{+}$, $CD56^{+/-}$, $CD2^{-}$, surface $CD3^{-}$, cytoplasmic $CD3^{+/-}$, $CD4^{-}$, $CD5^{-}$, $CD8^{-}$, $CD19^{-}$, $CD22^{-}$, $CD99^{+}$, $TCR\alpha\beta^{-}$, $TCR\gamma\delta^{-}$, cytoplasmic $MPO^{+/-}$, and TdT^{-} (Fig. 1b). Based on these findings, the diagnosis of MNKPL was established. A G-band analysis revealed the following karyotype: 46,XY,add(1)(p32)[10]/47,XY,+21[3]/46,XY[7].

The patient's clinical course is shown in Fig. 2. On the second day after admission, the patient experienced anaphylactic shock after an intrathecal injection of methotrexate, cytarabine, and dexamethasone, which improved with the administration of a catecholamine and steroid. No abnormal findings were observed in the cerebrospinal fluid.

The patient was initially treated with a hyper-fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone (CVAD) regimen for remission induction consisting of cyclophosphamide, vincristine, doxorubicin, and dexamethasone, which resulted in a reduction in blasts in the peripheral blood. However, neutrophil recovery was not observed even after one month, and a bone marrow examination showed residual blasts. After confirming the absence of hypersensitivity to cytarabine, the patient was treated with idarubicin and cytarabine as reinduction chemotherapy.

After one month, hematological recovery was achieved, and CR was established. Considering the poor prognosis associated with MNKPL, we decided to promptly perform allo-HSCT with an available cord blood unit. The conditioning regimen consisted of total body irradiation (12 Gy in 6 fractions), high-dose cyclophosphamide (60 mg/kg/day for 2 days), and high-dose cytarabine (2,000 mg/m^2 every 12 h for 2 days). The number of infused cord blood cells was 2.39×10^7/kg (CD34-positive cells: 0.93×10^5/kg). The HLA antigen and transplanted cord blood alleles were mismatched at three of the eight loci.

Tacrolimus and mycophenolate mofetil were administered as prophylaxis for graft-versus-host disease (GVHD). Soon after the transplantation, the patient developed a high-grade fever and swelling of the buttocks. *Clostridium perfringens* bacteremia was established using blood culture, which improved with intensive antibiotic treatment, intravenous immunoglobulin, and granulocyte infusion. Neutrophil engraft-

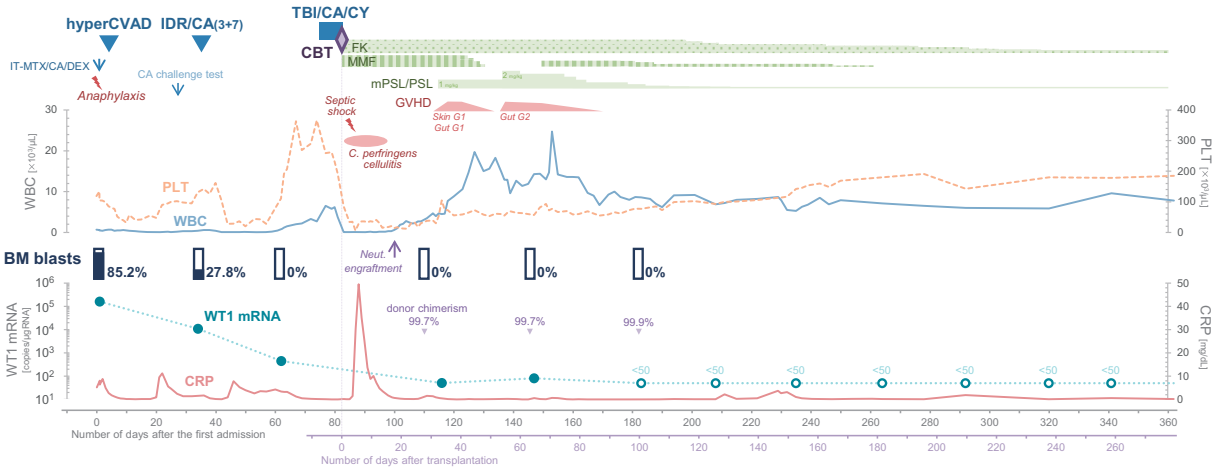

Figure 2. **Clinical course. BM: bone marrow, CA: cytarabine, CBT: cord blood transplantation, CY: cyclophosphamide, FK: tacrolimus, GVHD: graft-versus-host disease, hyper-CVAD: hyperfractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone, IT: intrathecal chemotherapy, MMF: mycophenolate mofetil, mPSL: methylprednisolone, PLT: platelet, PSL: prednisolone, MTX: methotrexate, TBI: total body irradiation, WBC: white blood cell**

ment was achieved on day 18, and full donor chimerism was established according to a bone marrow examination on day 28. Thereafter, acute GVHD of the skin (grade 1) and gut (grade 2) developed, which was controlled with steroid administration. The patient was discharged in good health on day 107 of hospitalization. CR has been sustained for more than nine months since transplantation.

Discussion

MNKPL is a rare subtype of acute leukemia, with both myeloid and NK cell phenotypes. Leukemic cells are characterized by an immature lymphoblastoid morphology without MPO reactivity or azurophilic granules, and have a $CD7^+$, $CD33^+$, $CD56^+$, $CD34^+$, $HLA\text{-}DR^+$, and TdT^- immunophenotype (1, 2). The latest 5th edition of the World Health Organization classification of myeloid neoplasms and acute leukemia does not mention MNKPL; it includes mixed-phenotype acute leukemia (MPAL), rare types, or acute leukemia of ambiguous lineage, not otherwise specified (3). Our patient was diagnosed with acute myeloid leukemia (AML) with minimal differentiation or CD56-positive AML; however, it was recently confirmed that MNKPL is genetically distinct from AML, T cell acute lymphoblastic leukemia, and MPAL and is characterized by NOTCH1 and RUNX3 activation and BCL11B downregulation (2). In the present case, although there was a wide range in the intensity of CD56 positivity, $CD7^+$, $CD33^+$, and TdT^- phenotypes were consistently observed, consistent with the diagnosis of MNKPL. In addition, favorable reactivity to an AML-type induction regimen, but not to an acute lymphoblastic leukemia-type regimen (i.e., hyperCVAD), might clinically support the diagnosis of MNKPL but not MPAL, for which AML-type regimens are less likely to achieve CR than ALL-type regimens (4).

MNKPL is associated with a poor prognosis, and a standard treatment strategy has not yet been established. It is reportedly refractory to CHOP-based chemotherapy regimens for lymphoid malignancies and is responsive to AML regimens (1). Recent studies have shown that conventional AML-type chemotherapy combined with L-asparaginase (L-Asp) can improve the prognosis of MNKPL (2). A novel regimen consisting of azacitidine and venetoclax (AZA/VEN) may be effective against MNKPL (5). Nevertheless, a long-term survival is rarely achieved with chemotherapy alone, and allo-HSCT may be required to cure this disease.

Several cases of MNKPL in which allo-HSCT was performed have been reported, and their characteristics and courses are summarized in Table. Their clinical features vary, including age and leukemic cell count in the peripheral blood at the diagnosis, which do not seem to be associated with the prognosis. As for remission induction therapy, AML regimens resulted in CR in five cases, whereas CR was achieved with ALL regimens in only one case. L-Asp administration after AML-type chemotherapy resulted in CR in two additional cases. A long-term survival without disease relapse was achieved in only five cases, including the present case, in which allo-HSCT was performed after CR was confirmed using various chemotherapies. Donor sources of allo-HSCT were cord blood in three cases, haploidentical donors in one case, and HLA-matched unrelated donors in one case. As for cord blood and haploidentical donors as a donor source, flexibility in the timing of transplantation and some HLA disparities, which could be associated with the exertion of the graft-versus-leukemia effect, might contribute to sustained disease control. Myeloablative conditioning regimens, including total-body irradiation, were administered to all patients with available information. Considering the above, MNKPL may be able to be most successfully treated with an initial AML-type induction regimen with or without

Table. **Reported Cases of MNKPL in Which allo-HSCT Was Performed.**

Reference	Age/Sex	WBC count at diagnosis (% of blasts)	Extramedullary lesions	Pretransplant therapy	Disease status at transplantation	Donor source	Conditioning regimen	Clinical course and outcome*
(6)	18/M	12,000/μL (98%)	LN	[ALL] → CR	CR	HLA-matched sibling	TBI/CA/CY	Relapsed after 4 years, died of VOD
(1)	19/M	1,300/μL (11%)	LN	CHOP+L-Asp → NR, [AML] → CR	CR	HLA-matched sibling	N/A	Relapsed after 13 months, died of leukemia after 19 months
(1)	29/F	1,100/μL (5%)	None	[AML] → CR	CR	HLA-matched sibling	N/A	Died of GVHD after 19 months
(7)	13/M	1,700/μL (0%)	LN	[AML] → CR1 → relapse, various regimens → CR2	CR	HLA-matched unrelated	TBI/MEL	Alive without leukemia for >2 years
(8)	34/M	N/A	N/A	N/A	CR	HLA-matched unrelated	TBI/CY	Relapsed after 10 months
(9)	36/M	36,000/μL (71%)	Skin	[AML] → CR	NR	HLA-matched unrelated	TBI/CY	MDS after 7 months (in CR for MNKPL), died of infection after 9 months
(10)	1/M	10,400/μL (0%)	Skin	[AML] → NR, [ALL] → NR	NR	Haploidentical	TBI/MEL	Relapsed after 2 months, died of sepsis
(11)	17/M	9,600/μL (64%)	None	[AML] → NR, [ALL] → NR, [HDAC] → NR	NR	Haploidentical	TBI/VP/CY	Relapsed after 5 months → 2nd CR by cessation of IST, DLI → relapse (2.2 years)
(5)	46/F	95,200/μL (97%)	LN, pleural and pericardial effusion	[AML] → NR, [HDAC] → NR, VEN/AZA → CR	CR	Haploidentical	N/A	Alive without leukemia for >2 years**
(12)	2/M	11,300/μL (33%)	LN	[ALL] → NR, [AML] → NR, L-Asp → CR	CR	Cord blood	TBI/CA/CY	Alive without disease for >2 years
(13)	6/F	58,800/μL (92%)	None	[AML] → NR, L-Asp → CR	CR	Cord blood	TBI/VP/CY	Alive without leukemia >3.8 years
This case	21/M	600/μL (18%)	None	[ALL] → NR, [AML] → CR	CR	Cord blood	TBI/CA/CY	Alive without leukemia for >9 months

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CA: cytarabine, CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone, CR: complete remission, CY: cyclophosphamide, DLI: donor lymphocyte infusion, F: female, GVHD: graft-versus-host disease, HDAC: regimen based on high-dose cytarabine, HLA: human leukocyte antigen, IST: immunosuppressant, L-Asp: L-asparaginase, LN: lymph node, M: male, MEL: melphalan, MDS: myelodysplastic syndrome, MNKPL: myeloid/natural killer precursor acute leukemia, N/A: not available, NR: non-remission, TBI: total body irradiation, VEN/AZA: venetoclax and azacitidine, VOD: veno-occlusive disease, VP: etoposide

*The duration described is counted from when allo-HSCT was performed.

**The duration described is counted from the diagnosis.

L-Asp, resulting in CR and immediate myeloablative allo-HSCT utilizing an available donor source at that time, if possible. However, it is unknown whether allo-HSCT with reduced-intensity conditioning is also effective for MNKPL in patients unfit for myeloablative regimens.

In summary, we encountered a case of MNKPL in which a sustained disease-free survival was achieved by cord blood transplantation under CR. The prompt performance of myeloablative allo-HSCT in CR utilizing an available donor source may be a reasonable treatment strategy.

The authors state that they have no Conflict of Interest (COI).

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