Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6796-20
Intern Med 60: 3015-3019, 2021
http://internmed.jp

【 CASE REPORT 】

Salvage Cord Blood Transplantation for Sustained Remission of Acute Megakaryoblastic Leukemia That Relapsed Early after Myeloablative Transplantation

Satoshi Ichikawa[1], Tohru Fujiwara[1], Kei Saito[1], Kazuki Sakurai[1], Kyoko Inokura[1], Noriko Fukuhara[1], Hisayuki Yokoyama[1], Koichi Onodera[1], Yasushi Onishi[1], Junichi Kameoka[2] and Hideo Harigae[1]

Abstract:

Acute megakaryoblastic leukemia (AMKL) is a rare subtype of acute myeloid leukemia accompanied by an aggressive clinical course and dismal prognosis. We herein report a case of AMKL preceded by mediastinal germ cell tumor that relapsed early after allogeneic hematopoietic stem cell transplantation with myeloablative conditioning but was successfully treated using salvage cord blood transplantation (CBT) with reduced-intensity conditioning. Although several serious complications developed, sustained remission with a favorable general condition was ultimately achieved. Although an optimal therapeutic strategy remains to be established, the graft-versus-leukemia effect of CBT may be promising, even for the treatment of refractory AMKL.

Key words: acute megakaryoblastic leukemia, allogeneic hematopoietic stem cell transplantation, cord blood transplantation, mediastinal germ cell tumor, disseminated fusariosis

(Intern Med 60: 3015-3019, 2021)
(DOI: 10.2169/internalmedicine.6796-20)

Introduction

Acute megakaryoblastic leukemia (AMKL) is a rare subtype of acute myeloid leukemia (AML) originating from megakaryoblasts. AMKL is a well-known malignancy occurring in children with Down syndrome (1); however, AMKL is rare among adults, with a reported incidence rate of less than 1% among all AML cases in a large study on patients with AML (2, 3). Some AMKL cases are associated with mediastinal non-seminomatous germ cell tumor (MGCT), and fewer than 30 such cases have been reported (4).

AMKL in adults is usually accompanied with an aggressive clinical course and is associated with worse clinical outcomes than other types of AML (2, 3). Furthermore, its prognosis is extremely poor, even after allogenic hematopoietic stem cell transplantation (alloHCT), compared with other types of AML (5). The prognosis of AMKL associated with MGCT is also dismal, and only a few cases documented in the literature have shown long-term remission after alloHCT (6, 7).

We herein report a case of AMKL that developed after resection of MGCT that relapsed early after the first conventional alloHCT session from a human leukocyte antigen (HLA)-matched sibling. However, subsequent cord blood transplantation (CBT) resulted in sustained remission of AMKL. To our knowledge, this is the first reported case of refractory AMKL for which salvage reduced-intensity alloHCT using cord blood resulted in long-term remission.

Case Report

A 26-year-old man who was an office worker and in good health suffered from worsening dyspnea. He had previously

[1]Department of Hematology, Tohoku University Hospital, Japan and [2]Department of Hematology and Rheumatology, Tohoku Medical and Pharmaceutical University Hospital, Japan
Received: November 30, 2020; Accepted: February 16, 2021; Advance Publication by J-STAGE: April 5, 2021
Correspondence to Dr. Satoshi Ichikawa, satoshi.ichikawa.b4@tohoku.ac.jp

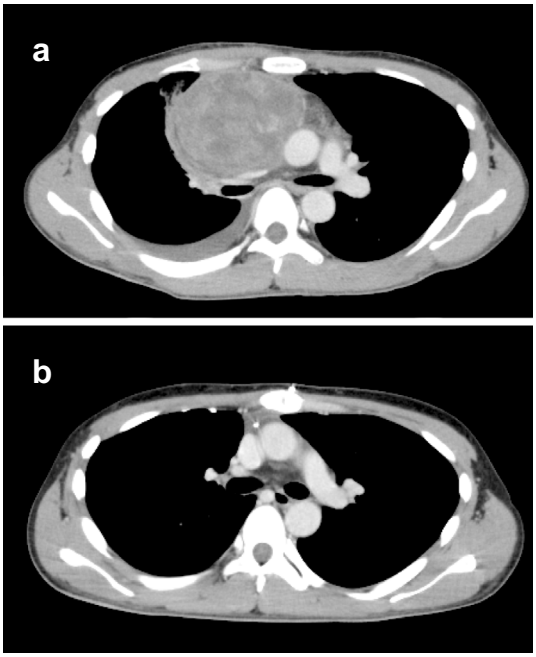

Figure 1. Computed tomography findings of the mediastinal germ cell tumor at the diagnosis (a) and at the presentation at our department (b).

been diagnosed with MGCT following detection of a bulky mediastinal tumor by computed tomography (CT; Fig. 1a) and elevated levels of serum α-fetoprotein (AFP, 811 ng/mL). The tumor was curatively resected (Fig. 1b) and pathologically diagnosed as teratoma with a malignant component. There were no particular issues in the postoperative clinical course. Five months after the surgery, he developed a sustained fever, malaise, and anorexia and was thus referred to us due to suspicion of an aggressive hematological malignancy based on progressive pancytopenia and the extreme elevation of serum lactate dehydrogenase (LD) levels.

Upon presentation, he was generally ill because of his fever, malaise, and abdominal distention. Complete blood tests revealed neutropenia with the emergence of myeloid progenitors and blasts (2,900/μL, with neutrophils 37%, eosinophils 3%, lymphocytes 30%, monocytes 10%, metamyelocytes 7%, myelocytes 6%, promyelocytes 1%, and blasts 6%), mild anemia (11.3 g/dL, corrected with red cell transfusion by the previous doctor), and severe thrombocytopenia (19,000/μL). Biochemistry analyses showed the marked elevation of LD (8,664 IU/L) and C-reactive protein (CRP, 15.73 mg/dL). The WT1 mRNA expression was markedly increased (2.4×10^4 copies/μgRNA). CT showed hepatosplenomegaly and sporadic osteolytic lesions in the spine and pelvis without recurrence or metastasis of MGCT. An attempt to aspirate bone marrow resulted in a dry tap, but large blastoid cells with marked nuclear atypia and basophilic cytoplasm were found within the barely aspirated marrow (Fig. 2a). The blasts in peripheral blood and bone marrow were $CD45^{dim+}$, $CD36^+$, $CD41^+$, $CD56^+$, $CD19^-$, $CD3^-$, $CD13^-$, $CD33^-$, $CD34^-$, and $HLA\text{-}DR^-$ on flow cytometry (Fig. 2b). A G-band analysis showed a complex karyotype in one of four evaluable cells, which could not be assessed as a significant finding. A bone marrow biopsy revealed the marked proliferation of multinuclear megakaryoblast-like aberrant cells with conspicuous nucleoli and blastoid cells with a high nuleocytoplasm ratio (Fig. 2c, d) that were positive for CD42b (Fig. 2e) and negative for myeloperoxidase. Furthermore, the expansion of interstitial reticular fibers was revealed on silver impregnation staining, which was deemed indicative of grade 2 myelofibrosis (Fig. 2f). Based on the above findings, the patient was diagnosed with AMKL.

The clinical course of the patient is shown in Fig. 3. He was successfully treated with conventional induction remission chemotherapy comprising daunorubicin (50 mg/m^2 for 5 days) and cytarabine (100 mg/m^2 for 7 days), and complete remission (CR) was confirmed 4 weeks after the initiation of the treatment. After subsequent consolidation chemotherapy with mitoxantrone (7 mg/m^2 for 3 days) and cytarabine (200 mg/m^2 for 5 days), he received allogeneic peripheral blood stem cell transplantation from an HLA-matched sibling with a conditioning regimen consisting of high-dose cyclophosphamide (60 mg/kg for 2 days) and total body irradiation (12 Gy in 6 fractions). Prophylaxis for graft-versus-host disease (GVHD) comprised cyclosporine and short-term methotrexate. Regimen-related toxicities, such as febrile neutropenia and gastrointestinal mucosal damage, were controllable. Neutrophil engraftment was achieved at day 11, and full donor chimerism was established at day 28. Stage 1 acute GVHD developed in the skin but was well-controlled by temporary administration of corticosteroids.

However, from around day 60, he began suffering from lumbago with progressive elevation of LD and CRP levels. Although leukemic blasts could not be detected in the peripheral blood, the WT1 mRNA expression was markedly increased (1.2×10^4 copies/μgRNA). A definite relapse of AMKL with myelofibrosis was confirmed by a bone marrow examination on day 74 (Fig. 2g, h), without the detection of cytogenetic aberrations by a G-banding analysis. At this time, biochemistry analyses showed the marked elevation of LD (710 IU/L) and CRP (24.87 mg/dL). Thereafter, dose-modified chemotherapy with daunorubicin (40 mg/m^2 for 3 days) and cytarabine (160 mg/m^2 for 5 days) was initiated with the abrupt cessation of immunosuppressants. Skin GVHD developed but was well-controlled using steroid ointment. Although hematological CR was achieved temporarily, leukemic blasts were increased (evaluated by a bone marrow biopsy) after consolidative chemotherapy with high-dose cytarabine (6 doses of 2,000 mg/m^2 each). Subsequently, the patient received CBT with a conditioning regimen comprising fludarabine (30 mg/m^2 for 6 days), busulfan (3.2 mg/kg for 4 days), and melphalan (40 mg/m^2 for 2 days). The number of infused cord blood cells was 2.71×10^7/kg ($CD34^+$ cells, 0.66×10^5/kg). HLA of the graft alleles was mismatched at four of eight loci in both the graft-versus-host and host-versus-graft directions. Prophylaxis for GVHD included tacrolimus and short-term methotrexate. Neutrophil

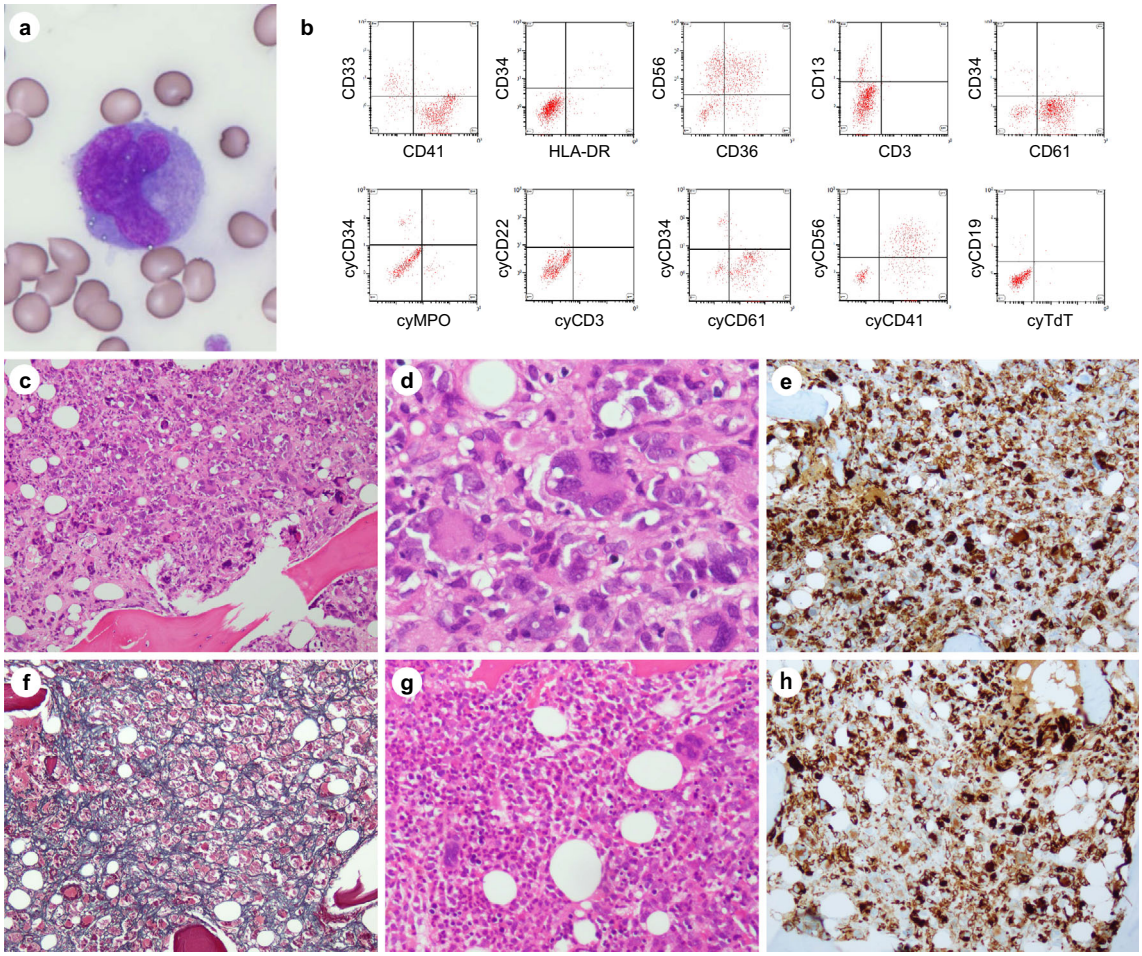

Figure 2. **Diagnostic findings of acute megakaryoblastic leukemia in the bone marrow. (a) May-Giemsa staining showed large blastoid cells with marked nuclear atypia and basophilic cytoplasm. (b) Flow cytometry revealed an abnormal cell population, comprising CD45^{dim+}, CD36^{+}, CD41^{+}, CD56^{+}, CD19^{-}, CD3^{-}, CD13^{-}, CD33^{-}, CD34^{-}, and HLA-DR^{-}. (c, d) Hematoxylin and Eosin staining showed the marked proliferation of multinuclear megakaryoblast-like cells with conspicuous nucleoli and blastoid cells with a high nuleocytoplasm ratio (c; ×10, d; ×100). (e) CD42b positivity was detected by immunohistochemistry. (f) Bone marrow fibrosis was revealed by silver staining. (g, h) The bone marrow biopsy at day 74 of the first transplantation showed proliferation of megakaryoblast-like blastoid cells (g) that were positive for CD42b (h).**

engraftment was achieved on day 21; full donor chimerism and CR were established by a bone marrow examination on day 28. Disseminated fusariosis, which developed during the neutropenic period, was diagnosed by a culture of skin lesion and controlled with the administration of liposomal amphotericin B. No apparent signs of GVHD were observed, and tacrolimus administration was stopped at day 71. Although several serious complications, such as hemorrhagic cystitis due to BK virus infection and duodenal ulcer with massive hemorrhaging, also developed during the course after CBT, they were all ultimately well-controlled.

The patient's general condition improved gradually, and he was discharged at day 165. He has been well without AMKL or MGCT relapse for more than a year since CBT, with continuous administration of posaconazole for fusariosis. Whole-exome sequencing using specimens collected for the initial diagnosis, which were concentrated by CD61-targeting magnetic cell separation, did not reveal any significant abnormal findings.

Discussion

AMKL is a generally chemotherapy-resistant malignancy with an extremely poor prognosis in adults. According to several clinical studies on AMKL (2, 8-10), the percentage of cases in which CR was achieved is below 50%, and the 5-year overall survival rate is around 10%. Although cases that received alloHCT were typically not included in the above studies, the prognosis of AMKL after alloHCT is also known to be extremely poor. In a Japanese retrospective study analyzing 108 cases of AMKL registered in a database (5), the 5-year overall and progression-free survival rates were 17% and 14%, respectively.

However, there is room to improve this dismal prognosis

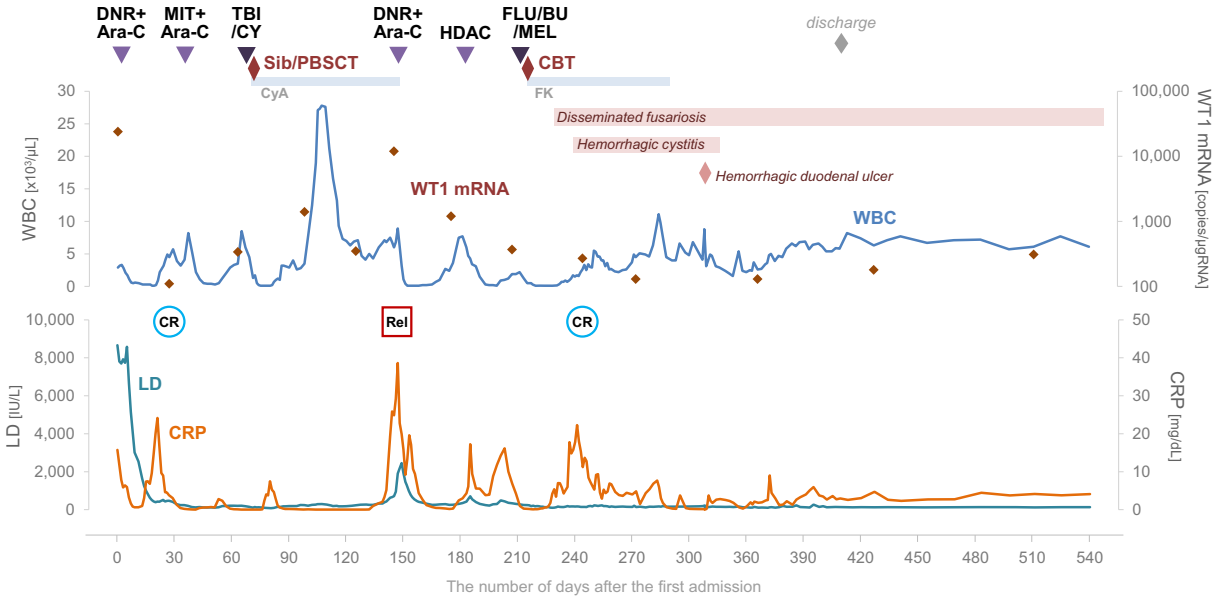

Figure 3. **Clinical course. Ara-C: cytarabine, BU: busulfan, CR: complete remission, CY: cyclophosphamide, CyA: cyclosporine, DNR: daunorubicin, FK: tacrolimus, FLU: fludarabine, HDAC: high-dose cytarabine, MEL: melphalan, MIT: mitoxantrone, Rel: relapse, Sib/PBSCT: allogeneic peripheral blood stem cell transplantation from an HLA-identical sibling donor, TBI: total body irradiation**

by optimizing the transplantation methodology. Recently, Yamamoto et al. showed that CBT preceded by a novel conditioning regimen consisting of fludarabine, busulfan, and melphalan showed significant antileukemic effects against non-remission myeloid malignancies (11). They reported that the 2-year overall and progression-free survival were both as high as 54.9%, and that none of the patients developed graft rejection. In the present case, despite early relapse after myeloablative alloHCT, sustained remission of AMKL was eventually achieved after reduced-intensity CBT preceded by a conditioning regimen comprising fludarabine, busulfan, and melphalan, suggesting that this transplantation protocol could be a promising treatment option for AMKL. In addition, the peculiar graft-versus-leukemia effect associated with HLA disparities in CBT may be essential for achieving long-term disease control of AMKL.

Various hematological malignancies are reported to be associated with MGCT, and the most common leukemia that occurs with MGCT is AMKL (12, 13). However, this condition is considered rare, and fewer than 30 cases of AMKL with MGCT have been reported in the literature (4). AMKL emergence is often preceded by MGCT, as in the present case, or both are diagnosed simultaneously. In a report that analyzed 17 cases of hematological disorders associated with MGCT, a cytogenetic analysis of leukemic cells detected isochromosome i(12p), the most common karyotypic abnormality of germ cell tumors, in some patients (13). Recently, some cases of AMKL associated with MGCT, both of which harbor PTEN and TP53 mutations, have been reported, suggesting the existence of a common founding clone (14, 15). Although such characteristic cytogenetic or molecular findings were not observed with whole-exome sequencing of AMKL, and such analyses of MGCT could not be performed in the present case, the consistency of clinical features with the previously reported cases (4) suggests that AMKL might have developed from a common clone of MGCT in this case as well. AMKL associated with MGCT is also reported to have an extremely poor prognosis (4). The present case may thus be valuable, as AMKL cases associated with MGCT in which CBT was successfully performed have been scarcely reported.

In summary, we encountered a case of AMKL preceded by MGCT that relapsed early after alloHCT with myeloablative conditioning but was successfully treated by salvage CBT with reduced-intensity conditioning comprising fludarabine, busulfan, and melphalan. Although several serious complications developed after CBT, long-term remission with a favorable general condition was finally achieved. The optimal therapeutic strategy for AMKL treatment, including the methodology of alloHCT, remains to be established; however, the graft-versus-leukemia response to CBT may aid in achieving sustained disease control in refractory AMKL. Overall, the further accumulation of clinical experience with such cases is necessary to improve the dismal prognosis of AMKL.

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

References

1. Saida S. Evolution of myeloid leukemia in children with Down syndrome. Int J Hematol **103**: 365-372, 2016.

2. Pagano L, Pulsoni A, Vignetti M, et al. Acute megakaryoblastic leukemia: experience of GIMEMA trials. Leukemia **16**: 1622-1626, 2002.
3. Giri S, Pathak R, Prouet P, Li B, Martin MG. Acute megakaryocytic leukemia is associated with worse outcomes than other types of acute myeloid leukemia. Blood **124**: 3833-3834, 2014.
4. Mukherjee S, Ibrahimi S, John S, et al. Non-seminomatous mediastinal germ cell tumor and acute megakaryoblastic leukemia. Ann Hematol **96**: 1435-1439, 2017.
5. Ishiyama K, Yamaguchi T, Eto T, et al. Acute megakaryoblastic leukemia, unlike acute erythroid leukemia, predicts an unfavorable outcome after allogeneic HSCT. Leuk Res **47**: 47-53, 2016.
6. Hiramatsu H, Morishima T, Nakanishi H, et al. Successful treatment of a patient with Klinefelter's syndrome complicated by mediastinal germ cell tumor and AML(M7). Bone Marrow Transplant **41**: 907-908, 2008.
7. Kassim Y, Penther D, Schneider P, Callat MP, Bastard C, Vannier JP. Malignant transformations in a patient with a mediastinal germ cell tumour: lack of efficacy of bone marrow transplantation after chemotherapy on tumour recurrence. BMJ Case Rep **2012**: 2012.
8. Hahn AW, Li B, Prouet P, Giri S, Pathak R, Martin MG. Acute megakaryocytic leukemia: what have we learned. Blood Rev **30**: 49-53, 2016.
9. Oki Y, Kantarjian HM, Zhou X, et al. Adult acute megakaryocytic leukemia: an analysis of 37 patients treated at M.D. Anderson Cancer Center. Blood **107**: 880-884, 2006.
10. Tallman MS, Neuberg D, Bennett JM, et al. Acute megakaryocytic leukemia: the Eastern Cooperative Oncology Group experience. Blood **96**: 2405-2411, 2000.
11. Yamamoto H, Uchida N, Yuasa M, et al. A novel reduced-toxicity myeloablative conditioning regimen using full-dose busulfan, fludarabine, and melphalan for single cord blood transplantation provides durable engraftment and remission in nonremission myeloid malignancies. Biol Blood Marrow Transplant **22**: 1844-1850, 2016.
12. Nichols CR, Roth BJ, Heerema N, Griep J, Tricot G. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. N Engl J Med **322**: 1425-1429, 1990.
13. Hartmann JT, Nichols CR, Droz JP, et al. Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. J Natl Cancer Inst **92**: 54-61, 2000.
14. Lu C, Riedell P, Miller CA, et al. A common founding clone with TP53 and PTEN mutations gives rise to a concurrent germ cell tumor and acute megakaryoblastic leukemia. Cold Spring Harb Mol Case Stud **2**: a000687, 2016.
15. Akizuki K, Sekine M, Kogure Y, et al. TP53 and PTEN mutations were shared in concurrent germ cell tumor and acute megakaryoblastic leukemia. BMC Cancer **20**: 5, 2020.