

## Case Report

# Related HLA-haploidentical T-cell replete peripheral stem cell transplantation with a reduced-intensity conditioning regimen to treat ANKL: a case report and literature review

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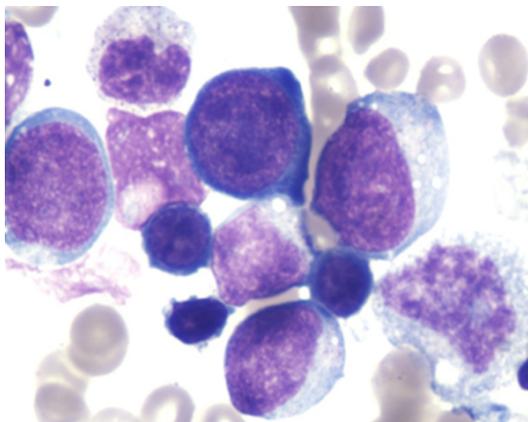
**Abstract:** Background: Aggressive natural killer cell leukemia (ANKL) is characterized by low incidence and high mortality. This study reported a case of aggressive ANKL treated with our unique, reduced-intensity conditioning regimen, haploid hematopoietic stem cell transplantation after complete remission (RIC-RHNT-PBSCT). Case presentation: A 51-year-old male had been diagnosed with acute cholecystitis and acute cholangitis due to jaundice and fever, and he received surgical treatment. After the operation, the patient reported a constant leukocyte rise, and he was finally diagnosed with ANKL based on a bone marrow puncture and leukemia immunophenotyping. After the diagnosis, with an active surgical incision and T-tube drainage, the very weak ANKL patient received the IAVD + asparaginase chemotherapy regimen and went into complete remission (CR) after two courses of the chemotherapy regimen. Our unique RIC-RHNT-PBSCT was performed to improve the long-term survival of this still weak patient. The hematopoietic stem cell donor was the patient's son, who was haploid 3/6 matched. In order to reduce the transplantation-related mortality, the intensity conditioning regimen of FAB was adopted. Starting at day 15 after the stem cell transplantation, a complete donor chimerism was observed, with a chimeric rate of 100%. At the end of follow-up period, the bone marrow aspiration result was normal, and testing found the chimerism was a complete donor chimerism. Conclusion: A rare and weak ANKL patient achieved long-term survival with our RIC-RHNT-PBSCT.

**Keywords:** Aggressive natural killer cell leukemia (ANKL), hematopoietic stem cell transplantation, reduced-intensity conditioning regimen, HLA-haploidentical transplantation

## Introduction

Aggressive natural killer cell leukemia (ANKL), a rare hematologic malignancy originating from the NK cells, accounts for less than 5% of lymphoid malignancies. ANKL has a highly invasive clinical course, which is clinically characterized by fever, hepatosplenomegaly, jaundice, abnormal liver function, and pancytopenia. Moreover, ANKL usually progresses rapidly and responds poorly to various therapeutic treatments, and it is accompanied by multiple organ failure within a short time period, with a median survival of approximately 2 months [1, 2]. In 1986, Fernandez [3] established the NK cell-derived tumor cell line from the peripheral blood of a 70-year-old male patient with leukemia, which features malignant proliferation.

At present, there is still no optimal treatment for ANKL, mainly because of the production of P-glycoprotein by ANKL tumor cells [1, 4]. Combination chemotherapy and hematopoietic stem cell transplantation have been reported as the treatment options for ANKL. In a prior case series by Ishida, the median survival of ANKL patients undergoing alloHCT (n = 6) was 9 months, while all non-transplanted subjects (n = 26) died due to progressive disease [2]. The majority of ANKL patients has a poor response or even no response to the traditional CHOP chemotherapy [5, 6], as indicated by rapid disease progression. Currently, the drugs considered to be effective for the treatment of ANKL include anthracyclines and L-asparaginase. Particularly, L-asparaginase cannot be affected by P-glycoprotein, which is effective in treating



**Figure 1.** Bone marrow cytology. Bone marrow nucleated cell hyperplasia was active, and primitive cells accounted for 38%, with varying cell sizes, partial nucleus distortion and depression, clear nucleoli 1-3, and fewer blue cytoplasm. The peripheral blood smear revealed 16% primitive cells ( × 2200).

NK/T-cell leukemia [1, 5]. A multivariate analysis has shown that the use of L-asparaginase might be the only clinical factor that could improve the overall survival of NK cell leukemia [7]. Moreover, a previous study of 22 patients with ANKL showed that, among the 13 ANKL cases receiving the chemotherapeutic treatment of anthracycline or anthraquinone, 3 cases reported complete remission [5, 8]. In these patients, 2 cases subsequently received allogeneic bone marrow transplantation or autologous hematopoietic stem cell transplantation, and the survival periods were 39 months and 22 months, respectively [5, 8].

Most ANKL patients die from multiple organ failure and coagulation dysfunction. There are several studies showing that young, healthy ANKL patients treated with allogeneic hematopoietic stem cell transplantation have reported complete remission [7, 9, 10]. However, allogeneic stem cell transplantation is an effective way to treat ANKL, but clinical reports are still rare. Here, based on the disease remission following the chemotherapy, we report a case of ANKL treated with allogeneic haploidentical stem cell transplantation with reduced intensity conditioning regimen.

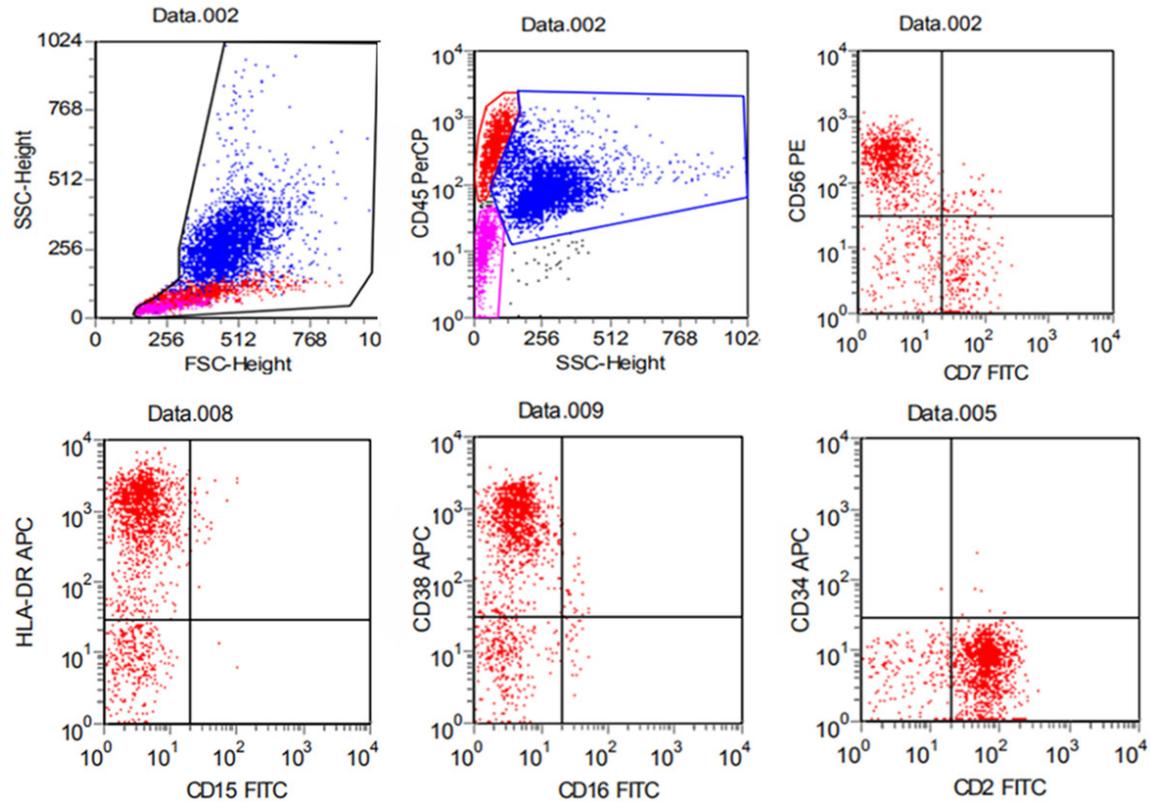
### Case report

In October 2015, a 51-year-old Han male named Chen was admitted to our hospital, who

reported persistent pain in the upper abdomen, accompanied by fever (with the highest temperature at 39°C), as well as scleral and skin jaundice. Based on the results from the physical examination and abdominal ultrasound detection, the patient was diagnosed with acute cholecystitis and acute cholangitis; therefore he underwent a cholecystectomy, a common bile duct exploration, and T-tube drainage.

After surgery, the patient had a persistent fever, with a poor anti-infective effect, and a progressive increase of white blood cells was observed, with decreased platelets and hemoglobin level. Bone marrow cytology indicated an active proliferation of nucleated cells, and primitive cells accounted for 38% (**Figure 1**). A blood smear detection indicated a level of 16% of primitive cells in the peripheral blood. A bone marrow biopsy revealed active bone marrow hyperplasia, eosinophilic with rich cytoplasm and interstitial fibrosis. Leukemia immunophenotyping showed that the lymphocytes accounted for about 20.5%, in which the NK cells accounted for about 68%, mainly expressing HLA-DR, CD2, CD38, and CD56 (**Figure 2**). Thoracoabdominal CT scanning indicated bilateral thickened dorsal pleura, multiple bilateral axillary and bilateral groin lymphadenectasis, and splenomegaly and partial splenic infarction. Based on these results, the patient was diagnosed with ANKL, a pulmonary infection, acute cholecystitis, and acute cholangitis. With active surgical incision and T-tube drainage, the patient received the IAVD + asparaginase chemotherapy regimen (IDA, 10 mg, d1 to d3; Ara-C, 200 mg, d1 to d7; VCR, 4 mg, d1; and DEX, 10 mg, d1 to d7; asparaginase d9), meanwhile cholanesis and anti-hepatitis B virus treatment was given. After the first course of chemotherapy, a partial remission was observed, and then CR was observed after the second course. Then the patient received another three courses. The bone marrow cytology indicated CR of the acute leukemia. Before the patient received the hematopoietic stem cell transplantation, cholangiography was conducted, which indicated a smooth bile duct, with satisfactory filling of the contrast agent. After a complete hospital consultation, the drainage tube was pulled out. Although the patient was still weak at this time (with the HCT-CI point of 4), due to this being a rare case and the likelihood of recurrence, we

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**Figure 2.** Results from leukemia immunophenotyping. Lymphocytes made up about 20.5% of the nuclear cells. NK cells accounted for 68% of the lymphocytes, and the proportion was significantly increased.

determined that transplantation should be performed as soon as possible. After a search, no all HLA-matched related or unrelated donors were found. Therefore, the patient's son was selected, and the high-dose PBSCT without in vitro T-cell depletion was performed using the unique RIC haploidentical scheme, which we designed and improved in 2013 (unpublished data).

In February 2016, the ANKL patient underwent the haploid HLA-matched peripheral hematopoietic stem cell transplantation with a reduced-intensity conditioning regimen. The hematopoietic stem cell donor was the patient's son, which was haploid 3/6 matched (the blood types for the patient and the donor were AB and B, respectively). The reduced-intensity conditioning regimen was FAB (fludarabine injection, 30 mg/m<sup>2</sup>, -9 to -5 day; cytarabine injection, 2 g/m<sup>2</sup>, -9 to -5 day; Busulfan (Maryland) injection, 3.2 mg/kg/d, -4 to -3 day; rabbit anti-human thymocyte immunoglobulin, ATG, 2.5 mg/kg, -4 to -1 day; basiliximab injection, +1

to +2 day). After conditioning, the high-dose untreated PBSCs from the donor were infused (MNC, 15 × 10<sup>8</sup>/kg; and CD34<sup>+</sup> cells, 8 × 10<sup>6</sup>/kg). For the donor, PBSC mobilization was conducted with G-CSF (8 µg/kg/d). On the 5<sup>th</sup> and 6<sup>th</sup> days after mobilization, PBSC apheresis was performed with the blood cell separator (COBE Spectra) (**Table 1**).

To prevent graft versus host disease (GVHD), the following treatment was given: a cyclosporine A injection, 2.5 mg/kg/d, maintained for 24 h, maintaining the cyclosporine concentration over 250-350 ng/ml; MTX intravenous infusion, 15 mg/m<sup>2</sup> on day +1, and 10 mg/m<sup>2</sup> on days +3, +6, and +11; MMF, 1 g/d, in 2 oral administrations, starting on day -1 (if no acute GVHD, aGVHD, the dose was reduced in half at day +40, which was stopped on day +90 to day +100); anti-CD25 monoclonal antibody, 20 mg, one time on day 0 before infusion of stem cells, and one time on day +2. To prevent infection, the patients orally took compound sulfamethoxazole, ganciclovir (days -8 to -12, and days +15

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**Table 1.** Analysis of the graft composition

	MNC	CD34	CD3	CD4	CD8
Day 1	$17.5 \times 10^8/\text{kg}$	$10.5 \times 10^6/\text{kg}$	$1230 \times 10^6/\text{kg}$	$572 \times 10^6/\text{kg}$	$546 \times 10^6/\text{kg}$
Day 2	$6.05 \times 10^8/\text{kg}$	$3.7 \times 10^6/\text{kg}$	$453 \times 10^6/\text{kg}$	$166 \times 10^6/\text{kg}$	$190 \times 10^6/\text{kg}$

Note: All the collected stem cells were frozen on day 2.

to +30), acyclovir (days +1 to +14), and net injection of micafungin. Apheresis platelets were infused during the period with no bone marrow function, and the BPC was maintained above  $20 \times 10^9/\text{L}$ , while the red blood cell suspension was infused when  $\text{Hb} < 80 \text{ g/L}$ . Immunoglobulin (400 mg/kg) was infused on days +1, +11, +21, and +31.

For the patient, the neutrophil level on day 15 after stem cell transplantation was  $1.1 \times 10^9/\text{L}$ , and the platelet level on day 18 was  $20 \times 10^9/\text{L}$  (no platelet infusion for 3 days). On day 15, a complete donor chimerism was observed, with a chimeric rate of 100%. The review on day +31 indicated the same results, with complete donor chimerism and a chimeric rate of 100%. On day +35, the patient's HLA genotype was transformed into the same type as the donor's. On month +5 after transplantation, the patient's blood type was changed from AB into B (the same as the donor). On day +70, the bilirubin and transaminase levels were elevated for no apparent reason, so the patient was diagnosed with grade II a GVHD. The patient was then given metoprolol, 20 mg, oral administration twice daily, together with tacrolimus, 0.5 mg, oral administration twice daily. After 1 week, the bilirubin and aminotransferase levels were significantly decreased, which then returned to the normal levels after another 2 weeks. On month 4.5 after transplantation, the bilirubin and transaminase levels were elevated, and the patient was diagnosed with chronic GVHD, cGVHD, and he received a net injection of methylprednisolone, 40 mg, twice daily, together with a net injection of anti-CD25 monoclonal antibody, on day +1 and day +4. On month 5.5 after transplantation, the bilirubin and transaminase levels returned to their normal levels. On month 6 after transplantation, the bilirubin level was elevated for no apparent reason (total bilirubin,  $97 \mu\text{mol/L}$ ; direct bilirubin,  $80 \mu\text{mol/L}$ ; unconjugated bilirubin,  $17 \mu\text{mol/L}$ ; ALT,  $33 \text{ U/L}$ ; and AST,  $30 \text{ U/L}$ ). According to the patient's treatment and clinical manifestations, the cGVHD was excluded.

MRCP indicated a congenital absence after the cholecystectomy, with a thickened extrahepatic bile duct wall, and stones within the

bile duct on the right liver lobe and the lower fragment of the common bile duct. The patient was subjected to the cholangiography + nipple incision + nipple dilatation + stone removing with baskets combined with biliary cleaning with balloons + biliary stent implantation. After surgery, the bilirubin level was gradually decreased. After two weeks, the total bilirubin level was  $27.96 \mu\text{mol/L}$ , the direct bilirubin level was  $12.42 \mu\text{mol/L}$ , and the indirect bilirubin level was  $15.54 \mu\text{mol/L}$ .

Follow-up lasted until October 2017. All the chimerism tests indicated a complete chimerism, with chimeric rates of 100%. Moreover, bone marrow aspiration in October 2017 indicated 1% of primitive cells.

Prior written and informed consent was obtained from this patient and the study was approved by the ethics review board of Xinjiang Medical University.

### Discussion

Cases of ANKL like the one reported here are rarely seen in the clinic, but the condition is prone to occur in middle-aged and young subjects, with obvious geographical features. A previous retrospective analysis of 98 ANKL cases has shown that onset can occur at any age, and 58.5% of the patients are between 10 and 40 years old, it is more common in males than females, and it is more commonly seen in Asia and the Caucasus regions [11]. At present, the etiology and pathogenesis of ANKL are not still yet clearly elucidated. Ruskova [12] retrospectively analyzed 73 patients with ANKL, and EB infection was detected in 34 of the patients, with 28 positive cases (85%). Moreover, the occurrence of ANKL may be related to the activation of oncogenes and the inactivation of tumor suppressor genes [13]. Siu [14] studied the methylation status of p73, p16, RAR, p15, and hMLH1 and suspects that the methylation status in the promoters of these tumor suppressor genes might promote the malignant transformation of NK cells.

The case reported here reported an elevated LDH level. Considering the disease history, liver and gallbladder lesions might result from ANKL. In the case of ANKL, the leukocytes could be abnormally elevated, mainly the lymphocytes, while other cases might show leukopenia. Some patients may be associated with a hemoglobin decrease and thrombocytopenia, which is usually accompanied by coagulation dysfunction. In the later stages, almost all the patients with ANKL would have liver dysfunction and pancytopenia. A majority of ANKL patients have an aggressive, fulminant clinical course, and multiple organ failure can occur within a short-term period, mainly liver failure, gradually involving other organs. During the disease's course, disseminated intravascular coagulation and hemophilic syndrome are often observed [15].

Currently, there are still no uniform diagnostic criteria for ANKL, and the disease diagnosis is mainly based on the clinical manifestations, cellular morphology, and immunological characteristics [5, 16, 17], such as: (1) patients often have fever, jaundice, and hepatosplenomegaly, and some patients could have lymphadenopathy, pleural effusion, and celiac effusion. (2) patients often have acute disease onset and rapid progress, accompanied by clinical invasive and explosive process, with poor prognosis. (3) Morphological detection indicates that there are mild immature large lymphocytes in the peripheral blood and/or bone marrow, with slightly stained cytoplasm and triphenyl-rosaniline granules, as well as thin chromatin and occasional nucleoli, while the immunophenotype indicates mature NK cells. (4) Typical immunophenotypes include  $sCD3^-$ ,  $cCD3e^{+/-}$  and  $CD16^{-/+}$ ,  $CD56^+$ , and  $CD57^-$ , while the patient is negative for the T cells, B cells ( $CD19$  and  $CD20$ ), and myeloid (myeloperoxidase) specific markers. (5) Germline configurations are observed for the T cell receptor (TCR) and immunoglobulin heavy chain (IgH). (6) Evidence for EB virus infection (supportive, not necessary). (7) Other diseases that would induce lymphocytosis should be excluded.

In this case, considering the patient's condition, with the partial remission after chemotherapy, allogeneic hematopoietic stem cell transplantation was performed to improve long-term patient survival. In order to reduce transplantation-related mortality, an intensity

conditioning regimen was adopted. Moreover, after the transplantation, the remaining tumor cells were cleared by the anti-leukemia effects of the transplants mediated by the immunocompetent cells from the donor, to achieve a complete cure, which is suitable for elder or young subjects with incorporated organ dysfunction. In 1997, Giralt [18] studied the patients with hematologic malignancies, for whom the allogeneic hematopoietic stem cell transplantation has been conducted, combined with the nonmyeloablative conditioning regimen (NMC). The results show that the patients tolerate the treatment generally well, under good implantation conditions.

At present, these are mainly retrospective studies concerning the HLA-matched sibling donor transplantation (MSDT), HLA-matched unrelated donor transplantation (MUDT), umbilical cord blood transplantation (UCBT), and Haplo-HSCT, with limited medical evidence [19-21]. Moreover, there are studies agreeing that Haplo-HSCT and MSDT, as well as MUDT and UCBT, have similar prognoses [19, 22-24]. Nevertheless, it has been well accepted that HLA-matched sibling donors should be preferred. For the case reported here, no complete matched unrelated donors were found in the China Marrow Donor Program. Moreover, the patient suffered from aggressive NK cell leukemia, and the disease is prone to relapse during treatment. Therefore, the haploidentical hematopoietic stem cell transplantation was recommended. The patient had 4 haploid match donors, i.e., his sister, brother, son, and daughter. Chang [25] showed that DSA positiveness is closely associated with transplant rejection and poor implantation, which represents the influencing factor for a poor prognosis. For the patients with DSA<sup>+</sup> serum, the donor should be replaced. Herein, the haploid donor was negative for DSA, and therefore, no perfect donor could be determined based on the DSA-related evidence. It has been shown that female donors could increase the risk of developing acute GVHD at stages II-IV in male patients [26, 27]. Therefore, to reduce the transplantation-related mortality and increase the chances of survival, the patient's son was chosen as the donor. Reisner [28] found that higher doses of stem cells could overcome the immune rejection. PBSCT has an advantage due to the fact that granulocyte colony-stimulating factor-mobilized donor hemopoietic stem cells have

been collected many times, thereby meeting the number of CD34<sup>+</sup> cells that transplantation requires. Therefore, high-dose CD34<sup>+</sup> cells were infused herein in the HLA-haploidentical transplantation with a reduced-intensity conditioning regimen, which could increase the rate of engraftment, speed up immune reconstitution, and reduce the incidence of infection. In addition to this patient, satisfactory results were achieved by the reduced-intensity conditioning regimen in the HLA-haploidentical hematopoietic stem cell transplantation to treat hematologic malignancies in another 21 cases.

ANKL is characterized by a low incidence and high mortality in the clinic. In the case reported herein, after the diagnosis of ANKL, chemotherapy with anthracyclines and L-asparaginase was chosen first. After disease remission, a hematopoietic stem cell transplantation was conducted. Our results showed that, for the male patient with ANKL, the allogeneic haploid hematopoietic stem cell transplantation with a reduced intensity conditioning regimen significantly promoted the patient's long-term survival, which is worthy of further in-depth clinical studies.

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### Disclosure of conflict of interest

None.

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