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Case report: a critically ill patient with aggressive NK-cell leukemia receiving emergency chemotherapy in the ICU

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Abstract

Aggressive NK-cell leukemia (ANKL) is a scarce mature NK-cell neoplasm frequently associated with Epstein-Barr virus (EBV) infection. We report the case of a 47-year-old male patient who was admitted to the hospital due to recurrent fever, jaundice, and dyspnea, and was diagnosed with ANKL accompanied by multi-organ failure. Upon transfer to the intensive care unit (ICU), he received emergency chemotherapy consisting of etoposide, pegaspargase, and gemcitabine, in conjunction with organ support therapies including DPMAS, LPE, and CVVHD. Subsequently, the patient's condition stabilized, and he was discharged. However, following the second cycle of chemotherapy, he was readmitted due to altered mental status. Due to financial constraints, the family decided not to pursue further treatment, leading to the patient's eventual demise. Overall, this case highlights the critical importance of multidisciplinary collaboration for managing critically ill ANKL patients. Careful evaluation of the risks associated with chemotherapy, combined with timely administration of emergency chemotherapy in the ICU and comprehensive multi-organ support, can potentially offer a survival opportunity.

Keywords Aggressive NK-cell leukemia (ANKL), Lymphoma/Leukemia, Emergency chemotherapy, ICU

Introduction

Aggressive Natural Killer Cell Leukemia (ANKL) is a rare and highly aggressive neoplastic disorder of mature NK cells, with rapid progression and a poor prognosis [1]. Over the past few years, advancements in medical research have enhanced our understanding and expanded therapeutic options for ANKL. Previous literature has predominantly concentrated on the management of ANKL patients in hematology departments. This report details a case of critically ill ANKL managed with artificial liver support and emergency chemotherapy in the Intensive Care Unit (ICU). This approach underscores the potential advantages for ANKL patients with multi-organ dysfunction, providing new perspectives into the comprehensive management of such cases.

Case presentation

A 47-year-old male patient was admitted to our hospital on July 4, 2024. He had been experiencing recurrent fever (Max Temp ≥ 38.5 °C) and jaundice for over half a month, followed by tonsillar enlargement and chest tightness. His dyspnea worsened three days prior to admission. Over the past two months, he had experienced a weight

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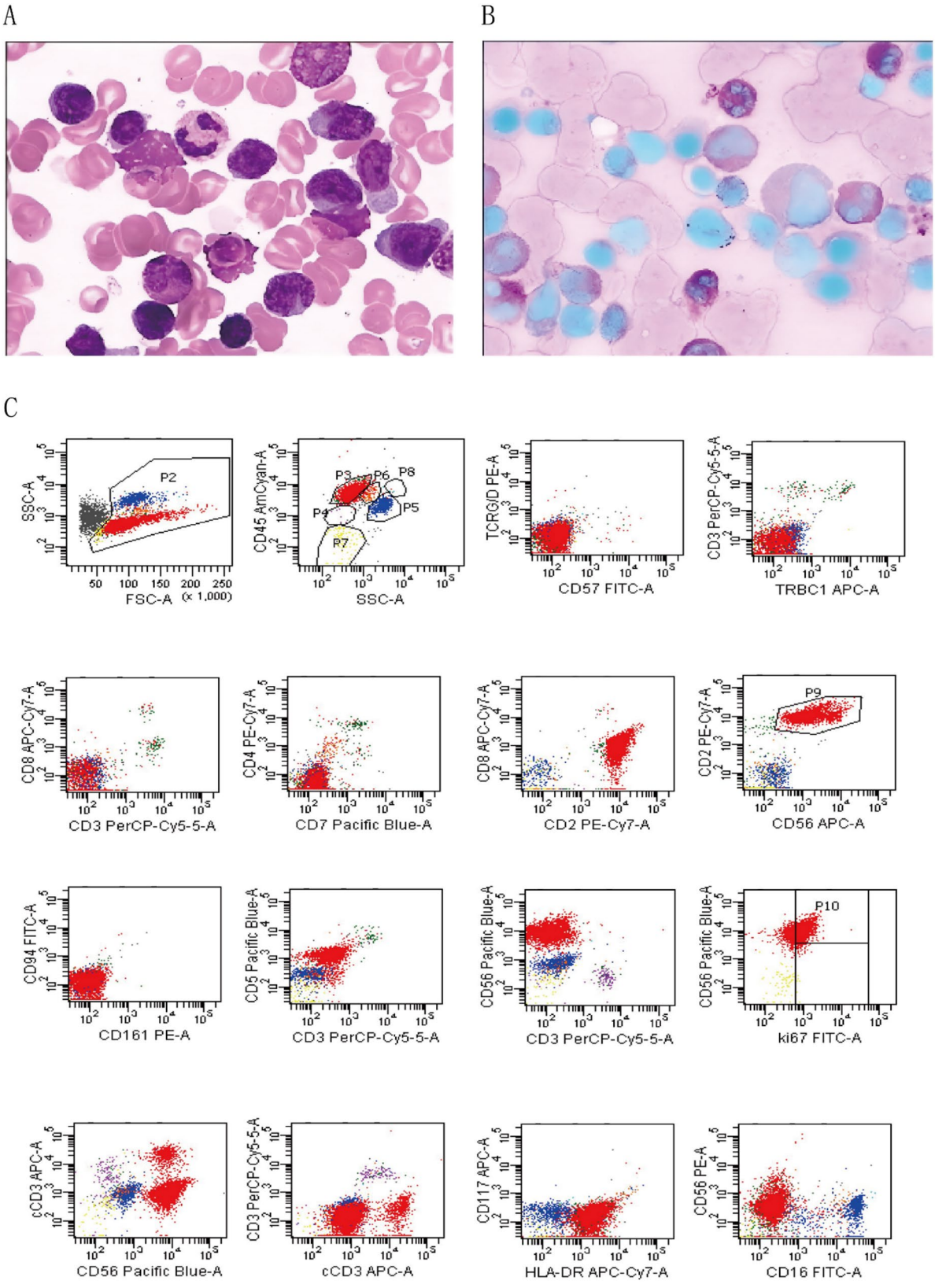

Fig. 1 (See legend on next page.)

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Fig. 1 Morphology and flow cytometry analysis of patient's bone marrow cells. **(A) Morphological Report of Bone Marrow Cells (Wright-Giemsa stain, 100×)** The bone marrow exhibits markedly active proliferation, with abnormal lymphocytes constituting 41% of nucleated cells. These cells show mild variability in size, characterized by coarse and dense chromatin. Nucleoli are evident in some cells, while most nuclei display irregular shapes with twisting and folding. The cytoplasm is scant and slightly basophilic, with occasional cells showing a few purple-red granules. A minority of cells contain cytoplasmic vacuoles. **(B) Cytochemical Staining Report (Periodic Acid-Schiff stain, 100×)** Abnormal lymphocytes have a 4% positivity rate, with a coarse granular staining pattern. **(C) Flow Cytometry Results** 75.3% of nucleated cells express CD5dim, CD2, CD56, CD38dim, Ki-67 (73.3%), and HLA-DR. A subset of these cells also expresses cCD3, which indicates phenotypically abnormal NK cells

loss of 5 kg. Previously, he had visited another hospital where leukocytosis (with a WBC count of 36.3×10^9/L) was detected, and a bone marrow biopsy indicated lymphoma. Further tests at our hospital, including examinations of the bone marrow structure and cell flow analysis (Fig. 1), confirmed the diagnosis of aggressive NK cell lymphoma/leukemia (stage IV). Upon admission, the patient's condition deteriorated rapidly, manifesting multiple organ failures (respiratory, hepatic, renal, and cardiac systems) and the onset of hemophagocytic lymphohistiocytosis (HLH), as defined by the HLH-2004 diagnostic criteria [2] [(1) persistent fever with a temperature ≥ 38.5℃, (2) presence of splenomegaly, (3) elevated ferritin levels ≥ 500 μg/L, (4) soluble CD25 ≥ 2,400 U/mL, and (5) reduced fibrinogen levels below 1.5 g/L]. Given the severity of his condition, he was transferred to the ICU. He received dual plasma molecular adsorption system (DPMAS) combined with low-volume plasma exchange (LPE), continuous renal replacement therapy (CRRT), mechanical ventilation, and symptomatic treatment. Concurrently, he underwent chemotherapy with a regimen of etoposide, pegaspargase, and gemcitabine. Despite the challenges, the treatment process was relatively smooth. Following three sessions of artificial liver support and six days of continuous renal replacement therapy (DPMAS + LPE + CVVHD), the patient exhibited significant improvements in white blood cell count, as well as hepatic and renal function markers (Fig. 2). Additionally, respiratory and circulatory functions were stabilized. He was ultimately discharged from the hospital. During the chemotherapy intermission, the patient's symptoms improved, and his routine blood tests and biochemical indicators remained stable. He was readmitted on July 29, 2024, for the initiation of a second cycle of chemotherapy using the L-GEMOX regimen, which comprises pegaspargase, gemcitabine, and oxaliplatin. On August 23, 2024, the patient was readmitted owing to altered mental status. After three days of symptomatic treatment, his family opted to discontinue chemotherapy and organ support because of financial constraints. Regrettably, the patient passed away on August 27, 2024.

Upon admission to our hospital, laboratory tests disclosed the following results: The glucose (Glu) was 1.7 mmol/L, the triglyceride (TG) was 3.93 mmol/L, the fibrinogen (Fbg) was 1.25 g/L, the lactate (Lac) was > 15 mmol/L, the procalcitonin (PCT) was 4.26 ng/mL, the interleukin-6 (IL-6) was 20.55 pg/mL, the interleukin-10 (IL-10) was 14.20 pg/mL, the ferritin (FERR) was 1,969.00 μg/L, the soluble CD25 (sCD25) was 87,104 pg/mL, the natural killer (NK) lymphocyte subset ($CD3^-CD16^+CD56^+$) was 97.12%, and the NK cell activity was 17.16%. The copy number of Epstein-Barr virus (EBV) DNA was measured at 1.04×10^5 IU/mL. For detailed results, see Table 1.

Discussion

ANKL was initially described in the 1980s. In 2016, the World Health Organization classified it as a subtype of mature NK cell neoplasms, which also includes extranodal NK-/T-cell lymphoma, nasal type (ENKTL-N), and chronic lymphoproliferative disorder of NK cells (NK-CLPD) [3]. ANKL has a higher prevalence in Asia, predominantly affecting young to middle-aged adults (aged 30–40 years), and is strongly associated with EBV infection [4, 5]. It typically manifests as a systemic disease involving multiple organ systems, characterized by fever, weight loss, hepatosplenomegaly, pancytopenia, and abnormal liver function. The clinical course is frequently fulminant, rapidly progressing to disseminated intravascular coagulation (DIC) and HLH, resulting in multiorgan failure [6]. In terms of molecular characteristics, the molecular abnormalities observed in ANKL can be categorized into four primary groups: hyperactivation of the JAK/STAT pathway, epigenetic deregulation, dysfunction in TP53 and DNA repair mechanisms, and overexpression of PD-1/PD-L1 [7, 8]. These genetic mutations are significantly correlated with a shorter survival duration. The median survival time following disease onset is only 2 months, with rapid disease progression typically culminating in mortality within days to weeks in most cases [9, 10].

Currently, there is no standardized treatment protocol for ANKL. Studies have demonstrated that NK tumor cells can express P-glycoprotein, which expels anthracycline drugs from the cells, thereby reducing intracellular drug concentrations and leading to drug resistance [11]. As a result, traditional CHOP and CHOP-like regimens demonstrate limited efficacy in the treatment of ANKL [12]. In contrast, L-asparaginase (L-ASP) is not influenced by P-glycoprotein and has the ability to induce apoptosis in NK cell tumors. Therefore, treatment regimens that incorporate L-ASP may enhance patient outcomes [13].

The currently used regimens are as follows [8, 14]:

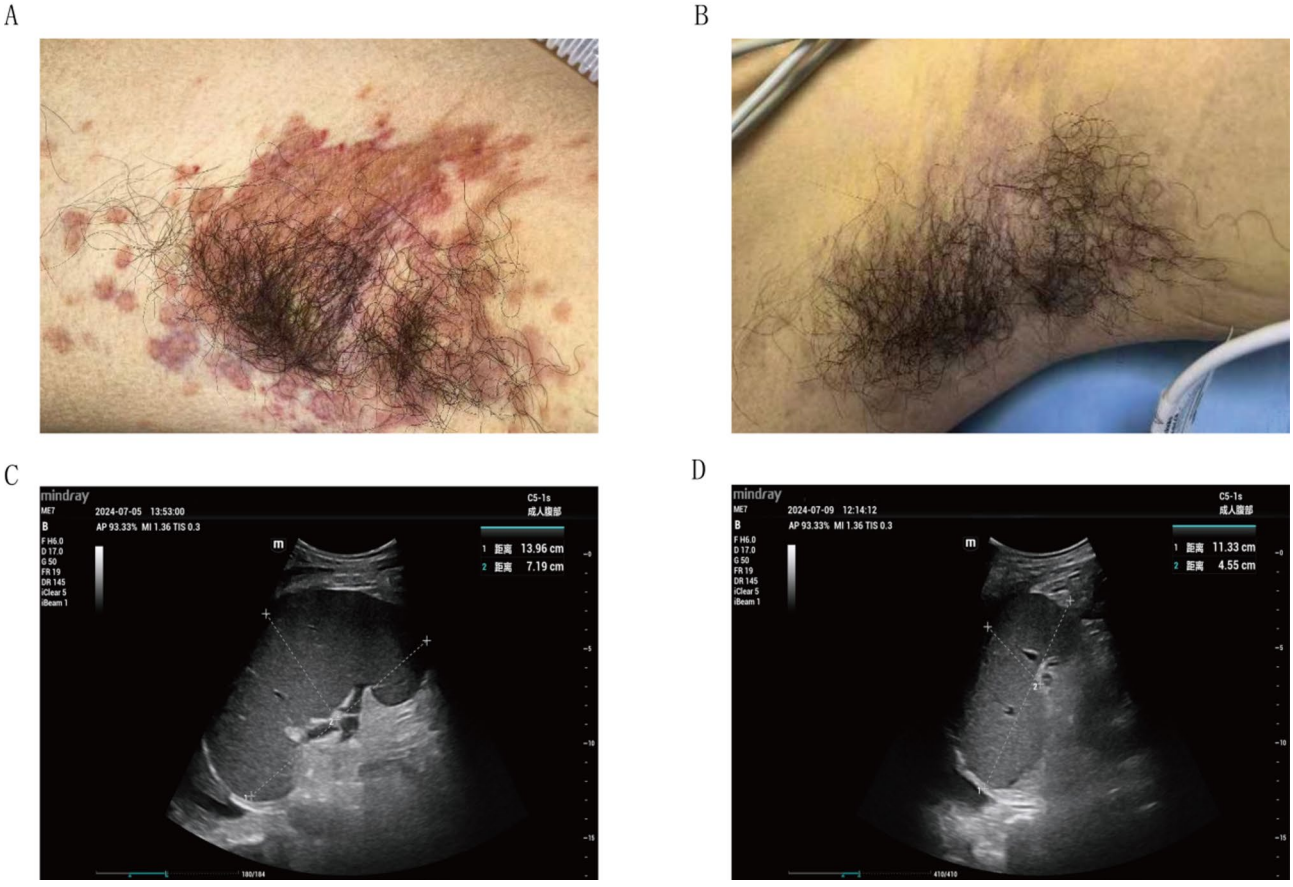

Fig. 2 Skin manifestations and imaging findings. **A and B.** Skin Involvement Before and After Treatment **C and D.** Ultrasound Findings of the Spleen Before (longitudinal length 13.96 cm, thickness 7.19 cm) and After (longitudinal length 11.33 cm, thickness 4.55 cm) Treatment

- **SMILE regimen**: Dexamethasone, Methotrexate, Ifosfamide, L-Asparaginase, and Etoposide.
- **VIDL regimen**: Etoposide, Ifosfamide, Dexamethasone, and L-Asparaginase.
- **AspMetDex regimen**: L-Asparaginase, Methotrexate, and Dexamethasone.
- **Pegaspargase in conjunction with GDP regimen**: Gemcitabine, Cisplatin, and Dexamethasone.
- **Pegaspargase in conjunction with GEMOX regimen**: Gemcitabine and Oxaliplatin.

For patients diagnosed with HLH, the HLH-1994 protocol may be employed as an initial therapeutic approach prior to chemotherapy [15]. Furthermore, the combination of L-ASP and Hematopoietic Stem Cell Transplantation (HSCT) represents a promising curative strategy for these patients [16, 17]. Numerous novel therapeutic agents have demonstrated significant efficacy in vitro against the ANKL cell line, including BCL2 inhibitors, JAK inhibitors, heat shock protein 90 (HSP90) inhibitors, and histone deacetylase inhibitors [18]. A retrospective analysis revealed that incorporating the immune checkpoint inhibitor anti-PD-1 antibody into chemotherapy regimens could enhance the survival rate of ANKL patients [19]. However, these emerging therapies necessitate further clinical trials for validation.

In the case of this critically ill patient, upon transfer to the ICU, we initiated artificial liver support therapy to detoxify the body, stabilize the internal environment, and preserve organ function. Meanwhile, in collaboration with hematologists, we have developed an emergency chemotherapy regimen for ANKL complicated by HLH. The patient exhibited promising therapeutic responses after completing two cycles of chemotherapy. Unfortunately, during the final hospitalization triggered by altered mental status, the family declined further active medical interventions, and as a result, lumbar puncture and head imaging were not conducted. This precluded us from effectively distinguishing between neuroinflammation associated with HLH and leukemic infiltration. Additionally, hepatic encephalopathy and sepsis-associated encephalopathy remain plausible contributors to the neurological symptoms and cannot be conclusively ruled out.

Research demonstrates that emergency chemotherapy in the ICU is primarily indicated for patients diagnosed

Table 1 Laboratory test results upon admission

Date	July 4	July 5	July 6	July 7	July 8	July 9	July 11	July 29	August 23	Reference Range
Treatment	MV DPMAS+LPE CVVHD	MV CVVHD etoposide (110 mg) pegaspargase (5 mL)	MV DPMAS+LPE CVVHD etoposide (110 mg)	MV CVVHD etoposide (100 mg)	MV CVVHD	MV DPMAS+LPE CVVHD	Gemcitabine (1 g)	Secondary chemotherapy	Last hospitalization	/
WBC (10^9/L)	123.73	109.38	32.12	24.38	16.04	11.27	1.38	7.31	20.76	3.5-9.5
LYM (10^9/L)	31.87	NA	6.10	8.72	4.55	1.93	0.95	2.14	2.46	1.1-3.2
LYM%	25.80	NA	19.00	35.80	28.40	17.10	68.80	29.30	11.80	20-50
RBC (10^{12}/L)	3.76	2.82	2.33	3.25	3.07	2.84	2.07	2.61	2.93	4.3-5.8
PLT (10^9/L)	162	138	115	87	62	89	70	1379	142	125-350
TBIL (μmol/L)	135.50	90.90	76.60	62.60	64.00	55.20	38.40	24.70	19.50	3.4-21
DBIL (μmol/L)	69.90	51.10	40.40	27.00	34.30	26.40	14.90	9.40	5.80	0-3.4
LDH (U/L)	5029	NA	NA	NA	2533	NA	NA	270	NA	120-250
PT (second)	21.70	23.20	22.70	16.00	14.40	16.60	17.10	13.70	19.30	9.8-12.1

MV: mechanical ventilation; **DPMAS**: dual plasma molecular adsorption system; **LPE**: Low-volume plasma exchange; **CVVHD**: continuous venous-venous hemodialysis

with acute leukemia or aggressive lymphoma, who may present with critical conditions such as leukostasis, DIC, HLH, and tumor lysis syndrome [20–22]. Historically, emergency chemotherapy in critically ill patients has been regarded as ineffective and associated with prolonged ICU stays and increased mortality rates. However, contemporary evidence suggests that elevated mortality rates are primarily observed in patients with solid tumors, whereas emergency chemotherapy does not significantly influence mortality in patients with hematologic malignancies [23]. Indeed, long-term outcomes for the latter group are promising, with a reported 12-month survival rate of 30%, and 70% achieving complete remission [22, 24].

It is undeniable that emergency chemotherapy possesses both beneficial and adverse effects. On the one hand, it can mitigate life-threatening complications associated with cancer and thereby reduce mortality. On the other hand, side effects such as bone marrow suppression and pulmonary toxicity may exacerbate organ dysfunction and contribute to increased mortality [23]. Nevertheless, for critically ill patients, emergency chemotherapy serves as a potentially life-saving last-resort intervention, providing a glimmer of hope to both patients and their families. Therefore, providing cancer treatment in the ICU is not only feasible but may be essential for patients experiencing severe exacerbation of hematologic disorders ICU physicians play a pivotal role in identifying patients who stand to benefit from emergency chemotherapy. Through close collaboration with a multidisciplinary expert team, individualized treatment plans have been developed for these patients. This approach may serve as a vital bridge, facilitating their progression toward recovery.

Abbreviations

ANKL	Aggressive natural killer cell leukemia
ICU	Intensive care unit
HLH	Hemophagocytic lymphohistiocytosis
DPMAS	Dual plasma molecular adsorption system
CRRT	Continuous renal replacement therapy
LPE	Low-volume plasma exchange
Glu	Glucose
TG	Triglyceride
Fbg	Fibrinogen
Lac	Lactate
PCT	Procalcitonin
IL-6	Interleukin-6
IL-10	Interleukin-10
FERR	Ferritin
sCD25	Soluble CD25
EBV	Epstein-Barr virus
MV	Mechanical ventilation
ENKTL-N	Extranodal NK-/T-cell lymphoma, nasal type
NK-CLPD	Chronic lymphoproliferative disorder of NK cells
DIC	Disseminated intravascular coagulation
L-ASP	L-asparaginase
HSCT	Hematopoietic Stem Cell Transplantation
HSP90	Heat Shock Protein 90

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Author contributions
Y.Z. and Y.Y. were responsible for collecting the clinical information and drafting the manuscript. J.H. and H.L. provided support in the analysis and interpretation of the data. X.L. and L.Q. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of The Affiliated Tumor Hospital of Harbin Medical University (Harbin, People's Republic of China). All methods were performed according to the relevant guidelines and regulations.

Consent for publication
Informed consent for this was obtained from the patient's legal guardian(s).

Competing interests
The authors declare no competing interests.

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References

1. Sumbly V, Vest M, Landry I. Aggressive natural killer cell leukemia: A brief overview of its genomic landscape, histological features, and current management. Cureus. 2022;14(2):e22537.
2. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–31.
3. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, et al. The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
4. Kwong YL, Anderson BO, Advani R, Kim WS, Levine AM, Lim ST. Management of T-cell and natural-killer-cell neoplasms in Asia: consensus statement from the Asian oncology summit 2009. Lancet Oncol. 2009;10(11):1093–101.
5. Lima M. Aggressive mature natural killer cell neoplasms: from epidemiology to diagnosis. Orphanet J Rare Dis. 2013;8:95.
6. Hoffmann JC, Maeda LS, Ohgami RS. Indolent and aggressive mature T-Cell and natural Killer–Cell Lymphomas - ScienceDirect. Atlas Diagn Hematol 2021:251–73.
7. El Hussein S, Medeiros LJ, Khoury JD. Aggressive NK cell leukemia: current state of the Art. Cancers (Basel) 2020, 12(10).
8. Zhang Y, Lee D, Gesiotto Q, Sokol L. Aggressive natural killer cell leukemia: diagnosis, treatment recommendations, and emerging therapies. Expert Rev Hematol. 2021;14(8):731–40.
9. Suzuki R, Suzumiya J, Yamaguchi M, Nakamura S, Kameoka J, Kojima H, Abe M, Kinoshita T, Yoshino T, Iwatsuki K, et al. Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. Ann Oncol. 2010;21(5):1032–40.
10. Tang YT, Wang D, Luo H, Xiao M, Zhou HS, Liu D, Ling SP, Wang N, Hu XL, Luo Y, et al. Aggressive NK-cell leukemia: clinical subtypes, molecular features, and treatment outcomes. Blood Cancer J. 2017;7(12):660.
11. Egashira M, Kawamata N, Sugimoto K, Kaneko T, Oshimi K. P-glycoprotein expression on normal and abnormally expanded natural killer cells and Inhibition of P-glycoprotein function by cyclosporin A and its analogue, PSC833. Blood. 1999;93(2):599–606.
12. Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. J Hematol Oncol. 2017;10(1):85.
13. Ando M, Sugimoto K, Kitoh T, Sasaki M, Mukai K, Ando J, Egashira M, Schuster SM, Oshimi K. Selective apoptosis of natural killer-cell tumours by l-asparaginase. Br J Haematol. 2005;130(6):860–8.
14. Ishida F. Aggressive NK-Cell leukemia. Front Pediatr. 2018;6:292.
15. Wu J, Lu AD, Zhang LP, Zuo YX, Jia YP. [Study of clinical outcome and prognosis in pediatric core binding factor-acute myeloid leukemia]. Zhonghua Xue Ye Xue Za Zhi. 2019;40(1):52–7.
16. Ishida F, Ko YH, Kim WS, Suzumiya J, Isobe Y, Oshimi K, Nakamura S, Suzuki R. Aggressive natural killer cell leukemia: therapeutic potential of L-asparaginase and allogeneic hematopoietic stem cell transplantation. Cancer Sci. 2012;103(6):1079–83.
17. Jung KS, Cho SH, Kim SJ, Ko YH, Kang ES, Kim WS. L-asparaginase-based regimens followed by allogeneic hematopoietic stem cell transplantation improve outcomes in aggressive natural killer cell leukemia. J Hematol Oncol. 2016;9:41.
18. Dufva O, Kankainen M, Kelkka T, Sekiguchi N, Awad SA, Eldfors S, Yadav B, Kuusanmäki H, Malani D, Andersson EI, et al. Aggressive natural killer-cell leukemia mutational landscape and drug profiling highlight JAK-STAT signaling as therapeutic target. Nat Commun. 2018;9(1):1567.
19. Shen K, Liao Y, Dai Y, Ji J, Kuang P, Liu Z, Xie L, Niu T, Jiang N, Ma H. Integration of anti-PD-1 antibody into chemotherapeutic regimens improved the outcome of aggressive NK cell leukemia: a single-center retrospective real-world analysis. Front Immunol. 2025;16:1576904.
20. Pastores SM, Goldman DA, Shaz DJ, Kostelecky N, Daley RJ, Peterson TJ, Tan KS, Halpern NA. Characteristics and outcomes of patients with hematologic malignancies receiving chemotherapy in the intensive care unit. Cancer. 2018;124(14):3025–36.
21. Moors I, Pène F, Lengline É, Benoit D. Urgent chemotherapy in hematological patients in the ICU. Curr Opin Crit Care. 2015;21(6):559–68.
22. Lafarge A, Chean D, Whiting L, Clere-Jehl R. Management of hematological patients requiring emergency chemotherapy in the intensive care unit. Intensive Care Med. 2024;50(6):849–60.
23. de Oliveira MCF, Ferreira JC, Nassar Junior AP, Dettino ALA, Caruso P. Impact of urgent chemotherapy in critically ill patients. J Intensive Care Med. 2020;35(4):347–53.
24. Wohlfarth P, Staudinger T, Sperr WR, Bojic A, Robak O, Hermann A, Laczika K, Carlström A, Riss K, Rabitsch W, et al. Prognostic factors, long-term survival, and outcome of cancer patients receiving chemotherapy in the intensive care unit. Ann Hematol. 2014;93(10):1629–36.

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