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Case report

Acute myeloid leukemia following remission of AIDS-associated extra-nodal NK/T-cell lymphoma

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ABSTRACT

Background: AIDS-related NK/T-cell lymphoma is a rare subtype of AIDS-related lymphomas, characterized by a poor prognosis and lack of standardized treatment protocols. To date, there have been no reported cases of AIDS-associated NK/T-cell lymphoma in remission followed by treatment-related acute myeloid leukemia (t-AML), where both the lymphoma and AML achieved remission and long-term survival through chemotherapy alone.

Case presentation: We report a case of a patient diagnosed with AIDS-related extra-nodal NK/T-cell lymphoma (ENKTCL). The patient achieved complete remission after receiving six cycles of chemotherapy, local radiotherapy, and combination antiretroviral therapy (cART). Throughout the follow-up period, the patient continued cART treatment, maintaining an HIV-RNA level below the lower limit of detection. However, 70 months later, the patient developed new symptoms and was subsequently diagnosed with acute myeloid leukemia (AML) M4 subtype. Following the completion of 10 cycles of chemotherapy and ongoing cART, the patient achieved complete remission of AML, with an overall survival time exceeding 103 months from the initial ENKTCL diagnosis.

Conclusions: This case highlights the effectiveness of chemotherapy combined with cART in the treatment of AIDS-associated NK/T-cell lymphoma and secondary treatment-related leukemia. This approach may serve as a viable option for patients who are not candidates for bone marrow transplantation. Furthermore, this case underscores the importance of long-term follow-up in the management of AIDS-associated malignancies.

1. Background

Acquired immunodeficiency syndrome (AIDS) is a serious global public health problem. AIDS-associated lymphomas are the most prevalent type of AIDS-associated tumors. The most common type of AIDS-related lymphoma is B-cell lymphoma, whereas NK/T-cell lymphomas are rare. The prognosis for patients with AIDS-associated NK/T-cell lymphoma is poor with no standard therapy. Prolonged chemotherapy often leads to secondary diseases, such as treatment-related acute leukemia. Treatment-associated acute

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leukemia is more complex and difficult to treat because of the presence of the original disease and usually requires a bone marrow transplant. On top of this, cases of HIV comorbidity are even more complicated. This case reports a patient with AIDS-related NK/T-cell lymphoma who went into remission secondary to chemotherapy-associated AML, and after refusing bone marrow transplantation for financial reasons, the patient underwent chemotherapy and again went into remission with prolonged survival. The rare case we reported here illustrated the promising efficacy of antiretroviral therapy combined with chemotherapy in HIV-associated NK/T-cell lymphoma, providing an option for patients unwilling or unable to undergo bone marrow transplantation and building the confidence.

2. Case presentation

2.1. AIDS-associated extra-nodal NK/T-cell lymphoma

A 32-year-old man was admitted to our hospital in October 2014, complaining of swelling, pain and ulceration in the left nasal cavity (Fig. 1A). The patient was diagnosed with AIDS in February 2014, and accepted a highly active antiretroviral therapy regimen (HAART) AZT + 3TC + EFV. Blood tests produced the following results: white blood cell count, $6.40*10^9$/L; hemoglobin, 96 g/L; lymphocytes, 31 %; lactate dehydrogenase, 540 U/L; CD4+T lymphocytes, 102 cells/μL; and HIV-RNA, <40 copies/ml. The nasopharynx CT identified lesions in the left nasal tract and septal sinus, and partial bone destruction of the left maxillary sinus lining (Fig. 1B). The nasal tissue biopsy identified $CD56^+$, $CD4^+$, $CD8^-$, Lys+, Ki-67+, GrB+, and CD79a− cells, which supports a diagnosis of extra-nodal NK/T-cell lymphoma (ENKTCL).

In order to avoid severe myelosuppression and minimize the interaction between antivirals and chemotherapy drugs, we changed cART regimen to TDF (300 mg/d) + 3TC (300 mg/d) + EFV (600 mg/d). The chemotherapy administered consisted of pegaspargase, 2625 U, D1; gemcitabine, 1.6 g, Dl; mitoxantrone, 10 mg, D1–D3; and dexamethasone 40 mg, D1–D4. At the end of six cycles of chemotherapy, the patient's left nasal wing defect was significantly smaller, and the left nasolabial groove rupture was healed (Fig. 1C). No lesions were detected on repeat CTs of the nasopharynx (Fig. 1D). Local radiotherapy was completed. After 70 months of follow-up, the patient was in complete remission (CR).

2.2. Secondary acute myeloid leukemia

In August 2020, the patient presented with dizziness, weakness, and fluid flow in the left ear. The physical examination identified the appearance of anemia and a 1.0 × 0.5 × 1.5 cm defect on the left part of the nose (Fig. 2A). Blood analysis reported the following results: white blood cells, $1.14*10^9$/L; hemoglobin, 41g/L; and platelets $18*10^9$/L. The bone marrow cytology result was consistent with acute myeloid leukemia (AML), showing bone marrow blasts (23 %) and peripheral blood smear blasts (8 %) (Fig. 2B). The bone marrow biopsy identified tumor cells with CD34 fraction (+), TdT(−), a CD117 fraction (+), an MPO fraction (+), CD3(−), CD20(−), PAX-5(−), and CD10(−). Karyotype analysis of bone marrow cells reported 45, XY, −7, inv [1] (p12q13) c [2]/45, idem, del [2]

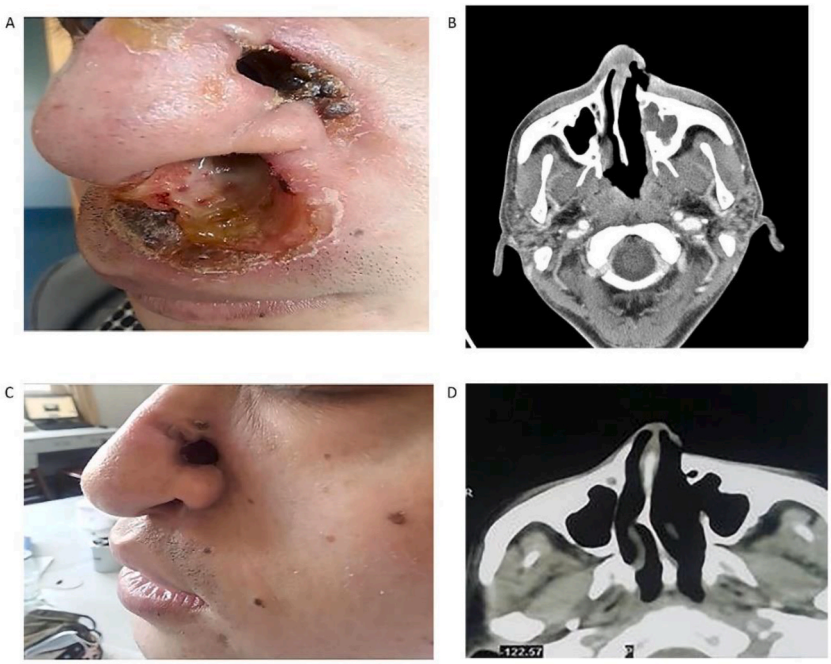

Fig. 1. Patient's nose appearance and CT tests. A and C were the appearance of nose before and after chemotherapy for AIDS-related ENKTL, respectively. B and D were nasopharynx CTs before and after chemotherapy for AIDS-related ENKTL, respectively.

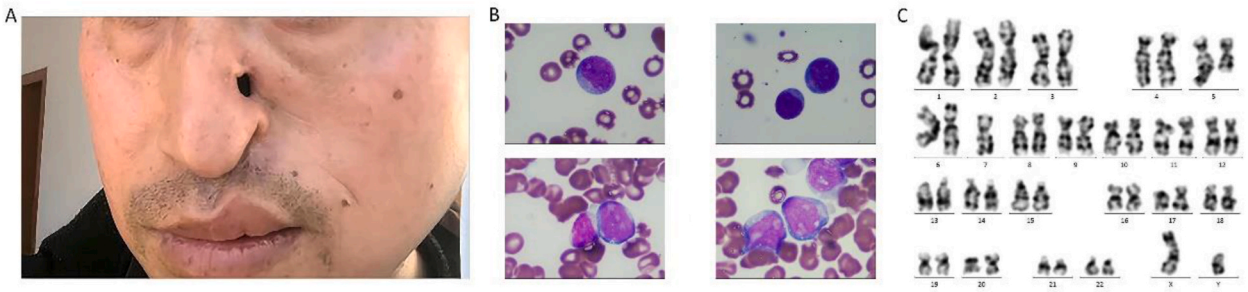

Fig. 2. Patient's nose appearance and examination results when diagnosed as t-AML. A was the appearance of patient's nose. B was the bone marrow test. C was the chromosomal karyotype of bone marrow cells.

(q13q31) [14] (Fig. 2C).

For financial reasons, the patient was unable to receive a hematopoietic stem cell transplant and received chemotherapy instead. The patient received 1 cycle of VDCLP regimen (Vincristine, 2mg, dl,8,15,22; Daunorubicin, 60mg, d1-3, d15-17; Cyclophosphamide, 1.2g, d1.15; Pegaspargase, 3750U, d1.15; Prednisone, 55mg, dl-28), 1 cycle of Ara-C regimen (Cytosine arabinoside, 150mg/m2, q12h, d1-3), 1 cycle of DA regimen (Daunorubicin, 90mg; Cytosine arabinoside, 150mg/m2, q12h, d1-7), 5 cycles of DOAP regimen (Daunorubicin, 90mg, d1-3; Vincristine, 2mg, d1; Cytosine arabinoside, 150mg/m2, q12h, d1-7; Prednisone, 50mg, d1-7), 1 cycle of COAP regimen (Cyclophosphamide, 1.2g, dl; Vincristine, 2mg, dl; Cytosine arabinoside, 100mg/m2, q12h, d1-7; Prednisone, 100mg, d1-7), and 1 cycle of HOAP regimen (Homoharringtonine, 3mg, qd; Cytosine arabinoside, 100mg/m2, ql2h; Vincristine, 2 mg, dl; Prednisone, 150mg, dl-15). After two cycles of chemotherapy, the patient's bone marrow cytology analysis produced an extremely hypo-proliferative bone marrow picture. Bone marrow flow cytometric immunofluorescence analysis revealed no significant abnormal primitive/naive cells. The disease was assessed as CR. The patient completed a total of ten chemotherapy sessions (Fig. 3). During each chemotherapy session, the patient developed myelosuppression (IV), with $0*10^9$/L neutrophils, which was difficult to treat, even with 29.5 units of blood transfused. The CD4+T levels fluctuated between 70 and 140 cells/μL.

The patient currently has survived over 103 months since the initial diagnosis of ENKTL (last follow-up was conducted on April 18, 2023). The survival time after the onset of secondary AML is about 32 months. The HIV-RNA levels were consistently less than the lower limit of detection and CD4 cell count was 450 cells/μL. A whole-body PET-CT scan, along with bone marrow cytology and bone marrow flow suggested a CR.

3. Discussion and conclusion

The relative risk of non-Hodgkin's lymphoma is 60–200 times higher in HIV-infected patients than in the general population before antiretroviral era [3]. Compared to HIV-negative lymphoma, HIV-positive lymphoma is characterized by early age of onset, late disease stage and poor prognosis [4]. The most common pathological type of AIDS-associated lymphoma is B-cell lymphoma, whereas NK/T-cell lymphomas are rare. Here, we report a rare case of AIDS-associated ENKTL with tortuous disease progression.

ENKTL is a kind of extra-nodal non-Hodgkin's lymphoma, often invading the nasal cavity, hard palate and midline areas such as the

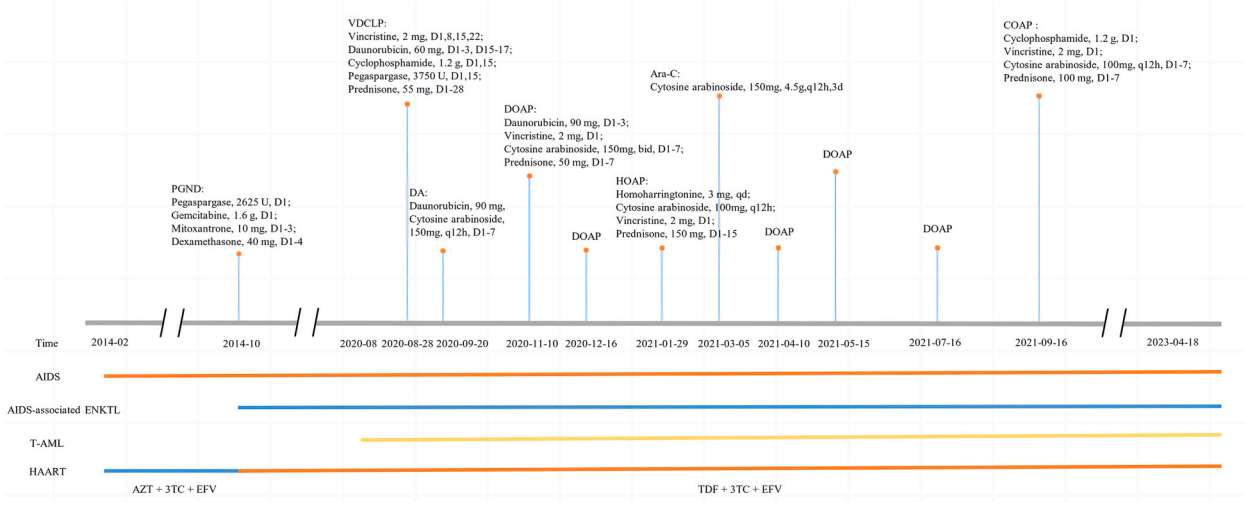

Fig. 3. Treatment history of the patient.

oropharynx. ENKTL is characterized by rapid progression, aggressiveness and poor prognosis [5]. Research has also demonstrated that NK/T-cell lymphomas in HIV-positive patients have a poorer prognosis compared with HIV-negative patients, and that those with CD4 cell counts <200 cells/μL had a poorer prognosis than those with CD4 cell counts greater than 200 cells/μL(4). No standard treatment protocol is available for ENKTL and AIDS-related cases.

ENKTL expressed MDR/ABCB1 gene and P-glycoprotein, and did not respond well to CHOP regimen, asparaginase-containing regimen or platinum-containing regimen were preferred. SMILE, AspaMetex, and P-Gemox were common solutions [2]. HAART should be continued along with chemotherapy in HIV-ENKTL patients. Since chemotherapy drugs can cause myelosuppression, and the myelosuppression of HIV-ENKTL is more severe than that of the general population, antiviral drugs such as AZT which can directly cause myelosuppression should be avoided. In addition, the interaction between chemotherapy agents and antiviral agents should be taken into account [6]. In this case, we used PGND combined with HAART and achieve CR with a survival time of more than 5 years, indicating this regimen can be used as a possible option.

Although the PGND regimen was effective, the drug-related side effects were not negligible, especially treatment-related AML (t-AML) in patients with prolonged survival. Studies found that 10 % of patients with NHL patients who receive conventional or high-dose chemotherapy or stem cell reinfusion are likely to develop treatment-related MDS/AML within 10 years after the initial diagnosis [7]. Alkylating agents and topoisomerase II inhibitors are typical drugs that could induce t-AML. Topoisomerase-induced t-AML usually presents as M4 or M5 types [8]. Chromosomal aberrations and gene mutations such as 5q-5, 7q-7, 11q23, and 21q22 occur frequently in t-AML, which also existed in our case. The median survival time for t- AML is 6–12 months, with low response rate to classical anti-leukemia drugs [1]. No standard treatment option for t-AML exists, and bone marrow transplantation may be a suitable alternative [9]. However, for patients who are unable to receive a bone marrow transplant because of their financial conditions or other reasons, similar to the patient in our article, chemotherapy combined with HAART is an option that may achieve good prognosis. Therefore, an individualized treatment should be provided. Due to limited conditions, we did not perform gene sequencing on this patient, which is a limitation of this study. TP53 mutation is common in therapy-related AML and often indicates a worse prognosis [10]. Future studies should include genomic profiling to better stratify the risk and guide treatment.

It should be noted that this is a single case report, and larger-scale studies are still needed to establish the standard treatment for AIDS-related ENKTL and secondary AML. The good prognosis of this case might be related to the following factors: early stage of lymphoma at initial diagnosis, appropriate choice of chemotherapy regimen, and good compliance of the patient. However, individual differences need to be taken into account in clinical practice.

In conclusion, this case report demonstrates that a combination of chemotherapy and cART can potentially lead to long-term survival in patients with AIDS-related ENKTL, even in the presence of secondary t-AML. This finding underscores the importance of providing individualized treatment strategies for patients with AIDS-related malignancies, particularly those who may not be suitable candidates for bone marrow transplantation.

Furthermore, this case highlights the critical role of long-term follow-up in the management of AIDS-related ENKTL. Regular monitoring is essential for the early detection and timely intervention of potential treatment-related malignancies, such as t-AML, which may develop several years after the initial diagnosis and treatment of ENKTL.

Given the rarity of AIDS-related ENKTL and the paucity of data regarding its optimal management, there is a pressing need for larger, multicenter studies with sufficient sample sizes to establish evidence-based, standardized treatment protocols. Such research efforts will not only improve our understanding of this complex disease but also help to guide clinical decision-making and ultimately enhance patient outcomes.

Ethics statement

Written informed consent was obtained for the publication of all images and data. And this report was approved by the medical ethics committee of the Yunnan Provincial Infectious Diseases Hospital/Yunnan AIDS Care Center.

Consent for publication

All authors have approved the manuscript and agree with the publication.

Data availability statement

Data included in article/supp. material/referenced in article. All data can be obtained from corresponding authors.

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CRediT authorship contribution statement

Shanshan Fan: Data curation, Conceptualization. **Qiwen Zhou:** Data curation, Conceptualization. **Zeping Zhou:** Investigation, Funding acquisition. **Danqing Wang:** Data curation. **Sen Lin:** Data curation. **Hui Bi:** Investigation. **Honghui Wang:** Writing – original draft, Conceptualization. **Haiyan Min:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] D.A. Eichenauer, I. Thielen, H. Haverkamp, J. Franklin, K. Behringer, T. Halbsguth, et al., Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group, Blood 123 (11) (2014) 1658–1664.
[2] Y. Zhang, S. Ma, J. Cai, Y. Yang, H. Jing, Y. Shuang, et al., Sequential P-GEMOX and radiotherapy for early-stage extranodal natural killer/T-cell lymphoma: a multicenter study, Am. J. Hematol. 96 (11) (2021) 1481–1490.
[3] A. Carbone, E. Vaccher, A. Gloghini, Hematologic cancers in individuals infected by HIV, Blood 139 (7) (2022) 995–1012.
[4] P.S. de Carvalho, F.E. Leal, M.A. Soares, Clinical and molecular properties of human immunodeficiency virus-related diffuse large B-cell lymphoma, Front. Oncol. 11 (2021) 675353.
[5] J. Xiong, B.W. Cui, N. Wang, Y.T. Dai, H. Zhang, C.F. Wang, et al., Genomic and transcriptomic characterization of natural killer T cell lymphoma, Cancer Cell 37 (3) (2020) 403, 19.e6.
[6] T. Welz, C. Wyen, M. Hensel, Drug interactions in the treatment of malignancy in HIV-infected patients, Oncol. Res. Treat. 40 (3) (2017) 120–127.
[7] D. Mani, R.K. Dorer, D.M. Aboulafia, Therapy-related acute myeloid leukemia following HIV-associated lymphoma, Clinical lymphoma & myeloma 9 (4) (2009) 316–319.
[8] J. Pedersen-Bjergaard, M.K. Andersen, D.H. Christiansen, C. Nerlov, Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia, Blood 99 (6) (2002) 1909–1912.
[9] R. Abrahão, A.M. Brunson, J.M. Kahn, Q.W. Li, T. Wun, T.H.M. Keegan, Second primary malignancy risk after Hodgkin lymphoma treatment among HIV-uninfected and HIV-infected survivors, Leuk. Lymphoma 63 (5) (2022) 1091–1101.
[10] O.K. Weinberg, A. Siddon, Y.F. Madanat, J. Gagan, D.A. Arber, P. Dal Cin, et al., TP53 mutation defines a unique subgroup within complex karyotype de novo and therapy-related MDS/AML, Blood advances 6 (9) (2022) 2847–2853.