


A Case of Central Nervous System Post-Transplant Lymphoproliferative Disorder Following Haploidentical Stem Cell Transplantation in a Patient With Acute Lymphoblastic Leukemia

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Haibo Zhu¹ , Qing Li¹, Yunyang Liu², Xuequan Feng², and Qi Deng¹

Abstract

We present a differential diagnosis of an intracranial lesion following haploidentical stem cell transplantation (haplo-SCT) in a female patient with acute lymphoblastic leukemia (ALL). This patient received an anti-CD19-chimeric antigen receptor (CAR) T-cell therapy for refractory B-cell ALL and obtained minimal residual disease (MRD)-positive (0.03%) complete remission (CR). Then the patient received a bridging therapy of haplo-SCT. After bridging therapy, the patient maintained MRD-negative and full donor chimerism in bone marrow (BM) and was negative for Epstein–Barr virus (EBV)-DNA copy in peripheral blood. At 91 days after haplo-SCT, the patient presented with dizziness and fatigue and magnetic resonance imaging (MRI) demonstrated an intracranial lesion. The diagnosis of isolated extramedullary relapse (IEMR) was temporarily considered. Then next-generation sequencing (NGS) identified positive EBV-DNA in the cerebrospinal fluid, although EBV-DNA in the peripheral blood was negative. Furthermore, the positive EBV-DNA by NGS and complete donor chimerism in the brain tissue confirmed the diagnosis of central nervous system post-transplant lymphoproliferative disorder (CNS-PTLD). However, the EBV-encoded small RNAs (EBERs) *in situ* hybridization was sparsely positive. The patient was subsequently treated with anti-CD22-CAR T cells in combination with Zanubrutinib, but the disease progressed quickly and died. Donor chimerism examination of focal biopsy provides important evidence for diagnosing PTLD. Furthermore, NGS detection of EBV-DNA in local lesions is more valuable for diagnosing PTLD than detection of EBV-DNA in the peripheral blood.

Trial registration: The patient was enrolled in a clinical trial of *ChiCTR1800019622* and *ChiCTR1800019298*.

Keywords

acute lymphoblastic leukemia, haploidentical stem cell transplantation, central nervous system, post-transplant lymphoproliferative disease, chimeric antigen receptor (CAR)

Background

Isolated extramedullary relapse (IEMR) is a special relapse pattern after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute leukemia, its incidence ranges from 0.65% to 7.4%¹. Soft tissues in the breast, kidneys, intestines, and liver are the usual relapse sites of IEMR in patients with relapsed acute leukemia after allo-HSCT^{2,3}. The incidence of IEMR in patients with acute lymphoblastic leukemia (ALL) following allo-HSCT is 29% within 2 years after allo-HSCT^{2,4}.

Post-transplant lymphoproliferative disorder (PTLD) following solid organ transplantation or allo-HSCT is a rare but fatal complication^{5,6}. Most PTLT is associated with the downregulation of viral proteins that are expressed in B cells infected with Epstein–Barr virus (EBV^{pos}), thereby aiding in

¹ Department of Hematology, Tianjin First Central Hospital, School of Medicine, Nankai University, Tianjin, China

² Department of Neurosurgery, Tianjin First Central Hospital, School of Medicine, Nankai University, Tianjin, China

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Corresponding Authors:

Xuequan Feng, Department of Neurosurgery, Tianjin First Central Hospital, School of Medicine, Nankai University, No. 24, Fukang Road, Tianjin 300192, China.
Email: fengxuequan@126.com

Qi Deng, Department of Hematology, Tianjin First Central Hospital, School of Medicine, Nankai University, No. 24, Fukang Road, Tianjin 300192, China.

Email: kachydeng@126.com



the escape of immune surveillance^{7,8}. Risk factors for EBV^{pos} PTLD after allo-HSCT were explored in a multifactorial analysis, including the use of antithymocyte globulin (ATG), human leukocyte antigen (HLA)-mismatched donor, aplastic anemia, and acute graft-versus-host disease (aGVHD)⁹. In previous studies, the incidence of PTLD after allo-HSCT was reported to range widely within 6 to 12 months after allo-HSCT¹⁰⁻¹⁴. EBV infection might be a major risk factor for PTLD, and reactivation of EBV needs to be carefully monitored in these patients with high-risk factors. Although EBV seropositivity can be a major risk factor, a few PTLDs could be EBV negative (EBV^{neg}) and might be activated by other viruses after allo-HSCT⁵.

Here, we present an ALL patient with central nervous system (CNS)-PTLD after haplo-SCT that was differentiated from CNS-IEMR after haploidentical stem cell transplantation (haplo-SCT).

Case Presentation

A 35-year-old female patient was admitted with major joint pain and fatigue for 1 month. There were 74.55% blasts in the bone marrow (BM) detected by BM aspiration, and 70.71% abnormal B lymphocytes in the BM measured by flow cytometry (FCM). The patient's leukemia cells expressed CD19+CD22+CD10+CD38+CD20- (Fig. 1A). She was diagnosed with B-cell ALL. Cytogenetic studies showed a complex karyotype: 47, XX, +5, t(12; 17) (p13, q21) [4]/47, idem, add (1) (p36.1), add (18) (q23), inc [cp6]/46, XX[15]. No genetic mutation was found in the leukemia cells. After two courses of induction therapy with vincristine, daunorubicin, cyclophosphamide, and prednisolone (VDCP), 1.98% leukemia blasts in the BM measured by FCM were revealed, which indicates there was no remission of B-cell acute lymphoblastic leukemia (B-ALL). Then a lumbar puncture and intrathecal injection of cytarabine, methotrexate, and dexamethasone were performed. After a following two courses of Hyper-CVAD B (methotrexate, leucovorin, and cytarabine) and one cycle of inter-median dose cytarabine chemotherapy, the patient never achieved complete remission (CR), and the leukemia cells in the BM reached 50.45% measured by FCM.

The patient was enrolled in a clinical trial of anti-CD19-chimeric antigen receptor (CAR) T-cell therapy (*ChiCTR1800019622*) as a treatment for refractory B-ALL in our hospital. The expression of leukemia cells measured by FCM was consistent with the initial diagnosis of leukemia. After her autogenous peripheral blood mononuclear cells (PBMCs) were collected¹⁴, she received lymphodepleting chemotherapy with fludarabine (30 mg/m²) and cytarabine (1,000 mg/m²) from day -12 to day -8 before anti-CD19 CAR T-cell infusion. Autologous anti-CD19-CAR T cells were infused on day 0 (1 × 10⁶ cells/kg). During anti-CD19-CAR T-cell therapy, adverse events (AEs) manifested by fever with chills, fatigue, weakness, headache, dizziness,

edema, increased transaminas, cough, and tachycardia started 3 days after CAR T-cell infusion. The highest temperature was 39.2°C, recorded on day 7 after the infusion. The patient was diagnosed with grade 2 cytokine release syndrome (CRS) according to the National Cancer Institute Common Terminology Criteria for AE v4.03¹⁵ and grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS)¹⁶. Antipyretic drugs, methylprednisolone, and symptomatic treatment were used to overcome these AEs. The amplification of anti-CD19-CAR T cells in CD3+ T cells in the peripheral blood was detected on days 0, 4, 7, 14, and 28 after infusion measured by FCM. The anti-CD19-CAR T-cell peak reached 35.24% on day 7. DNA levels of the anti-CD19-CAR gene were detected by quantitative polymerase chain reaction (qPCR) and reached their peak of 24,500 copies/ng gDNA on day 14. The cytokines, including interleukin-6 (IL-6), IL-2R, and tumor necrosis factor-alpha (TNF-α) in peripheral blood were detected by enzyme linked immunosorbent assay (ELISA) and reached their peaks on day 7 after infusion (134 pg/mL, 6,800 U/mL, and 56.3 pg/mL, respectively). The patient achieved minimal residual disease (MRD)-positive (0.03%) CR with incomplete count recovery (Cri) measured by FCM at 14 days after anti-CD19-CAR T-cell infusion with no evidence of leukemic cells in cerebrospinal fluid (CSF) analysis.

At 28 days after anti-CD19-CAR T-cell therapy, the patient received a bridging therapy of haplo-SCT. Before the transplantation, computed tomography (CT) of the head, chest, abdomen, and pelvis showed no abnormalities. The patient had no extramedullary disease before haplo-SCT. DNA copy numbers of EBV and cytomegalovirus (CMV) measured by real-time qPCR were negative. The patient underwent haplo-SCT from a haploid donor (daughter, 5/10 HLA match). Prior to haplo-SCT treatment, the patient underwent regimens including total body irradiation (TBI, 3 Gy/day, -9 to -7 day), cyclophosphamide (Cy, 50 mg/kg/day, -6, and -5 day), fludarabine (Flu, 30 mg/m²/day, -4 to -2 days), and cytarabine (Ara-C, 3.0 g/m²/day, -4 to -2 days). Graft-versus-host disease (GVHD) prophylaxis consisted of ATG, cyclosporin A (CsA), and mycophenolate mofetil (MMF). The dose of CD34+ cells from PBMCs from her donor was 4.28 × 10⁶ cells/kg. The patient's neutrophils and platelets were engrafted on 12 and 25 days after haplo-SCT, respectively. She achieved MRD-negative Cri determined by FCM at 14 days after haplo-SCT, and full donor chimerism according to short-tandem repeat (STR) at 28 days after haplo-SCT. Grade 1 aGVHD of the skin occurred 32 days after haplo-SCT and was in remission after short course of glucocorticoids and CsA therapy. EBV and CMV DNA copies in the blood were measured by qPCR and monitored weekly after haplo-SCT. The patient maintained an MRD-negative in the BM, full donor chimerism in the BM, and negative DNA copy numbers of EBV and CMV in peripheral blood. The patient received intrathecal chemotherapy monthly after haplo-SCT to prevent central nervous system leukemia.

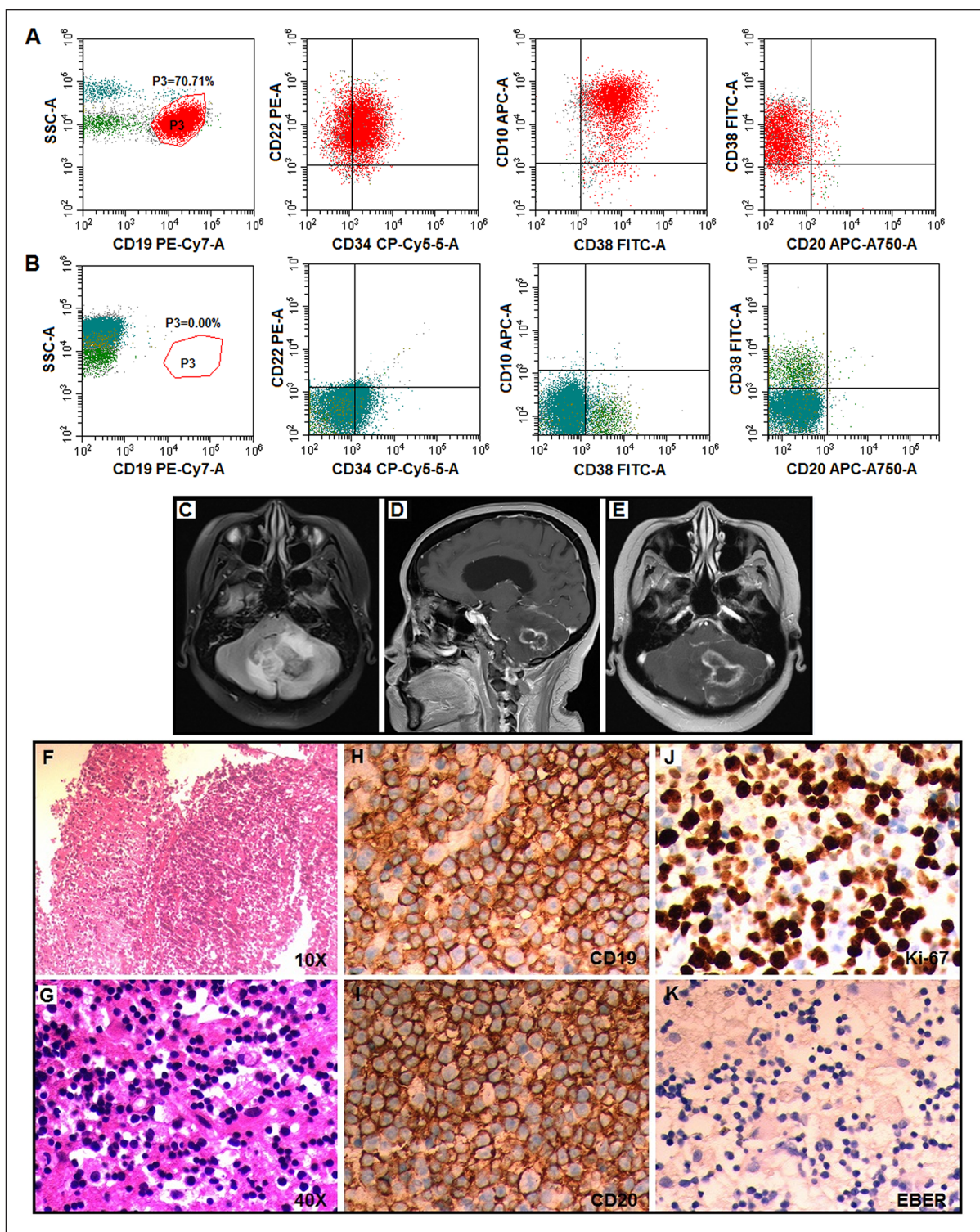


Figure 1. Clinical examination results. (A) Expression of AL cells at diagnosis. (B) MRD in BM was negative after haplo-SCT when the neurological symptoms appeared. (C) MRI demonstrated multiple abnormal hyperintensity lesions surrounded by edema in cerebellar vermis and left cerebellar hemisphere. (D and E) The intracranial neoplasm was considered intracranial invasion of leukemia by dynamic enhanced MRI. (F and G) The brain tissue showed that diffuse infiltration of small round cells with deep staining. (H) The tumor cells stained positive for CD19. (I) The tumor cells stained positive for CD20. (J) The tumor cells stained approximately 75% for Ki-67. (K) EBER *in situ* hybridization was sparsely sparse positive. MRD: minimal residual disease; BM: bone marrow; SCT: stem cell transplantation; MRI: magnetic resonance imaging; EBER: Epstein–Barr virus-encoded RNA; AL: all events; SSC-A: side scatter-area.

At 91 days after haplo-SCT, the patient presented with dizziness and fatigue, without fever, nausea, vomiting, and lymphadenopathy. After admission to our center, the patient was MRD-negative in the BM (Fig. 1B), and donor chimerism in the BM was at 100%. The DNA copies of EBV and CMV in the peripheral blood were negative. Lumbar puncture revealed that the intracranial pressure exceeded 280 mmH₂O, and protein in the CSF was 130.60 mg/dk. No leukemia cells or abnormal expression cells were detected in the CSF by FCM. The patient received methotrexate (MTX, 10 mg) combined with Ara-C (25 mg) by intrathecal injection. CT of the chest, abdomen, and pelvis showed no abnormalities. Magnetic resonance imaging (MRI) demonstrated multiple abnormal hyperintensity lesions surrounded by edema in the cerebellar vermis and the left cerebellar hemisphere (Fig. 1C). Dynamic enhanced MRI demonstrated intracranial neoplasm surrounded by edema in the cerebellar vermis and the left cerebellar hemisphere, which was considered to be an intracranial invasion of leukemia (Fig. 1D, E). At this time, the patient was temporarily diagnosed with IEMR after haplo-SC. Therefore, CsA administration (50 mg/day) was discontinued immediately and symptomatic dehydration treatment was started. The patient enrolled in another clinical trial of anti-CD22-CAR T-cell therapy (*ChiCTR1800019298*) as a relapsed or refractory (R/R) B-ALL in our center. Her donor provided the PBMCs for anti-CD22-CAR T-cell therapy, but the symptoms of dizziness and fatigue were not relieved, there was still no fever, nausea, vomiting, or lymphadenopathy.

A second lumbar puncture and intrathecal injection were performed. The intracranial pressure was 280 mm H₂O, and protein in the CSF was 142.80 mg/dk. No leukemia cells were detected in the CSF by FCM. Next-generation sequencing (NGS) of the CSF was performed to rule out a diagnosis of infectious disease of the CNS. The DNA analysis showed 2,782 EBV sequences, and RNA analysis showed 174 EBV sequences in the CSF measured by NGS methods. We clarified the diagnosis of IEMR after haplo-SCT. Although the patient was EBV-DNA negative in peripheral blood, she did have EBV-DNA in her CSF, suggesting a diagnosis of PTLD. The patient underwent a cerebellar lesion biopsy and a left ventricular external drainage via robotic surgical assistant (ROSA, Medtech, Montpellier, France) using the assisted stereostatic method. The external ventricular drainage tube was kept open intermittently after surgery. The symptoms of dizziness and fatigue were slightly relieved after the surgery. The biopsy of the brain tissue showed diffuse infiltration of small round cells with deep staining (Fig. 1F, G). The tumor cells stained positive for CD19, CD20, Ki-67 (approximately 75%) (Fig. 1H–J), and C-myc (approximately 25%). Although the result of EBV-encoded RNA (EBER) *in situ* hybridization was sparsely positive (Fig. 1K), NGS of the brain tissue was positive for EBV. The brain tissue DNA analysis showed 3,815 EBV sequences, while the brain

tissue RNA analysis showed 3,140 EBV sequences. The brain tissue and the BM specimens showed full donor chimerism and were of great diagnostic value. Based on these results, we confirmed the diagnosis of CNS-PTLD and identified monomorphic small B-cell lymphoma with EBV infection. A ventriculoperitoneal shunt was placed first before an anti-CD22-CAR T-cell Zanubrutinib combination therapy. Unfortunately, the patient suddenly developed drowsiness and cognitive impairment and died during the combination therapy.

Discussion

Intracranial lesions were first diagnosed as IEMR after haplo-SCT in this B-ALL patient because the DNA copy of EBV in peripheral blood continued to be negative. However, we unexpectedly detected EBV-DNA in the CSF by NGS methods. Finally, the diagnosis of CNS-PTLD was further confirmed by brain histopathology and donor chimerism testing method.

IEMR after allo-HSCT is relatively rare, and in acute leukemia after allo-HSCT, the incidence of IEMR (5.8%) is lower than the incidence of bone marrow relapse (BMR) (41.0%), while the occurrence time of IEMR (10 months) is later than that of the BMR (4 months)¹⁷. In this study, the risk factors included diagnosis of ALL, poor cytogenetics, advanced disease phase at transplantation, prior extramedullary disease, and chronic GVHD^{17,18}. The intracranial lesion of our patient had two risk factors for diagnosing IEMR, diagnosis of ALL and advanced disease phase at the time of transplantation. Considering the patient's negative EBV-DNA in the peripheral blood after haplo-SCT, we first diagnosed IEMR.

A Japanese study reported that the probability of developing EBV-positive PTLD at 2 years post-HSCT was 0.79%⁹. In addition, the incidence rate of PTLD reported in other studies was lower than that of IEMR^{10–12,17}. Different from the risk factors for IEMR after allo-HSCT, the risk factors for EBV-positive PTLD are⁹ ATG in a conditioning regimen and ATG in treatment of acute GVHD, non-HLA-matched related donor, aplastic anemia, second or subsequent allo-HSCT, allo-HSCT in the last year, and aGVHD. Another study constructed a risk stratification tool to identify patients at high risk for PTLD¹⁹. The tool assigns points for different risk factors: ATG use in conditioning regimen (high dose: 2 points, low dose: 1 point), donor type (HLA-mismatched related donor: 1 point, unrelated donor: 1 point, cord blood: 2 points), and a diagnosis of aplastic anemia (1 point). The risk scores are classified as low risk (0–1 points), intermediate risk (2 points), high risk (3 points), and very high risk (4–5 points). The intracranial lesion of our patient had two risk factors for the diagnosis of EBV-positive PTLD: the ATG in conditioning regimen and HLA-mismatched related donor. Her risk score was classified into the high-risk group

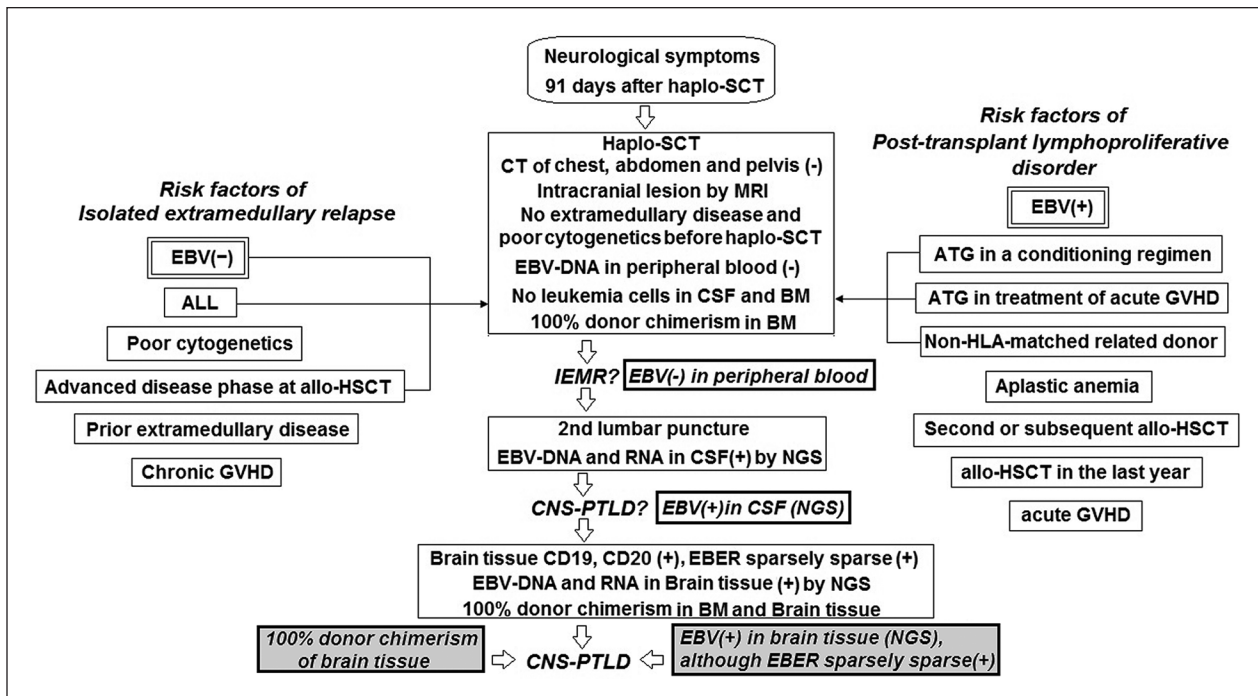


Figure 2. Differential diagnostic procedure. SCT: stem cell transplantation; EBV: Epstein–Barr virus; ALL: acute lymphoblastic leukemia; HSCT: hematopoietic stem cell transplantation; GVHD: graft-versus-host disease; CT: computed tomography; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; BM: bone marrow; IEMR: isolated extramedullary relapse; NGS: next-generation sequencing; CNS-PTLD: central nervous system post-transplant lymphoproliferative disorder; EBER: Epstein–Barr virus-encoded RNA; ATG: antithymocyte globulin; HLA: human leukocyte antigen.

(3 points), and the incidence of PTLD was 4.09% according to Fujimoto’s risk score using the Taiwan Bone Marrow Transplant Registry Database⁹. The incidence of CNS-PTLD after allo-HSCT in acute leukemia is rare, and it is lower than that after transplantations in solid organs^{20–22}.

The patient developed neurological symptoms 91 days after haplo-SCT, and was diagnosed with IEMR. The diagnostic basis for this diagnosis was negative EBV-DNA in the peripheral blood, complete donor chimerism in the BM, negative CSF examination, and intracranial lesion in the head MRI examination. Then positive EBV sequence determined by NGS was found in the CSF during a second lumbar puncture, although EBV-DNA in the peripheral blood was negative. Therefore, we began to consider the diagnosis of PTLD. After analyzing the risk factors for IEMR and PTLD, we decided to perform a brain biopsy and a left ventricular external drainage to confirm the diagnosis and relieve neurological symptoms. NGS found EBV sequences and complete donor chimerism in the brain tissue confirmed the diagnosis of CNS-PTLD, although the EBER *in situ* hybridization was sparsely positive (Fig. 2).

After the CNS-PTLD diagnosis was confirmed as monomorphic small B-cell lymphoma with EBV infection, we selected the anti-CD22-CAR T-cell zanubrutinib combination therapy for this patient. There were no definitive guidelines for the optimal treatment of CNS-PTLD after allo-HSCT.

Treatment options included the withdrawal of immunosuppressive agents, high-dose MTX and cytarabine, adoptive immunotherapy with EBV-specific cytotoxic T lymphocytes²³, and anti-CD19 CAR T-cell therapy^{24–26}. A refractory PTLD patient with a high tumor burden after kidney transplantation had been successfully treated with anti-CD19-CAR T cell combined with programmed cell death 1 (PD-1) inhibitors at our center previously²⁷. A Bruton’s tyrosine kinase (BTK) inhibitor has shown promising results for CNS B-cell non-Hodgkin’s lymphoma^{28,29}, a study reported the efficacy of the BTK inhibitor zanubrutinib in the therapy of CNS-PTLD³⁰. Hence, we formulated a scheme of anti-CD22-CAR T cell and zanubrutinib combination therapy for this CNS-PTLD patient.

Conclusion

Differential diagnosis of IEMR or PTLD is required in ALL patients after allo-HSCT with CNS lesions. Patients who have extramedullary lesions and negative EBV-DNA in the peripheral blood are easily misdiagnosed with extramedullary recurrence. Donor chimerism results from a focal biopsy of brain tissue could be selected as important evidence for the diagnosis of PTLD. Furthermore, NGS detection of EBV-DNA in the CSF and brain tissue is more valuable for diagnosing PTLD than detection of EBV-DNA in the peripheral blood.

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Author Contributions

Concept and design: QD and XF. Drafted or revised the manuscript: HZ. Acquisition of data: QL. Analysis and interpretation of data: HZ and YL. Writing, review, and/or revision of manuscript: HZ and QD.

Ethical Approval

This study was approved by the Medical Ethics Committee of the Department of Hematology, Tianjin First Center Hospital (Tianjin, China). (Approved No. of ethic committee: 2018N105KY and 2015002X). This Clinical trial was registered at <http://www.chictr.org.cn/index.aspx> as *ChiCTR1800019622* and <http://www.chictr.org.cn/index.aspx> as *ChiCTR1800019298*.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

Patient Consent for Publication

Obtained.

Data and Resource Availability

The data sets generated from the current study are available from the corresponding author upon request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Haibo Zhu  <https://orcid.org/0000-0002-0515-9833>

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