Successful treatment of early onset Epstein-Barr virus-negative T-cell lymphoproliferative disorder after allogeneic hematopoietic stem cell transplantation with histone deacetylase inhibitor chidamide

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To the Editor: A 58-year-old man, who diagnosed with chronic myelomonocytic leukemia in June 2019, achieved complete bone marrow remission after five courses of chemotherapy (decitabine 35 mg, days 1–5). In December 2019, he underwent an allogeneic hematopoietic stem cell transplant (allo-HSCT) from his human leukocyte antigen-haploidentical daughter. The donor and host pre-transplant Epstein-Barr virus (EBV) serologies were negative. The myeloablative conditioning regimen was administered with cytarabine, busulfan, cyclophosphamide, methyl-N-(2-chloroethyl)-N-cyclohexyl-N-nitrosourea, and anti-thymocyte globulin. The numbers of mononuclear cells and CD34+ cells were 12.23×10^8/kg and 7.57×10^8/kg, respectively. Graft-versus-host disease (GVHD) prophylaxis included cyclosporin A (CSA) and mycophenolate mofetil (MMF). CSA was later changed to tacrolimus due to a gastrointestinal reaction on day +15. The patient had a history of tuberculosis (TB) and received isoniazid and rifapentine for prevention. Neutrophil and platelet engraftment occurred on day +12 and +18, respectively. Cytogenetic studies showed complete donor chimerism on day +26.

On day +20, the patient developed recurrent fever with a peak temperature of up to 40°C. No evidence of bacterial and virus infection was observed. Investigations showed an increase in the lactic dehydrogenase levels from 170 to 270 U/L and a slightly higher hypersensitive C-reactive protein level (19.1 mg/L). The procalcitonin and immunoglobulin M were normal, and ferritin was slightly higher than that detected before transplantation (1795.3 *vs.* 2069.6 ng/mL). A lung computed tomography (CT) was normal. On day +25, the patient was found to have left cervical lymphadenopathy that rapidly progressed to bilateral lymph nodes. The ultrasound examination of superficial lymph nodes identified multiple lymphadenopathies in the neck and axilla. Two cervical lymph node biopsies were performed on days +30 and +40, which was suggestive of post-transplantation lymphoproliferative disorder (PTLD). Immunohistochemical studies revealed positive staining for CD3, CD43, CD5, CD68, CD8, Bcl-2, Bcl-6, and T-cell intracellular antigen-1, and focally positive staining for CD20, CD30, and CD4, whereas negative staining for CD10, CD34, and CD56 [Figure 1A–1D]. The Ki-67 proliferation index was found to be approximately 60%. Gene rearrangement studies of the T-cell receptor were positive. EBV *in situ* hybridization using Epstein-Barr-encoded RNA also showed a negative result in the tumor cells. TB and fungi evaluated by fluorescence *in situ* hybridization analysis were also negative. ^{18}F-fluorodeoxyglucose positron emission tomography/CT performed on day +42 also demonstrated increased fluorodeoxyglucose uptake at multiple enlarged lymph nodes of the neck and axilla, and no other abnormal uptake was observed on the whole body. Based on these findings, the final pathological diagnosis of EBV-negative PTLD, peripheral T-cell lymphoma (PTCL), was established.

Tacrolimus and MMF were discontinued as soon as the diagnosis of T-cell PTLD (T-PTLD) was confirmed. Considering that patients in the early stage of HSCT have poor tolerance to chemotherapy, we initiated dexamethasone (10 mg/day) combined with ruxolitinib (5 mg/day) to control fever and prevent GVHD on day +40. The patient's body temperature temporarily returned to normal, but

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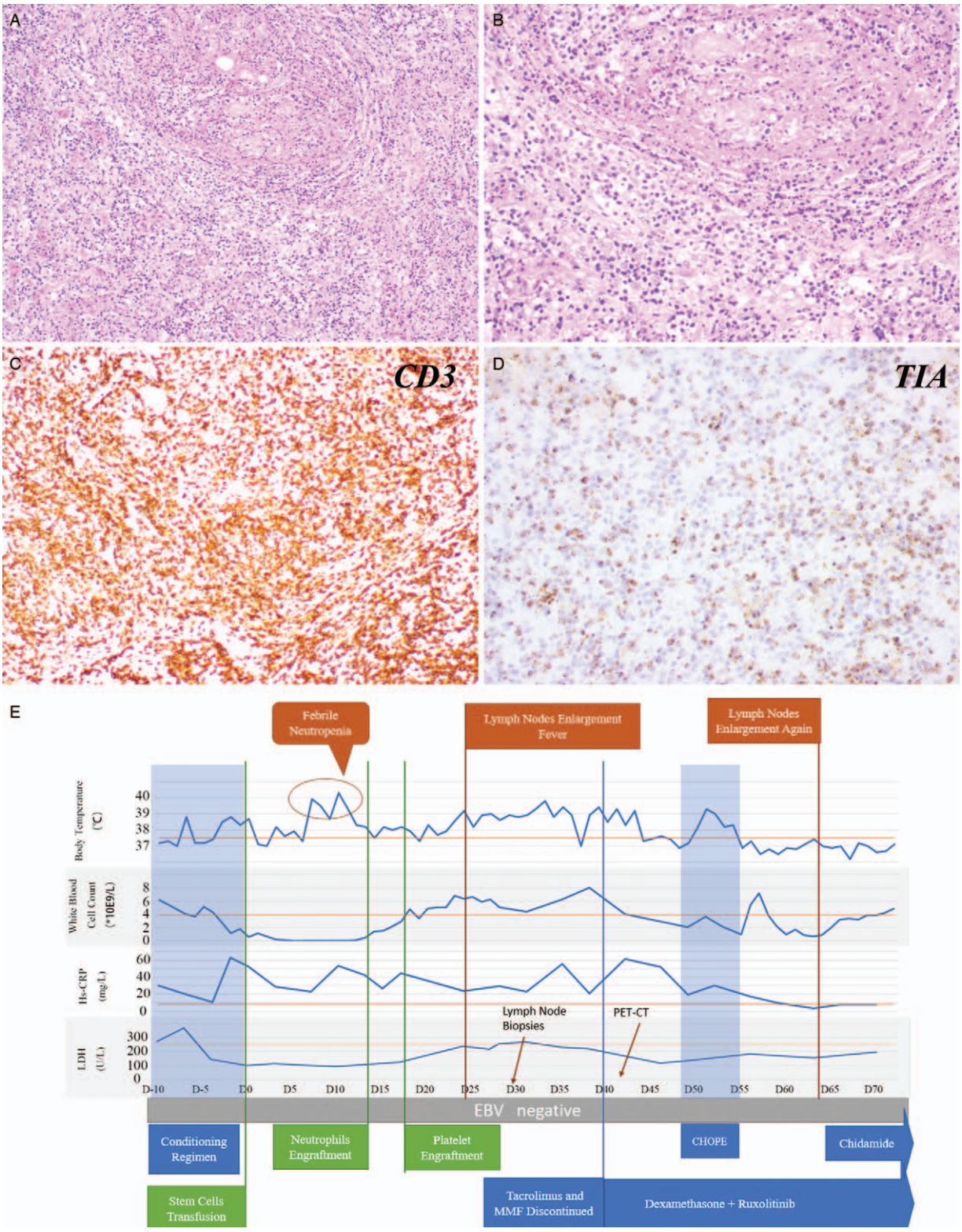

Figure 1: Lymph node biopsy of the left neck by hematoxylin-eosin staining showing diffuse proliferation of abnormal T-lymphocytes in PTCL ([A] original magnification ×100; [B] original magnification ×200). Immunohistochemical studies revealed positive staining for CD3 (C, original magnification ×200) and TIA (D, original magnification ×200). (E) Shows the summary of clinical treatment events and laboratory data after hematopoietic stem cell transplantation. CHOPE: Etoposide, cyclophosphamide, liposome doxorubicin, vindesine, dexamethasone; EBV: Epstein-Barr virus; Hs-CRP: Hypersensitive C-reactive protein; LDH: Lactic dehydrogenase; MMF: Mycophenolate mofetil; PET-CT: Positron emission tomography/computed tomography; PTCL: Peripheral T-cell lymphoma; TIA: T-cell intracellular antigen.

lymphadenopathy did not improve. On day +45, the patient's temperature increased to 40°C, and we thus increased the dose of ruxolitinib to 10 mg/day, but little effect was achieved. During that time, the counts of neutrophils and platelets were normal. On day +49, the patient was treated with cyclophosphamide, liposome doxorubicin, vindesine, dexamethasone, etoposide (CHOPE) chemotherapeutic regimen including etoposide (100 mg on days 1, 3, and 5), dexamethasone (10 mg on days 1–5), vindesine (4 mg on day 1), cyclophosphamide (600 mg on day 1), and liposome doxorubicin (20 mg on day 1) over a period of 5 days. The lymphoid lesions decreased after chemotherapy. During chemotherapy, the white blood cell (WBC) and platelet counts decreased to minimal levels of 0.7×10^9/L and 40.0×10^9/L, respectively. On day +64, the patient developed multiple lymphadenopathies again. We added 30 mg of chidamide biweekly at day +66, and the enlarged lymph nodes showed gradual improvement. Three weeks later, the lymphoid lesions had resolved. Thus, chidamide was discontinued in the fourth week. During treatment with chidamide, the patient's body temperature was consistently normal. The platelet and WBC counts decreased temporarily to minimal levels of 38.0×10^9/L and 2.8×10^9/L over this period and returned to normal 2 weeks after chidamide withdrawal. Up to the completion of this report (13 months after HSCT), no further lymphadenopathy was observed. The treatment process is summarized in Figure 1E.

PTLD is well recognized as a life-threatening complication after HSCT, with a 3-year survival rate of 20% to 47%.[1] Most PTLDs originate from B cells, and T-PTLD has rarely been reported, representing approximately 7% to 15% of all PTLDs.[2] The median interval from HSCT to the onset of PTLD was about 5 months, ranging from 2 to 43 months.[3] Probably, PTLD started as early as on post-transplant day +25 in our patient based on the examination findings and clinical symptoms. EBV-negative T-PTLD was diagnosed through lymph node biopsy on day +30. To our knowledge, such early onset of T-PTLD after HSCT has not been previously reported.

Immunosuppression withdrawal and chemotherapy with CHOPE-based regimens are often the treatments of choice for early onset T-PTLD.[4] However, at the early stage of HSCT, hematopoietic reconstruction has not fully recovered, which makes treatment more difficult. In our case, although the patient's body temperature returned to normal and the lymph node enlargement showed improvement after immunosuppressant withdrawal and chemotherapy, the patient soon experienced recurrence accompanied by myelosuppression.

As a novel histone deacetylase inhibitor (HDACi), chidamide was approved by the China Food and Drug Administration in December 2014 for the treatment of relapsed/refractory (R/R) PTCL.[5] In a single-arm, multicenter phase II clinical trial, Shi *et al*[5] evaluated the efficacy of chidamide in 79 Chinese patients with R/R PTCL and found that 14% of patients achieved a complete response (CR)/unconfirmed CR. The median progression-free survival and overall survival were 2.1 and 21.4 months, respectively. In our case, the patient achieved CR after chidamide treatment and was asymptomatic as of the report. Treatment with chidamide was generally well tolerated by the patient, although side effects such as thrombocytopenia and leukopenia were observed. After stopping chidamide, WBC and platelet counts were quickly recovered. A longer follow-up period is needed to address the therapeutic advantage of HDAC inhibitors in PTCL.

To conclude, our case represents a rare, very early onset EBV-negative PTLD with monomorphic PTCL involving the neck and axillary lymph nodes. A timely lymph node biopsy is helpful for determining a diagnosis. Chidamide achieved promising outcomes with few side effects in our case, but more studies are needed to further confirm the effects of chidamide.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patient has given his consent for the publication of her images and other clinical information in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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