Ann Hematol (2011) 90:113–114
DOI 10.1007/s00277-010-0947-8

LETTER TO THE EDITOR

Cytomegalovirus and Epstein–Barr virus-associated post-transplant lymphoproliferative disorder after allogeneic hematopoietic stem cell transplantation

Shu-Yi Tsao · Kung-Chao Chang · Ya-Ping Chen · Yu-Min Yeh · Wu-Chou Su · Tsai-Yun Chen

Received: 2 December 2009 / Accepted: 16 March 2010 / Published online: 6 April 2010

Dear Editor,

Post-transplant lymphoproliferative disorder (PTLD) is a group of diseases ranging from reactive hyperplasia to aggressive lymphomas. The incidence after allogeneic hematopoietic stem cell transplantation (allo-HSCT) is about 1% [1]. It is believed that PTLD is related to the overgrowth of Epstein–Barr virus (EBV)-infected B-lymphocytes, but the role of cytomegalovirus (CMV) is still unclear [1, 2]. We present a case of PTLD with histological evidence of CMV and EBV coinfection in an HSCT recipient.

A 36-year-old man with diabetes mellitus and acute myeloid leukemia, M5b, t(9;11) achieved complete remission after I3A7 induction chemotherapy. He received a right hemicolectomy because of persistent CMV-associated neutropenic enterocolitis after induction chemotherapy, and then, in March 2008, underwent allogeneic peripheral blood stem cell transplantation from an HLA-matched sibling donor. Pre-transplant viral serology studies of the recipient were positive for CMV IgG and EBV IgG and negative for CMV IgM and EBV IgM. The conditioning regimen was BuCy2, and methotrexate and cyclosporine were given as prophylaxes for graft-versus-host disease (GVHD). On day 0, an unmanipulated graft from a CMV-naïve and EBV-IgG-positive sibling donor was infused (3.25×10^6 CD34+ cells per kilogram of recipient body weight). On day+23, grade II acute GVHD was diagnosed from an enteroscopic intestinal biopsy. Methylprednisolone (2 mg/kg/day) was given and tapered gradually after the recipient showed a complete response. On day+28, ganciclovir was prescribed for 2 weeks as pre-empty therapy for CMV reactivation with positive CMV antigenemia. The CMV antigenemia was resolved after ganciclovir therapy.

On day+157, palpable lymph nodes were found over the bilateral neck. Cyclosporine was discontinued because we suspected PTLD. The lymph node biopsy showed (1) polymorphic B-cell hyperplasia (Fig. 1a) with EBER in situ hybridization-positive cells (EBER probe; Ventana Medical System, Tucson, AZ, USA; Fig. 1b) and (2) enlarged endothelial cells with cytoplasmic and nuclear inclusions, which are positive for CMV monoclonal antibody (Clone CMV 01, Neomarkers; Fig. 1c). At that time, blood CMV antigenemia was negative. The EBV viral load in peripheral blood was 32 copies per milliliters (Light Mix® kit; TIB MOLBIOL GmbH, Germany). Based on the histology result, PTLD/infectious mononucleosis-like disease with CMV coinfection was diagnosed. The patient was treated with valganciclovir for 3 weeks, and the cervical lymphadenopathy completely subsided after antiviral therapy and the tapering of cyclosporine.

PTLD with CMV and EBV coinfection is rare. There are EBER-positive B-lymphocytes and CMV monoclonal antibody-positive endothelial cells in the same affected lymph node. In heart, liver, and renal transplant recipients, CMV may contribute to the development of EBV-associated lymphomas [3–5]. Paraskevas et al. [6] found an association between CMV infection and PTLD in pancreas transplant recipients, but they found no detectable CMV in the specimens. Hou et al. [7] suggested that

S.-Y. Tsao · Y.-P. Chen · Y.-M. Yeh · W.-C. Su · T.-Y. Chen (✉)
Section of Hematology/Oncology,
Department of Internal Medicine, College of Medicine,
National Cheng Kung University,
138 Sheng-Li Road,
Tainan 704, Taiwan
e-mail: teresa@mail.ncku.edu.tw

K.-C. Chang
Department of Pathology, College of Medicine,
National Cheng Kung University,
Tainan, Taiwan

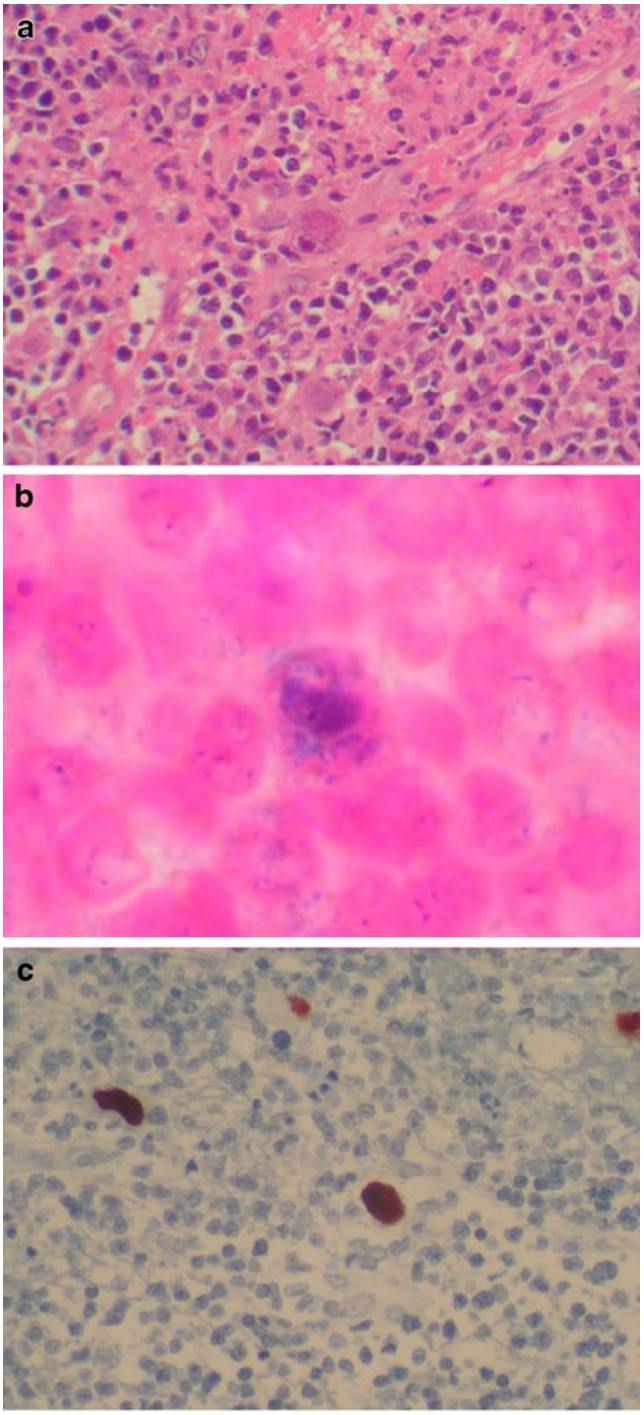

Fig. 1 **a** Hematoxylin and eosin stain showed lymphocyte hyperplasia and enlarged endothelial cells with cytoplasmic and nuclear inclusion bodies. **b** Immunohistochemical stain showed some EBER-positive cells in the background. **c** Immunohistochemical stain showed some enlarged cells positive for CMV monoclonal antibody

CMV infection was a risk factor of PTLD in HSCT as well. Brion et al. [8] detected the CMV genome in one of three specimens from HSCT recipients with EBV-associated PTLD. Our case implied that EBV and CMV infection may occur concurrently in PTLD, and CMV may contribute to the development of EBV-associated lymphomas. Latent CMV infection may inhibit T cell responses, which may contribute to insufficient EBV-specific T cell responses and the subsequent proliferation of EBV-transformed B cells.

PTLD is a heterogeneous group of lymphoproliferative disorders ranging from early polyclonal lesions to aggressive lymphomas [9]. The treatment strategies for PTLD include reducing immunosuppression, infusing EBV-specific cytotoxic T cells, local therapy with surgery or radiotherapy, rituximab for CD20+ disease, systemic chemotherapy, and antiviral therapy [10]. Based on the results of our case and previous studies, we conclude that antiviral therapy and reducing immunosuppression are effective against early polyclonal lesions, as in our case.

References

1. Gottschalk S, Rooney CM, Heslop HE (2005) Post-transplant lymphoproliferative disorders. Annu Rev Med 56:29–44
2. Opelz G, Daniel V, Naujokat C, Fickenscher H, Dohler B (2007) Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis. Lancet Oncol 8:212–218
3. Manez R, Breinig MC, Linden P, Wilson J, Torre-Cisneros J, Kusne S, Dummer S, Ho M (1997) Posttransplant lymphoproliferative disease in primary Epstein–Barr virus infection after liver transplantation: the role of cytomegalovirus disease. J Infect Dis 176:1462–1467
4. Mattila PS, Aalto SM, Heikkila L, Mattila S, Nieminen M, Auvinen E, Hedman K, Tarkkanen J (2001) Malignancies after heart transplantation: presence of Epstein–Barr virus and cytomegalovirus. Clin Transplant 15:337–342
5. Vila L, Moreno L, Andres MM, Fernandez JM, Verdeguer A, Perez-Valle S, Sanguesa C, Berbel O, Castel V (2008) Could other viruses cause pediatric posttransplant lymphoproliferative disorder? Clin Transl Oncol 10:422–425
6. Paraskevas S, Coad JE, Gruessner A, Kandaswamy R, Humar A, Sutherland DE, Gruessner RW (2005) Posttransplant lymphoproliferative disorder in pancreas transplantation: a single-center experience. Transplantation 80:613–622
7. Hou HA, Yao M, Tang JL, Chen YK, Ko BS, Huang SY, Tien HF, Chang HH, Lu MY, Lin TT, Lin KH, Hsiao CH, Lin CW, Chen YC (2009) Poor outcome in post transplant lymphoproliferative disorder with pulmonary involvement after allogeneic hematopoietic SCT: 13 years' experience in a single institute. Bone Marrow Transplant 43:315–321
8. Brion A, Cahn JY, Mougin C, Angonin R, Flesch M, Deschaseaux ML, Plouvier E, Deconinck E, Voillat L, Racadot E, Carbillet JP, Herve P (1995) Herpes virus-related lymphoproliferative disorders following allogeneic bone marrow transplantation: clinical and biological characteristics of six cases. Nouv Rev Fr Hematol 37:289–296
9. Swerdlow SH, Harris NL, Jaffe ES, Pileri SA (2008) World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. Lyon, France: International Agency for Research on Cancer (IARC) 343–349
10. Frey NV, Tsai DE (2007) The management of posttransplant lymphoproliferative disorder. Med Oncol 24:125–136