EBV Associated Post-Transplant Lymphoproliferative Disorder Complicated with Haemophagocytic Lymphhistiocytosis After Allogeneic Stem Cell Transplant: A Rare Complication with Fatal Outcome

Tangia Muquitth1*

1Department of Haematology-Oncology, National University Cancer Institute, Singapore.

ABSTRACT

Epstein–Barr virus related post-transplant lymphoproliferative disorder is a fatal and life-threatening complication because of immunocompromised state. Haemophagocytic lymphohistiocytosis is a sign of poor outcome in EBV associated PTLD after allogeneic stem cell transplantation. It is particularly common when in vivo T cell depletion strategies have been applied. In both situations, post-transplant lymphoproliferative disorder and Haemophagocytic lymphohistiocytosis, infection with EBV is the key mechanism. Here I present a case of 29 years old female with acute myeloid leukaemia after second allogeneic stem cell transplant, who developed PTLD complicated with Haemophagocytic lymphohistiocytosis secondary to Epstein – Barr virus (EBV) infection. Patient was treated with chemo immunotherapy and responded but ultimately died after 100 days of transplant. The association of HLH and EBV related PTLD is rare and data on outcome of these patients are limited with very high mortality.

Key words: EBV (Epstein –Barr virus), PTLD (Post transplant lymphoproliferative disorder), HLH (Haemophagocytic lymphohistiocytosis), ATG (Anti thymocyte globulin).

Introduction

A 29 -years old woman, presented with low-grade fever, generalized weakness and cervical lymphadenopathy after 61 days of her second allogeneic stem cell transplant. Her underlying diagnosis was acute myeloid leukaemia-high risk with poor cytogenetics, treated with sequential allogeneic stem cell transplant from matched unrelated donor in her first complete remission. She relapsed 1 year after transplant and second allogeneic transplant with reduced intensity conditioning was again done from matched unrelated donor because of lack of family donor. She received rabbit ATG as part of immunosuppression – in vivo T cell depletion both stem cell transplant procedure.

She presented with fever, sore throat and painful bilateral cervical lymphadenopathy two months posttransplant. Her EBV load was 53000 IU/ml (4.72 Log). 18 FDG-PET CT scan showed extensive
lymphadenopathy both above and below the diaphragm. Biopsy of cervical lymphadenopathy was done. Histology showed monomorphic post-transplant lymphoproliferative disorder and immunohistochemistry showed CD79A, MUM1 positivity with weak positive CD20, lambda light chain restriction and high Ki67 proliferation index. In situ hybridization for EBV encoded RNA - EBER was strongly positive. Minority of neoplastic cells were also positive for CD138. It was negative for myeloid markers including CD34, CD117. LDH was very high, 3402 U/L (Normal: 250U/L).

Figure 1: Lymph node biopsy A) H& E stain B) EBV coded small RNA EBER showing EBV driven lymphoproliferation.

Simultaneously she also developed pancytopenia with haemoglobin 7.2gm/dl, total WBC 1.82x10^9/L, Platelet- 55x10^9/L. Bone marrow examination was done and showed haemophagocytosis. Liver function was impaired with high bilirubin 182mmol/L (Normal range: 3.4-17.1 mmol/L) with very high transaminases. Her triglyceride was 7.32 (Normal range <1.7), Ferritin – 25000ug/L (Normal range: 30-300ug/L), Fibrinogen 1.39g/L (Normal range: 2-4g/L).

Immunosuppression was minimized with low dose of mycophenolate mofetil and high dose steroid was started along with chemo-immunotherapy including rituximab, etoposide, cyclophosphamide. Her cytopenia was persistent because of chemotherapy related myelosuppression but hepatitis and hyperferritinaemia were improved. After four doses of weekly Rituximab, PET CT scan showed complete metabolic remission but EBV viral load was high 8400U/L. She died on day +137 of her transplant from persistent infections complicated with multi-organ failure.

Discussion

EBV related disease can present with a wide and heterogeneous spectrum of clinical and histopathological manifestations, ranging from EBV driven lymphoproliferation and systemic inflammatory response like syndromes e.g. HLH. Post-transplant lymphoproliferative disorders (PTLDs) are lymphomas that can develop after a transplant. ‘Lymphoproliferative’ means relating to proliferation (rapid growth) of lymphocytes. PTLD can develop in people who are taking medicines to suppress their immune system in order to prevent rejection and GvHD after an allogeneic (donor) stem cell transplant PTLD is rare. Most cases occur within the first 6 months after transplant. It is a heterogeneous group of neoplastic lymphoproliferation, developing after stem cell transplant because of iatrogenic T cell suppression. Others high risk factors including HLA mismatch stem cell transplant, EBV serology mismatch, GvHD requiring intensive immunosuppressive therapy. The incidence of PTLD is generally less than 2% after Allo-SCT; it may increase to 20% on patients with established risk factors such as unrelated Donor SCT, the use of T cell depletion allograft, use of ATG, and immunosuppression for prevention and treatment of GvHD. A diagnosis of PTLD is preferably based on lymph node histology. In situ hybridization is used to detect EBV encoded small RNA molecules (EBER). PTLD presentations vary greatly. Some found incidentally, some present with vague symptoms such as fever, malaise. Others present with very extensive disease both nodal and extra nodal sites occasionally with widely disseminated disease. In this case, patient presented initially with vague symptoms within 100 days post-transplant and progresses to extensive disease with concurrent HLH manifestations.

Another feature of this case is the diagnosis of HLH. HLH is uncommon after Allo SCT with a reported prevalence of 1.09%. HLH can occur in the context of malignancies. It has been well described in association with EBV infection. HLH represents a spectrum of disorders associated with activation of cytotoxic T and natural killer cells. The excessive immune activation results in the clinical hallmarks of HLH including fever, organomegaly, cytopenia combined with a characteristic set of laboratory parameters (elevated ferritin, triglycerides, soluble CD25, transaminases, LDH; decreased fibrinogen, albumin, sodium). The presented case met up the diagnostic criteria of HLH – fever, pancytopenia, haemophagocytosis in bone marrow, hyperferritinaemia, increased triglyceride level, hepatitis, hypofibrinogenemia with very high EBV viral load.

In patients with malignancy triggered HLH, Viral infection may act as co triggers. This is exemplified by EBV associated lymphomas where both the virus and lymphoma can drive HLH. The substantial

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overlap between the features of HLH and features of neoplasms makes the identification of HLH very difficult when it occurs in the context of malignancies.7

PTLD after Allogeneic HSCT with concurrent manifestation of HLH is associated with high mortality. One retrospective study showed high mortality (37.5%) in EBV PTLD within 100days post-transplant and all deceased patients developed HLH manifestations.8 The presented case also responded initially with tapering of immunosuppression, high dose steroid and weekly rituximab with chemotherapy directed against HLH but ultimately died on day +137 post-transplant.

This rare syndrome with high mortality addressed to improvement of prophylactic as well as pre-emptive approach to manage EBV driven heterogeneous disease.

References