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Adult secondary hemophagocytic lymphohistiocytosis with cerebromeningeal symptoms early after allogeneic hematopoietic stem cell transplantation

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Short title: EBV-related HLH after alloHSCT

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A 28-year-old male patient diagnosed with Ph-negative acute lymphoblastic leukemia was readmitted to the Bone Marrow Transplant Unit on day+42 after matched unrelated donor allogeneic hematopoietic stem cell transplantation (alloHSCT) presenting fever, general malaise, tonsillitis, lymphadenopathy, and splenomegaly. Pretransplant patient/donor Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) status were positive/negative and positive/positive, respectively. On admission, high blood EBV load (1.2x10^5 copies/ml) was detected. Due to progressing organomegaly and elevation of lactate dehydrogenase level after standard treatment with rituximab 375 mg/m^2 IV, 18F-fluorodeoxyglucose positron emission tomography/computed tomography was performed. It revealed pathologically increased metabolic activity in multiple enlarged lymph nodes and spleen (Figure 1A, 1B). Due to trilineage cytopenia progression additional blood tests were performed.

Prominent hyperferritinemia 74000µg/L with hypertriglyceridemia 3.73 mmol/L were noted. Peripheral blood lymphocyte immunophenotyping showed a sparse natural killer (NK) cell population. Probable post-transplant lymphoproliferative disorder (PTLD) was diagnosed, accompanied by hemophagocytic lymphohistiocytosis (HLH) [1,2]. Despite application of the second and third rituximab dose and cyclosporine A (CsA) reduction, the patient developed neurological symptoms, particularly expressed in the range of cortical activities - deterioration in verbal contact, memory impairment, disorientation followed by coma. Brain MRI results suggested meningitis (Figure 1C,1D). Central system fluid analysis revealed high protein level 283mg/dl, pleocytosis 70/µl, and high EBV load 6.2x10^3 copies/ml. Subsequently, immunosuppression was modified – dexamethasone was introduced (8mgTID) with complete CsA cessation. Due to the severity of the neurologic condition, antiviral acyclovir was converted to foscarnet, three doses of IV etoposide 100mg and two intrathecal methotrexate 15mg were administered, in parallel with weekly rituximab -
up to 5 infusions. The above-mentioned therapeutic interventions efficiently improved the general condition of the patient. Finally, EBV clearance was achieved. The systemic dexamethasone dose was gradually tapered, simultaneously with CsA reintroduction. Presently, five years after transplant, the patient is alive in continued complete remission.

EBV is a highly immunogenic γ-herpesvirus. Severely immunosuppressed patients develop B-cell proliferation and diminished EBV-specific cytotoxic T-cell population [3]. EBV-associated B-cell PTLD is a life-threatening complication after alloHSCT resulting from an outgrowth of infected donor-origin B cells [3]. In HSCT patients EBV is a second, after Human herpesvirus 6, viral encephalitis etiology [4]. HLH, characterized by molecular abnormalities or/and clinical/laboratory criteria: fever, splenomegaly, cytopenia, reduced NK cells activity, hypofibrinogenemia, increased sCD25, ferritin and triglycerides and hemophagocytosis, has become more widely recognized in adults, dominated by secondary forms of the disease [5]. The EBV-driven HLH treatment strategy depends on the patient’s condition, from short course corticosteroids with or without immunoglobulins in less severe disease to intensive treatment with early etoposide application in rapidly deteriorating patients [5]. There is no established standard of care in patients fulfilling HLH-2004 diagnostic criteria after alloHSCT. In the above patient, based on high EBV load and imaging, probable PTLD was diagnosed, complicated by HLH. EBV meningoencephalitis and advanced central nervous system HLH involvement may by differentiated. Focusing on HLH as a major life-threatening event, adoption of HLH2004 regimen modalities provided an excellent clinical outcome in rituximab refractory disease. However, negative pre-transplant donor EBV immunity status and co-reactivating viruses may impede treatment.
References:


Figure 1A: Coronal 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) scans - maximal intensity projection (MIP) scan showing increased 18F-fluorodeoxyglucose uptake in lymph nodes and spleen
Figure 1B: Coronal 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) scans - fusion scan showing diffuse 18F-fluorodeoxyglucose uptake of lymphoid tissue – highest in para-aortic and liver hilar and pancreas area lymph node groups (maximum standardized uptake value / SUVmax -18.8) and left side neck lymph nodes (maximum standardized uptake value / SUVmax 16.6), medium in spleen (maximum standardized uptake value / SUVmax 10.7) and peripheral lymph nodes (maximum standardized uptake value / SUVmax 3.1-9.8).
Figure 1C: Brain magnetic resonance imaging (MRI) scans – T1W sequence presenting global meningeal thickening (arrowed).
Figure 1D: Brain magnetic resonance imaging (MRI) scans – T1W sequence presenting postcontrast meningeal enhancement (arrowed).