EBV-INFECTION AFTER TRANSPLANTATION

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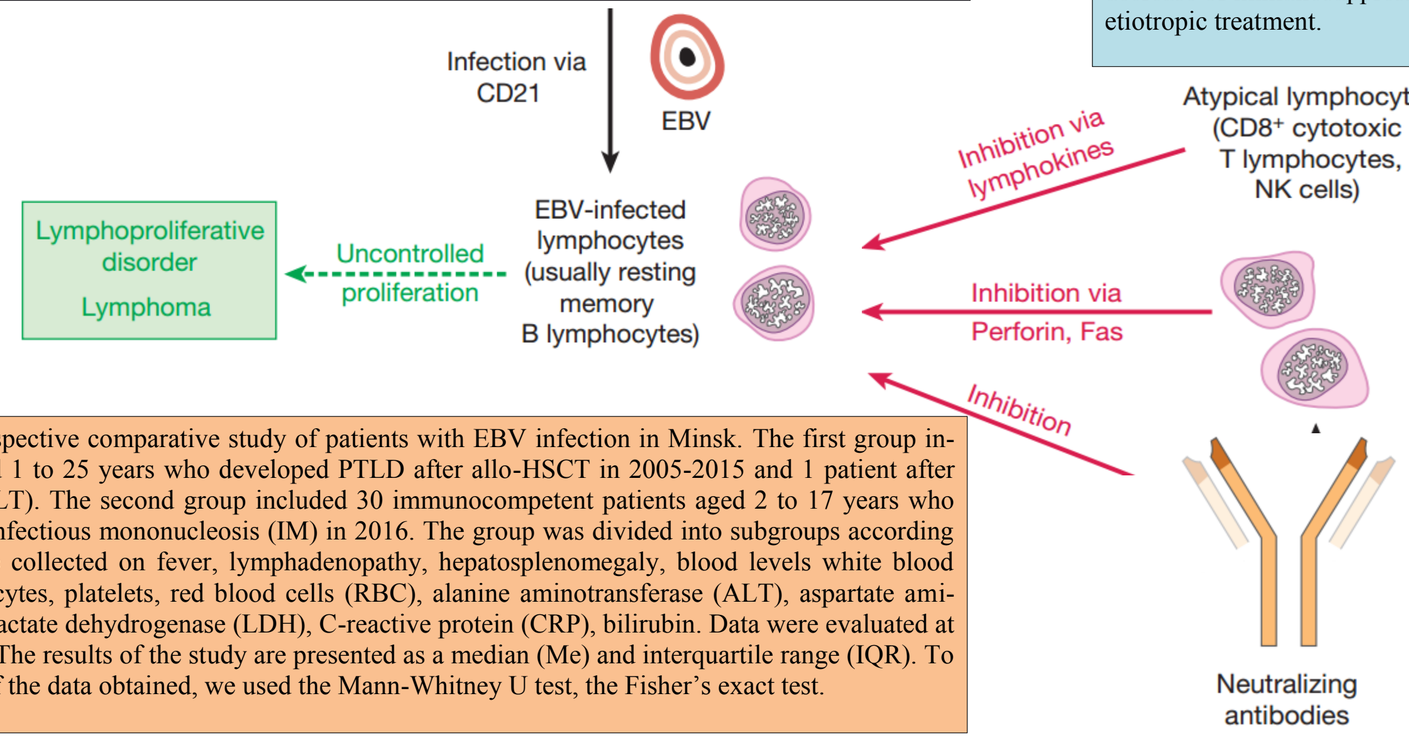
Background

splant lymphoproliferative disorders (PTLDs) — also referred to occasionally as post-transplant lymphoproliferative diseases — are characterized by abnormal proliferation of lymphoid in the context of extrinsic immunosuppression after transplantation. PTLDs can be associated with solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). The oncogenic Epstein–Barr virus (EBV) drives abnormal lymphocyte proliferation in 50–80% of PTLDs, especially in early onset disease (that is, <1–2 years after transplantation). The remaining 20–50% of PTLDs are EBV-negative and the etiological trigger is not yet known. PTLDs represent a spectrum of abnormal lymphoproliferations, but the most prevalent life-threatening form originates from EBV infection of the transplant recipient's B cells. However, impaired immune response as a result of post-transplant immunosuppression (especially CD8+, CD4+, NK cells) can lead to reactivation of latent EBV infection or a hampered response to a new infection, which increases the risk of developing potentially fatal EBV-positive PTLD. The incidence of PTLD is up to 20% of SOT recipients overall, but varies by transplanted organ. The overall incidence of PTLD after allogeneic HSCT was 3.2%, varying from 1.2% in matched family done to 11.2% in mismatched unrelated donor recipients. PTLD is one of the most severe complications associated with transplantation - mortality remains high; approximately one-third of diagnosed patients.

Aim: To compare EBV infection course in immunocompetent individuals and patients undergoing immunosuppression.



Methods

We conducted a retrospective comparative study of patients with EBV infection in Minsk. The first group included 9 patients aged 1 to 25 years who developed PTLD after allo-HSCT in 2005-2015 and 1 patient after liver transplantation (LT). The second group included 30 immunocompetent patients aged 2 to 17 years who had undergone EBV infectious mononucleosis (IM) in 2016. The group was divided into subgroups according to the age. Data were collected on fever, lymphadenopathy, hepatosplenomegaly, blood levels white blood cells (WBC), lymphocytes, platelets, red blood cells (RBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP), bilirubin. Data were evaluated at the time of diagnosis. The results of the study are presented as a median (Me) and interquartile range (IQR). To assess the reliability of the data obtained, we used the Mann-Whitney U test, the Fisher's exact test.

Results:

Fever was observed in 60% of patients with IM (Me=38.0 °C) and in 44% of patients with PTLD (Me=38.0 °C).

Generalized lymphadenopathy and splenomegaly were observed in all patients in each group.

In the PTLD group were observed significantly lower blood levels ($p < 0.05$) of (Me; IQR) RBC - 3.3×10^{12}/L (IQR 3.2-3.4x10^{12}/L), platelets - 48.5x10^9/L (IQR 35-88x10^9/L), leukocytes - 2.9x10^9/L (IQR 2.2-6.6x10^9/L), the relative number of lymphocytes – 23% (IQR 5-24%), the absolute number of lymphocytes - 0.51x10^9/L (IQR 0.46-0.99x10^9/L) (Fig.1); AST level 35.5U/L (IQR 27-49.4 U/L), CRP - 34.4 mg/L (IQR 25.7-74.1 mg/L). Differences are established both between general groups and between PTLD group and age subgroups.

One of the predicted risk factors may be the level of lymphocytes in the peripheral blood, because more than 70% are T-cells. To assess the correlation of low lymphocyte count in peripheral blood and development of PTLD, a four-field conjugation table was compiled. The evaluation was carried out according to Fisher's exact criterion. The risk factor is the level of lymphocytes less than **1000/µl**. In the PTLD group, this level was observed in 7 out of 9 patients, and in the IM group in a subgroup of 7-12 years in 1 patient out of 9. Correlation is confirmed by the Fisher's exact test ($p=0.0076$).

In the patient after liver transplantation, the absolute number of lymphocytes exceeded 3000/µl. The decrease of immunosuppressive load subsequently led to clinical recovery of the patient without the use of etiotropic treatment.

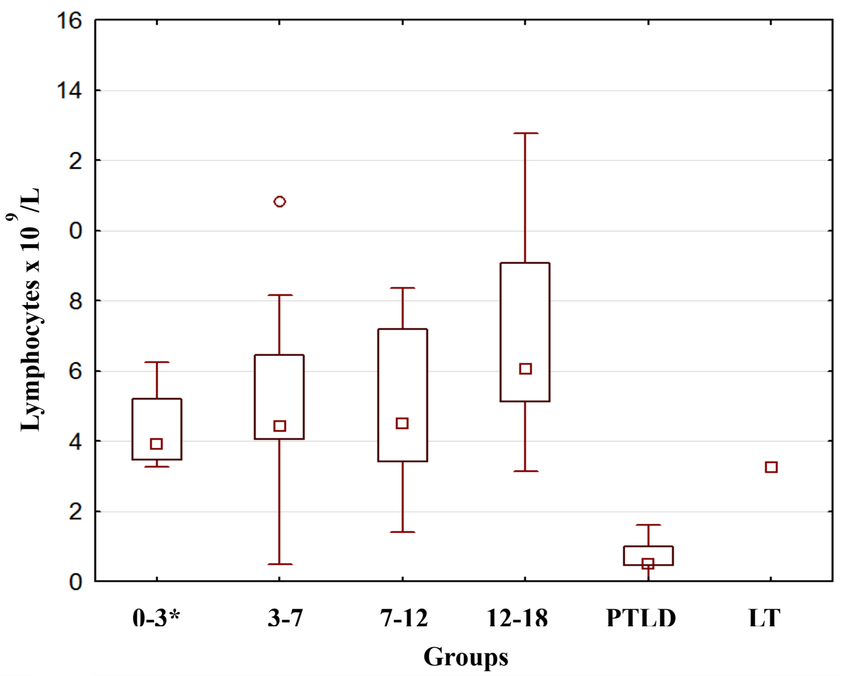


Figure 1 - Number of lymphocytes in IM age groups, PTLD after HSCT and PTLD after LT. Mann-Whitney U test $p<0.05$; *$p>0.05$

Conclusion:

1 The course of EBV infection in patients who are susceptible to immunosuppression has its own characteristic objective features: low levels of RBC, platelets, leukocytes, the relative and the absolute number of lymphocytes, AST and CRP.

2 Patients tend to develop PTLD with a lymphocyte level less than 1000/µl. The number of lymphocyte can be one more risk factor of the syndrome development.

3 To resolve the issue of the using preventive etiotropic therapy of EBV-PTLD, it is possible to evaluate lymphocytes level: initiate therapy with a level of cells in the peripheral blood <1000/µl. Otherwise it can be limited to decrease of the immunosuppression intensity only.