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Early-Onset Epstein-Barr Virus-Negative Post-Kidney Transplantation Lymphoproliferative Diseases, with High Expression of Peripheral Blood Regulatory B Cell Subsets

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1. Abstract

Post-transplant lymphoproliferative disease (PTLD) is a group of lymphoid disorders and one of the most serious complications after transplantation. The risk factors include the level/duration of T-cell immune suppression, which also leads to disordered tumor cell proliferation and immune inflammation, and Epstein-Barr virus (EBV) infection. The extension of immunosuppression and uncontrolled progressive infection leads to the proliferation of malignant B lymphocytes, resulting in PTLD after transplantation. However, a small number of PTLD cases have been unrelated to EBV or are EBV-driven but all have typical late-onset manifestations.

Regulatory B cells (Bregs) extensively proliferate in tumors and third lymphoid structures, draining lymph nodes and major secondary lymphoid organs, and can produce immunosuppressive and inflammatory cytokines. Both anti-tumor and pro-tumor effects may be associated with Bregs, but the specific effect depends on the tumor type, immune microenvironment, differentiation, and proliferation of Bregs subsets. The diagnostic suspicion threshold for PTLD is low, with atypical symptoms; some patients only show malaise or are asymptomatic in the early stage. Therefore, the early detection of PTLD is of great significance for the prevention of aggressive lymphoma. The pathogenesis of EBV-negative PTLD and association between the driving factors and characteristics of regulatory B cell subsets require further study.

We present the case of a 42-year-old Asian male who developed EBV-negative early-onset PTLD, with no clinical symptoms and no excessive immunosuppression status, four months after receiving a deceased-donor renal transplant. The patient presented with high expression of Breg subsets, including unswitched memory B cells CD19+CD27+IgD+ and plasma cells CD19+CD27+CD38+ in peripheral blood compared to no change in T-cell levels in the earlier stages.

2. Introduction

Although post-transplant lymphoproliferative disease (PTLD) can be Epstein-Barr virus (EBV)- seronegative or EBV-seropositive, EBV-seropositive lymphoma is more acute, common, and life-threatening [1]. The majority of PTLD cases (80%–90%) are derived from B cells and seropositive for EBV; hence, early onset PTLD tends to be EBV-driven [1]. In EBV-positive PTLD, circulating B cells are infected by EBV, inducing primary latent membrane proteins (LMP1, 2A-B) and EBV nuclear antigens (EBVNA1, 2, 3A-C) to simultaneously express. Late-onset PTLD is usually unrelated to EBV but involves different extranodal organs [2-4].

However, the risk factors for PTLD depend on the intensity and duration of immunosuppressive therapy and the type of transplanted organ [5]. Regulatory B-cell subsets within reactive tumors are more clonally diverse and contain markedly more memory B cells and plasma cells, suggesting a robust immunological responses in reactive tumors [6]. Human CD19+CD27+IgD+ B cells, also termed as unswitched memory B cells, were considered to be innate-like B cells (ILBs), while CD19+CD27+CD38+ are considered as plasma cells [7], which can inhibit the ability of dendritic cells (DCs)to generate pathogenic T cells in autoimmune encephalitis [8,9]. Higher expression of B-cell and plasma cell gene markers from The Cancer Genome Atlas (TCGA) correlate with poor clinical prognosis in glioblastoma [10].

Moreover, regulatory B cells (Bregs) can abundantly proliferate in tumors, tertiary lymphoid structures, draining lymph nodes, and major secondary lymphoid organs and can promote immunosuppressive cytokines such as IL-35 and IL-10 in reaaction to tumor-associated inflammation [11]. B-cell-secreted IL-35 can block the response of effector T cells by inhibiting the response of CD4+ and CD8+ cells, enhancing the proliferation of regulatory T cells (Treg), and influencing the response of the body to tumors. Analyses of RNA sequencing data from TCGA have also shown the association of high transcription of B-cell and plasma cell genes with patient survival in bladder, melanoma, ovarian, and pancreatic adenocarcinoma [12].

Bregs are associated with both pro-tumor and antitumor effects; however, whether Bregs are a risk factor or the result of tumor progression in different tumors and different levels of immunosuppression and differentiation subsets has not been established. Therefore, the functional features and characteristics of these cells in PTLD are not well understood.

Our unique case report presents a 42-year-old male with EBV negative, slightly serum creatinine levels increase and stable immune levels but highly expressed peripheral blood regulatory B cell subset [8,13,14]. After kidney transplantation from an organ donation after cardiac death, a diffuse large B-cell lymphoma developed in the early postoperative four months, unlike EBV seropositive PTLD.

3. Case Presentation, Diagnostic Assessment, and Therapeutic Intervention

A 42-year-old male patient underwent kidney transplantation from a deceased donor due to chronic kidney disease and dialysis for more than one year on January 30, 2022. The patient was successfully discharged three weeks after surgery (Figure 1A, Timeline). Cytomegalovirus (CMV) and EBV donor/recipient negativity. The post-transplant course was uneventful for four months. After discharge, the immunosuppressive state of the patient was stable and the FK506 concentration was stable at 7–9 ng/ml. On June 13, 2022, the routine outpatient review showed slightly increased serum creatinine levels (from 130 μmol/L to 157 μmol/L) without other clinical symptoms, and a color ultrasound of the transplanted kidney suggested hypoechoic lesions. The patient was then admitted to the hospital.

On admission, the patient had stable vital signs, a heart rate of 82 beats per minute, and a urine albumin/creatinine ratio of 31.2 μg/mg on initial laboratory tests. Creatinine (157 μmol/L), white blood cell count (7.72), glycan antigen 72-4 (7.65 μ/ml; reference range: <6.9 U/ml), and other tumor indicators were normal. Serological tests for CMV, EBV, JC virus, and BK virus were negative. A physical examination revealed no lymphadenopathy. FK506 concentration was 4.5 ng/ml.

On the second day after admission, enhanced computed tomography (CT) showed enhancement of lesions in the transplanted kidney. The number of retroperitoneal lymph nodes also increased (Figure 1A, 1B). The patient temporarily stopped taking immunosuppressants. On June 24, 2022, positron emission tomography-computed tomography (PET-CT) revealed multiple nodules with increased metabolism in the transplanted kidney, which was considered a neoplastic lesion. The number of retroperitoneal lymph nodes increased but the metabolism did not increase. The elevated metabolism of neck lymph nodes in zone II was considered an inflammatory change (Figure 1A, 1C, 1D). Subsequently, the patient underwent a renal graft biopsy. In July 2022, a pathological examination revealed a renal cortical malignant tumor with a sarcomatoid structure under a microscope (Figure 1E). Immunohistochemistry confirmed CD10+, VIM+, PAX-8 +, CD117 −, FH +, and Ki-67+. Subsequently, the patient underwent nephrectomy and the postoperative pathology of the transplanted kidney suggested

B-cell non-Hodgkin lymphoma (NHL) with a large cell component (Figure 1F). MYC/IgH and BCL2/IgH gene rearrangement tests were negative (Figure 1G). After the operation, the patient recovered well and was started on continuous renal replacement therapy (CRRT). During this period, the patient was symptomatic.

The patient was discharged two weeks after surgery and planned to undergo PTLD treatment one month later.

EBV was negative before and after PTLD and occurred within four months after PTLD without other clinical symptoms. The level of immunosuppression was stable and there was no excessive immunosuppression, which was contrary to PTLD after renal transplantation reported in the literature and medical records. In addition, the final pathology of the graft was PTLD, which differed from the malignancy suggested by CT and graft biopsy. Although CT and direct biopsy are important criteria for the diagnosis of PTLD, this case report is different. This may suggest that there are additional test results that could further support the diagnosis of PTLD.

Recent studies have demonstrated how B cells positively and negatively modulate immune responses, providing mechanistic insights. The negative regulation of immune responses in cancer can be mediated by regulatory B cells because of the increased differentiation and proliferation of regulatory B cell subsets. To understand the changes in the immune levels of our patient, we analyzed the changes in lymphocyte populations in the peripheral blood. The expression of peripheral blood regulatory B cell subsets on admission revealed unswitched memory B cells (CD19+CD27+IgD+) of 16.01% and plasma cells (CD19 + CD27 + CD38 +) of 1.03% (Figure 2L and 2M). One week after admission, the number of unswitched memory B cells was 15.83%, and plasma cells rapidly increased to 20.77%. However, there was no significant change in the proportion of total T cells (Figure 2A) and total B cells (Figure 2B) in the first and second peripheral blood tests, which were within the normal range. One week after the surgical removal of the graft, unswitched memory B cells and plasma cells reached a peak of peripheral blood (26.62% and 34.88%, respectively) (Figure 2L and 2M). Meanwhile, one and four weeks post-surgery, the levels of total T cells decreased to 36.49% and 36.18%, respectively, with no significant change in the level of B cells, which remained at a relatively normal level (Figure 2A and 2B). Furthermore, the proportion of central memory CD4+T cells (CD3+CD4+CD45RA-CCR7+/Th) was increased, and effector memory CD4+ T cells (CD3+CD4+CD45RA-CCR7-/Th) were decreased in the third test of peripheral blood, with a sharp rise in plasma cells. Four weeks after surgery, the peripheral blood in patients with unswitched memory B cells was 0.96% and plasma cells were 24.1% (Figure 2L and 2M).

An EBV-negative PTLD was diagnosed, and treatment was started with rituximab-CHOP (RCHOP) every 21 days. On the first day of treatment, the patient received an intravenous infusion of rituximab (375 mg/m2, a total of 700 mg). On the second day, epirubicin 75 mg/m2, cyclophosphamide 750 mg/m2, and vindesine 2.25 mg/m2 were successively administered. Oral prednisone (100 mg per day) was administered, and a total of 500 mg was administered from the second to the sixth day. During this period, dexrazoxane, amifostine, and tropisetron were administered to reduce toxic reactions. At the end of the first phase of treatment, the last peripheral blood examination of the patient suggested that T cells continued to decrease to 14.74%, central memory T cells increased to 72.6%, and effector T cells decreased to 0.68%. At the same time, un-switched memory B cells remained at 26.22%; however, plasma cells remained at a high expression level of 23.29% (Figure 2L and 2M).

The increase in plasma cell levels occurred earlier than the decrease in T cell levels, meaning that PTLD still occurred in the immunostable state, and was more significant than the presence of symptoms and other tumor markers. This may indicate that Bregs are a new risk factor in EBV-negative early-onset PTLD. On the other hand, high levels of plasma cells and un-switched memory B cells were maintained even after the end of RCHOP phase I treatment, which may suggest that high expression of plasma cells is also a result of PTLD. Overall, these results may have significance for the diagnosis of early-onset EBV-negative PTLD.

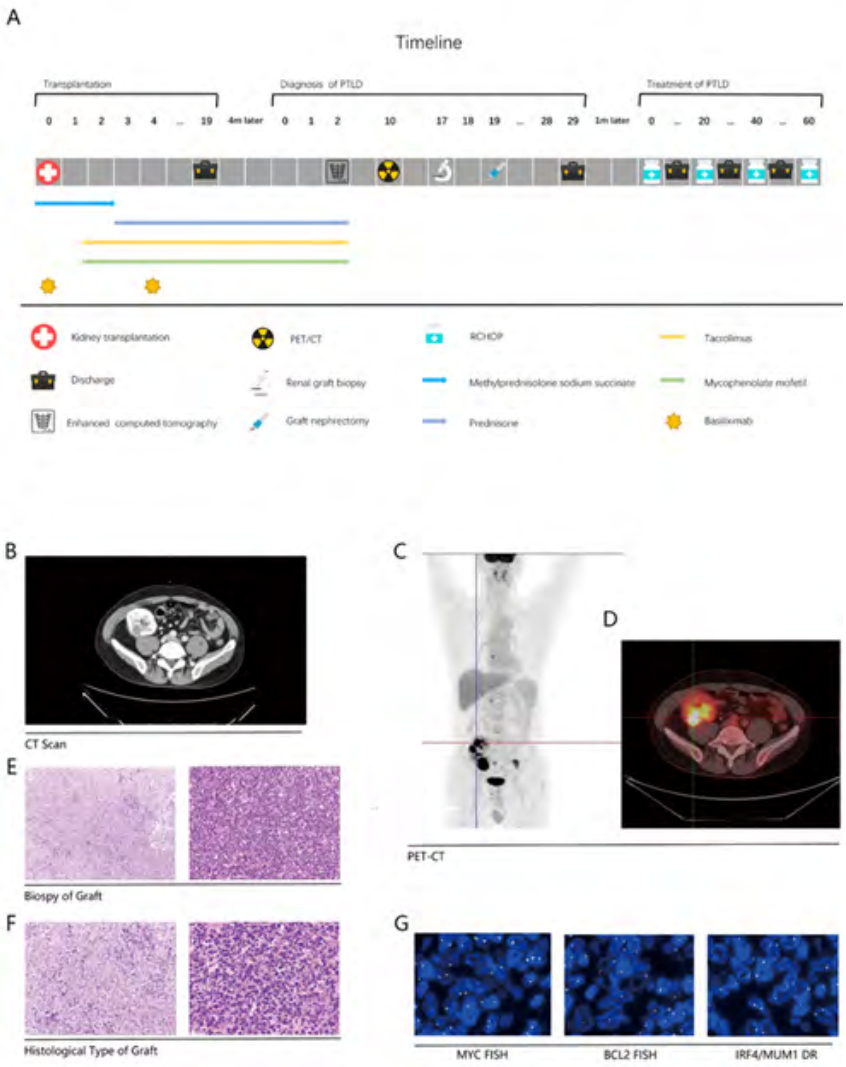

Figure 1: Timeline

A. Timeline of PTLD patients: including relevant physical examination and other clinical findings, relevant past interventions, and their outcomes. B. Enhanced computerized tomography (CT) imaging of the graft. C and D. Positron emission tomography-computed tomography (PET-CT) of the patient. E. Renal graft biopsy. F. Histological type of the renal graft. G. Gene rearrangement tests.

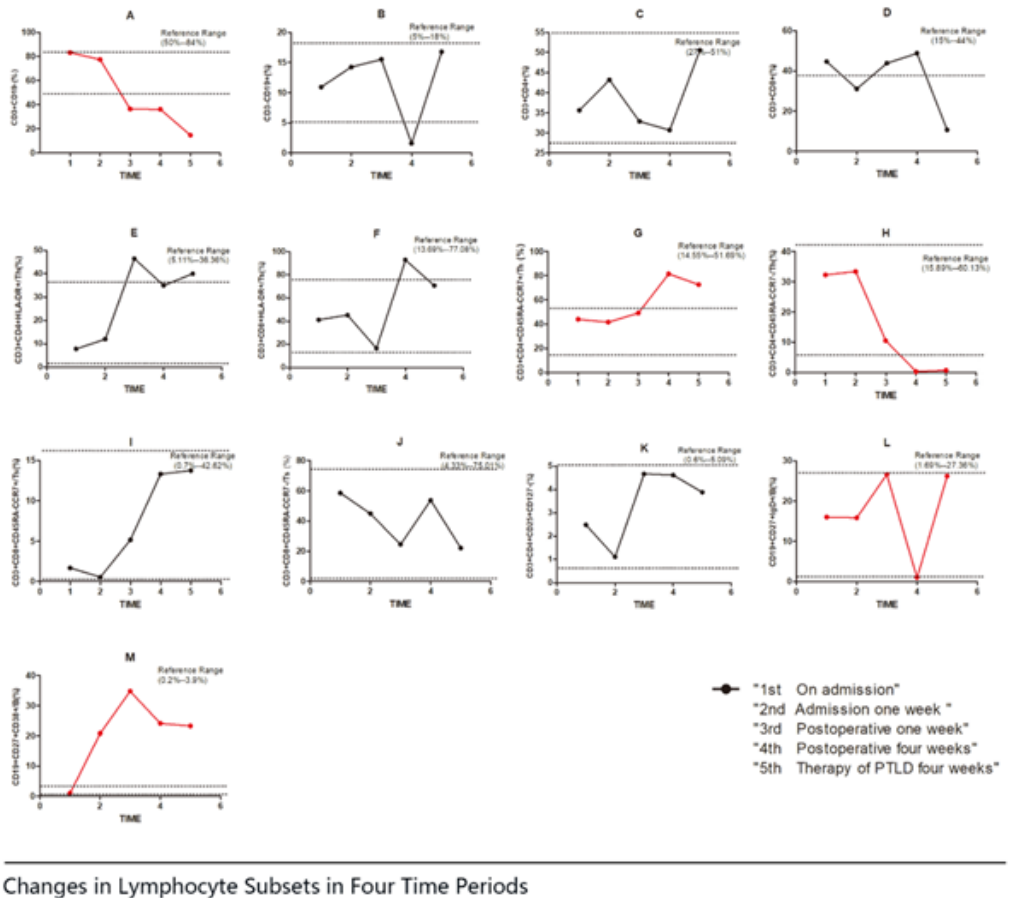

Figure 2: Changes in Lymphocyte Subsets in Four Time Periods

A. Total T Cells (CD3+CD19-). B. Total B Cells (CD3-CD19+). C. Helper T Cells (CD3+CD4+). D. Cytotoxic T Cells (CD3+CD8+). E. Activated Helper T Cells (CD3+CD4+HLA-DR+/Th). F. Activated Cytotoxic T Cells (CD3+CD8+HLA-DR+/Th). G. Central Memory CD4+T Cells (CD3+CD4+CD45RA-CCR7+/Th). H. Effector Memory CD4+T Cells (CD3+CD4+CD45RA-CCR7-/Th). I. Central Memory CD8+T Cells ((CD3+CD8+CD45RA-CCR7+/Ts). J. Effector Memory CD8+T Cells ((CD3+CD8+CD45RA-CCR7-/Ts). K. Regulatory T Cells (CD3+CD4+CD25+CD127-). L. Unswitched Memory B Cells (CD19+CD27+IgD+/B). M. Plasma Cells (CD19+CD27+CD38+/B).

4. Discussion

PTLD is one of the most devastating complications of organ transplantation [15]. EBV is considered to play a key role in the development of EBV-positive PTLD, and most (>90%) early onset (within the first year) B-cell PTLD is found within the EBV genome. However, PTLD occurring later after transplantation is associated with EBV negativity [15,16].

The pathophysiology of EBV-positive PTLD and EBV-negative PTLD is different because genome analysis shows that individuals with EBV-negative PTLD are similar to the normal immune function of sporadic lymphoma that usually contains TP53 mutations [17]. A small subset of PTLD is T cell-derived and not EBV-driven, and has a typical late-onset occurrence. Another hypothesis suggests that the microenvironment may differ between EBV-positive and EBV-negative PTLD, thereby influencing the clinical symptoms and laboratory tests. Therefore, the clinical features of early and late PTLD differ. Early onset PTLD takes to be EBV-driven and usually involves the use of allografts. In contrast, late-onset PTLD is usually EBV-negative and affects multiple extranodal organs [18]. Although the risk of early PTLD is reduced, the risk of late PTLD is prolonged, which may be due to the high survival time of renal transplant patients. PTLD after renal transplant is more attributed to host factors, and the incidence of PTLD presents a bimodal pattern [19].

Although sex and age are important risk factors for the occurrence of PTLD [20,21], these two characteristics cannot improve the prognosis and provide direct help for the diagnosis of PTLD. The connection of human leukocyte antigen (HLA) haplotypes with PTLD has been confirmed, such that the frequency of HLA-3 is decreased in EBV-positive PTLD, and the frequency of HLA-B18 is increased in EBV-negative [22]. However, we did not find any related HLA alleles in our patient.

The overall level of immunosuppression appears to be another critical driver of the increased occurrence of PTLD in transplantation patients. Because PTLD is often presented with allograft dysfunction and acute rejection in differential diagnosis, standardized criteria need to be developed that include not only EBV testing but also Bregs subsets testing before introducing more effective

antirejection therapy. Even though pathological diagnostic evaluation of rejection is also important to distinguish early PTLD from rejection. However, in this case, we found that the patient had no obvious clinical symptoms such as fever, malaise, exudative pharyngitis, lymphadenopathy, and hepatosplenomegaly in the early stages. Additionally, the serum EBV was negative in the early preoperative and postoperative stages. Furthermore, by analyzing the changes in lymphocyte subsets in the peripheral blood of the patient, we found that T cell subsets remained at a normal level for the first two weeks after the patient was admitted to the hospital, and the drug concentration of the patient before admission was also maintained at a relatively normal level (FK50:7-9 ng/ml). However, the plasma cells were still highly expressed even after the immunosuppressant was stopped when the patient was admitted and the graft mass was found.

Collectively, many studies reflect the multifaceted functional properties of Bregs and their subsets. The capacity to promote antigen presentation, cytokine production, antibody-dependent cellular inflammation, and isotype switching is thought to contribute to the promotion of anti-tumor responses, whereas the presence of specific immunosuppressive Bregs phenotypes and antibody isotypes are associated with tumor promotions [6,23].

The pathogenic roles of Bregs, especially plasmablasts and switched memory B cells, which contribute to the progress of the immune disease by producing ACPAs autoantibodies and secreting cytokines, have been well studied [7]. Other Bregs, including CD19+CD27+IgD+ B cells and CD19+CD27+CD38+ B cells, further improved our understanding of the role of B cells in PTLD [13,24]. Nevertheless, the characteristics of CD19+CD27+IgD+ B cells and CD19+CD27+CD38+ B cells [8] and their potential roles in PTLD are largely unknown. Many more markers in predicting PTLD risk should be the subject of future research, particularly atypical PTLD [25]. All these results further demonstrate the necessity of Bregs subsets testing as an auxiliary diagnosis for PTLD, especially EBV-negative PTLD.

5. Conclusion

In conclusion, at the beginning of the disease, there may be no significant changes in T cells in EBV-negative patients with stable immunosuppression. The gradual increase and rapid decline of unswitched B cells and the continuous increase of plasma cells may be the same as the results of no increase in tumor markers, suggesting that regulatory B cell subsets have certain preoperative diagnostic significance for PTLD without clinical symptoms, EBV negativity, and early onset after surgery.

Our report demonstrate a novel immunoregulatory property of Bregs subsets, The high expression of plasma cells at early stage and the high level after treatment suggested that Bregs subsets may be either a novel risk factor or a result of PTLD. Our findings could be useful for surgeons performing organ transplantation and immunologists studying transplantation immunity and inflammatory factors.

6. Author Contributions

BL had full access to all the data in the study and was responsible for the integrity of the data and accuracy of the data analysis. Study design: C. D., F. C, and B. L. Acquisition of data: Q. L., and F. C. Analysis and interpretation of data: C.D., G. H, and M. Z. Drafting of the manuscript: C. D., F. C., Q. L., H. S. and B. L. Critical revision of the manuscript for important intellectual content: C. D and B. L. Statistical analysis: Q. L. , S. L., G. H. and B. L. Obtaining funding: C. D. Administrative, technical, or material support: H. S. and B. L. Supervision: B. L. All authors contributed to the article and approved the submitted version.

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8. Patient Perspective

During the entire process, the patient and his family were informed of the treatment options and risks. They were aware of the complexity of this unusual case, and the patient provided written informed consent for the publication of this case. The case report was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patient and his family were satisfied with the relative improvement of his clinical condition.

9. Data Availability Statement

The data used to support the findings of this case may be released upon application to the Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; Key Laboratory of Organ Transplantation, Ministry of Education; NHC Key Laboratory of Organ Transplantation; Key Laboratory of Organ Transplantation, Chinese Academy of Medical Sciences, Wuhan, China. 430030, Bin Liu, Wuhan, China. binliu@tjh.tjmu.edu.cn can be contacted at the corresponding author upon request.

10. Acknowledgments

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11. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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