Burkitt’s lymphoma following a pediatric liver transplantation: predictive negative value of serologic response to Epstein-Barr virus

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Post-transplant lymphoproliferative disorder (PTLD) represents a spectrum of Epstein–Barr virus (EBV)-related clinical diseases, from a benign mononucleosis-like illness to a fulminant non-Hodgkin’s lymphoma. Because a large proportion of children are seronegative at the time of transplantation, recipients are at high risk of contracting primary EBV infection and subsequently developing PTLD. Surveillance techniques with antibody titers and/or polymerase chain reaction (PCR) may have a role in some high-risk settings. A 12-year-old boy whose serologic response to EBV was negative during follow-up after liver transplantation (LTx) developed Burkitt’s lymphoma, a rare and the most severe variant of EBV-related PTLD, 32 months after LTx. He expired possibly due to side effects of treatment. We recommend that viral monitoring must be done using PCR during follow-up of pediatric LTx to prevent dramatic outcomes.

Key words: liver transplantation, post-transplant lymphoproliferative disorder, Burkitt’s lymphoma, children, serologic response, polymerase chain reaction, Epstein-Barr virus.

Post-transplant lymphoproliferative disorder (PTLD) is an unusual entity that has many of the features of immune system malignancy. Epstein–Barr virus (EBV)-associated PTLD has emerged as a significant complication of solid organ transplantation in a context of immunosuppression¹. Occurrence rates of PTLD after liver transplantation (LTx) in children were reported as much as 13%, with an average post-transplant onset of 10.1±2.1 months². New generation immunosuppressive agents such as tacrolimus used in LTx may result in an increasing incidence of PTLD, especially in young pediatric recipients³. Burkitt’s lymphoma (BL) is a very rarely observed entity as a PTLD in children⁴. Since EBV culture and polymerase chain reaction (PCR) are not readily available in all transplantation centers, a serologic response (SR) to the virus with elevation of anti-viral capsid antigen (VCA) IgM or marked elevations of anti-VCA IgG or anti early antigen (EA) has been used to determine acute infection or reactivation of previous infection⁵.

Herein, we present a 12-year-old boy whose SR to EBV was negative (anti-VCA IgM and IgG) both before and after transplantation and who developed BL as a variant of EBV-associated PTLD.

Case Report
A 12-year-old boy underwent cadaveric LTx at the age of nine years for Wilson cirrhosis. EBV VCA IgM and IgG were negative before transplantation. Quantification of viral sequences was not available at the time of transplantation. SR to EBV that was periodically checked every
three months was negative during follow-up period after LTx. Oral acyclovir prophylaxis was given to prevent herpetic viral infections during the first six months. His post-transplant immunosuppression included tacrolimus and low-dose prednisolone. Tacrolimus dosages were adjusted to reach blood levels between 10-15 ng/dl during the first month and 5-10 ng/dl thereafter.

He complained of weakness and dyspnea 32 months after transplantation. Tachycardia, abdominal distension, ascites and hepatomegaly were positive physical examination findings. His hemoglobin level, leukocyte and thrombocyte counts were 7.3 g/dl, 15100/mm$^3$, and 751000/mm$^3$, respectively. Serum biochemistry showed no abnormality except for elevated uric acid (10.4 mg/dl) and phosphorus (5.2 mg/dl) levels. Tumor lysis syndrome was diagnosed and treated appropriately. EBV VCA IgM-IgG and cytomegalovirus (CMV) pp65 antigen were negative. Samples obtained from plasma and ascitic fluid were highly positive for EBV DNA ($7 \times 10^6$ and $17 \times 10^9$ copies/ml, respectively). Nodular lesions in liver and soft tissue masses in preaortic area were demonstrated by abdominal ultrasonography and computed tomography. Ascites cytology revealed predominance of L3 type blasts. Bone marrow aspirate and biopsy showed 5% of L3 type blast infiltration. Flow cytometric analysis of ascitic fluid revealed B-cell lineage phenotype (CD10 96%, CD19 96%, CD20 96%, and CD22 85%). Upper gastrointestinal endoscopy showed fragile, nodular lesions of 3-5 mm in diameter in anterior corporeal area of stomach. Biopsy obtained from this area was reported as high grade non-Hodgkin’s lymphoma (NHL). He was diagnosed as BL as a variant of EBV-related PTLD and his immunosuppressive therapy was withdrawn. Ganciclovir (Cymevene, Roche, 10 mg/kg/d) and appropriate chemotherapy were planned to be started. The patient died suddenly on the first day of chemotherapy, which may have been due to the side effect of daunorubicin as it was the only drug he received up to that time. The histological features of post-mortem tissue specimens revealed diffuse neoplastic lymphoid infiltration in portal areas and parenchyma of liver, in interstitial area of kidney and in colonic mucosa. The tumor cells had round oval nuclei with prominent nucleoli, which is consistent with BL (Fig. 1).

Discussion

Conversion of pretransplant EBV seronegativity to posttransplant seropositivity has been shown to be a major contributing risk factor for developing PTLD. Because a large proportion of children are EBV-seronegative at the time of LTx, recipients are at high risk of contracting primary EBV infection and subsequently developing PTLD. It is thought that the initial event of PTLD development could be proliferation of B lymphocytes infected by EBV that are not restrained in immunosuppressed patients by anti-EBV cytotoxic T populations, as occurs in normal conditions. BL is a very rare and highly aggressive variant of PTLD and early diagnosis is very important. Other types of PTLD are likely to respond well to a decrease in immunosuppression. However, BL is not likely to be affected by this regulation in therapy and characteristically requires adjuvant aggressive chemotherapy. Our case is the first reported BL among recipients of LTx (adult and pediatric) in our country.

While the diagnosis of PTLD probably will continue to be based on the histopathologic appearance, a laboratory test in determining which patients may be at significant risk for developing or having the disorder would be valuable. Since EBV culture and PCR are not readily available in most centers, a SR to EBV has been used to determine status of patients both before and after LTx. However, an increased level of anti-VCA and anti-EA without clinical suspicion was not considered sufficient to diagnose EBV reactivation during long-term post-transplant follow-up. In addition, viral SR, which is used...
for confirmation of the diagnosis, has been difficult to interpret because the SR is possibly depressed in patients at the time of diagnosis of PTLD, as in our case. Therefore, PCR has been widely used to establish diagnosis of EBV-related PTLD and to determine the amount of circulating EBV viral load in the peripheral blood. A previous report describing a quantitative EBV PCR test has shown higher circulating viral burdens in patients with PTLD than in those without PTLD. Campe et al. reported that pediatric transplant recipients with recurrent mononucleosis-like symptoms and with a sustained high EBV genome load are at increased risk for severe EBV-related PTLD. Rogers et al., in their study, revealed that SRs to the virus at the time of PTLD were blunted in five of seven patients, whereas EBV PCR results were positive in all of them.

In conclusion, we highly recommend that viral monitoring should be done using PCR during follow-up of pediatric LTx cases to prevent delays in diagnosis of PTLD.

REFERENCES

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