American Journal of Pediatrics
2019; 5(3): 148-151
http://www.sciencepublishinggroup.com/j/ajp
doi: 10.11648/j.ajp.20190503.22
ISSN: 2472-0887 (Print); ISSN: 2472-0909 (Online)

Case Report

Effect of Everolimus on Epstein-Barr Virus-positive T Cell PTLD After CHOP Chemotherapy and Angiofibroma in Pediatric Tuberous Sclerosis Complex

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To cite this article:

Hiroko Nagata, Hiroshi Tamura, Yusuke Miyashita, Yuko Hidaka, Ken-Ichi Imadome, Hitoshi Nakazato. Effect of Everolimus on Epstein-Barr Virus-positive T Cell PTLD After CHOP Chemotherapy and Angiofibroma in Pediatric Tuberous Sclerosis Complex. *American Journal of Pediatrics.* Vol. 5, No. 3, 2019, pp. 148-151. doi: 10.11648/j.ajp.20190503.22

Received: June 30, 2019; **Accepted**: July24, 2019; **Published**: August 13, 2019

Abstract: A 15-year-old Japanese female with end-stage kidney disease, kidney cysts, and angiomyolipoma due to tuberous sclerosis complex (TSC) received an ABO-matched preemptive kidney transplantation from her father. Basiliximab induction therapy was done on days 0 and 4, and tacrolimus, mycophenolate mofetil, and methylprednisolone were administered. Six months later, cervical lymphadenopathy developed, and computed tomography revealed an abdominal mass. Epstein-Barr virus-positive T cell post-transplant lymphoproliferative disorders (PTLD) was diagnosed. The pathology showed a monomorphic type lymphoma, and the Ki-67 index, a cell proliferation marker, was above 90%. The patient received four courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy, and tacrolimus was switched to everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway. Everolimus acts not only as an immunosuppressant, but also has an anti-tumor effect which may inhibit lymphoma development and proliferation. Three years later, the patient has shown no sign of PTLD recurrence. Her kidney function remains good, and a pathological examination detected no sign of rejection. In addition, her facial angiofibroma has improved. Although this study is based only on a single case observed over a short period of time, we consider everolimus to be a possible option in the treatment of PTLD after CHOP chemotherapy, especially in patients with TSC.

Keywords: Post-transplant Lymphoproliferative Disorder, Tuberous Sclerosis Complex, Everolimus, Epstein-Barr Virus-positive T-cell Proliferation

1. Introduction

Post-transplant lymphoproliferative disorder (PTLD), a severe complication of solid organ transplantation, is strongly associated with Epstein-Barr virus (EBV) infection in pediatric patients. More than 85% of PTLD cases consist of EBV-positive B-cell proliferation whereas the remaining cases reportedly consist of T cell receptor (TcR)-positive T cell lymphoma (T cell PTLD). T cell PTLD has a worse prognosis than B cell PTLD [1, 2]. Ki-67, a nuclear antigen protein and cell proliferation marker, has been used as a prognostic and predictive indicator of malignant tumors including non-Hodgkin's lymphoma. The proportion of Ki-67- positive cells in tissue is determined by immunohistochemical staining, with a proportion of 70% or more indicating a poor prognosis [1, 2].

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by mutations of either TSC1 or TSC2, the gene products of which are involved in the inhibition of the mammalian target of rapamycin (mTOR)

pathway. Under normal cellular conditions, mTOR regulates cell growth and proliferation, but the loss of TSC1 or TSC2 leads to overactivation of mTOR and uncontrolled cellular proliferation. One of the most common clinical manifestations is the unexpected overgrowth of benign mesenchymal tumors in many parts of the body, including the heart, lungs, kidneys, brain, skin, and eyes. The clinical manifestations of TSC vary widely and depend on the patient's age [3]. Kidney disease is the most significant threat to the life of patients with TSC, especially those over age 10 years. The renal manifestations of TSC include kidney cysts and angiomyolipomas. The median age at the diagnosis of angiomyolipoma is 8.6 years, and 80% of adult patients with TSC have angiomyolipomas, frequently in both kidneys [3]. The overall risk of end stage kidney disease (ESKD) in TSC is estimated to reach 7%, with a strong association existing between angiomyolipoma development and advanced chronic kidney disease [3].

Everolimus reduces mTOR activity by binding to intracellular immunophilin FKBP-12 and forming an inhibitory complex with mTORC1, which reduces mTOR kinase activity [4]. Everolimus inhibits the proliferation of antigen-activated T cells and arrests the cells at the G1 stage of the cell cycle. Consequently, everolimus inhibits the proliferation of vascular muscle and cancer cells [5] and thereby affects lymphoma development. Everolimus is itself an immunosuppressant, and an everolimus-based, calicineurin-inhibitor regimen following kidney transplantation is reportedly equivalent to the calicineurin-inhibitor regimen in terms of safety and effectiveness [6, 7].

We herein report a case demonstrating the effectiveness of everolimus against T cell PTLD with a high Ki-67 index after CHOP therapy and anigiofibroma in a patient with TSC. In our experience, everolimus is a potential first choice among immunosuppressant agents for patients with TSC after kidney transplantation.

2. Case Report

A 15-year-old Japanese female with ESKD due to kidney cysts and an angiomyolipoma received an ABO-matched preemptive kidney transplant from her father in February 2016. She had epilepsy and was taking two anticonvulsants. She had a history of kidney bleeding due to falls and needed a blood transfusion when she was 5 years old. The recipient was EBV-negative while the donor was EBV-positive. The patient had no panel reactive antibodies before transplantation and received a transplant with a negative T and B cell cross-match. The HLA typing for the recipient was A2, A11; B62, B35; and DR4, DR12 while for the donor it was A2, A2; B35, B46; and DR12, DR15. The patient was placed on triple immunosuppressive therapy (tacrolimus (target trough concentrations 3-5ng/ml), mycophenolate mofetil (MMF), and methylprednisolone) and basiliximab, and was discharged one month after transplantation with good kidney function (BUN 14.5mg/dl, serum creatinine 0.80 mg/dl, eGFR 76.98ml/min/1.73m^2 [8]). The patient's kidney function remained stable until December 2016 when she presented with fever and bilateral cervical lymphadenitis. Despite MMF withdrawal, the fever did not resolve. Antibiotics were administered, but her condition failed to improve. Cervical computed tomography (CT) showed lymphadenopathy of approximately 40 mm while an abdominal CT revealed a mass of approximately 60 mm inside the renal cortex of the left native kidney (Figure 1A). Antibody tests for EBV by enzyme immunoassay showed that the IgM antibody to EBV viral capsid antigen (VCA) was negative, IgG antibody to EBV VCA was positive, and EBV nuclear antigen was negative. The EBV-DNA load in the peripheral whole blood cells was 560 copies/μgDNA. Positron emission tomography (PET) also detected malignant tissue in the same part of the abdomen and the bilateral cervical lymph nodes (Figure 1B). A biopsy of the mass inside the renal cortex of the left native kidney was performed and a pathological examination demonstrated monomorphic PTLD and positivity for EB encoding region (EBER) in situ hybridization (ISH) (Figure 2 AB). The Ki-67 index was higher than 90% for the abdominal mass. EBV–positive PTLD was diagnosed. Flow cytometry showed that the EBV-infected cells had cell surface marker CD4 but did not express CD19 or CD20, thus indicating EBV-positive T-cell lymphoma. Four courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy were administered, and tacrolimus was switched to everolimus. After CHOP treatment in April 2017, the cervical mass resolved, the PTLD mass decreased to a diameter 38 mm, the EBV-DNA copies/μgDNA decreased to 52, and PET did not detect high levels of the tracer in the cervical lymphadenopathy or native kidney. In addition, the patient's facial angiofibroma also showed clear signs of improvement.

A kidney biopsy performed in April 2017 revealed no evidence of rejection, and the transplanted kidney was negative for EBER-ISH. PET imaging showed no signs of PTLD.

3. Discussion

The most serious manifestation of PTLD is the development of lymphomas, which are strongly associated with Epstein-Barr virus infection, especially in children, as a large number of children are EBV-negative. PTLD develops in EBV-negative recipients approximately four to 70 times more than in EBV-positive recipients [9, 10]. Treatment after transplantation designed to prevent graft rejection has often caused excessive immunosuppression leading to PTLD. The standard approach for the treatment of PTLD has been to reduce immunosuppression but is often insufficient to induce tumor regression if the pathology demonstrates a monomorphic type lymphoma, in which PTLD remission is more difficult to achieve than in a polymorphic pattern lymphoma. Moreover, remission in even more difficult to achieve T-cell lymphoma [10]. In addition, the Ki-67 value in the present case was higher than 90%. The normal proportion of Ki-67 positive cells in tissue is not clear, but a Ki-67 of 70% or more indicates a poor prognosis [1, 2]. The patient in the

present case therefore required four courses of CHOP therapy, to ameliorate the PTLD.

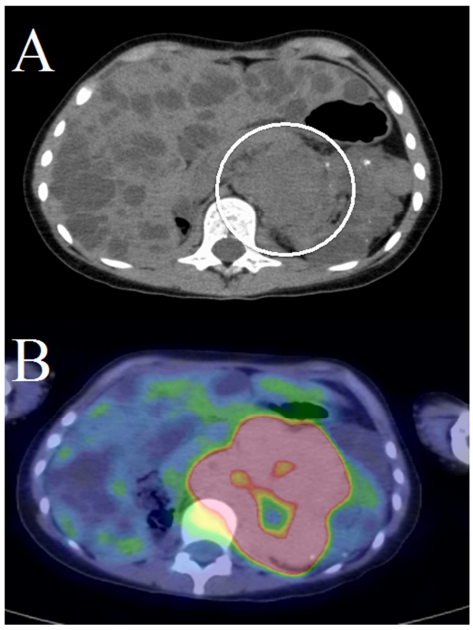

Figure 1. *Abdominal computed tomography (A) showed an approximately 60 mm-long mass (circle) inside the renal cortex of the left kidney. Positron emission tomography (B) demonstrated a tracer hot spot around the mass.*

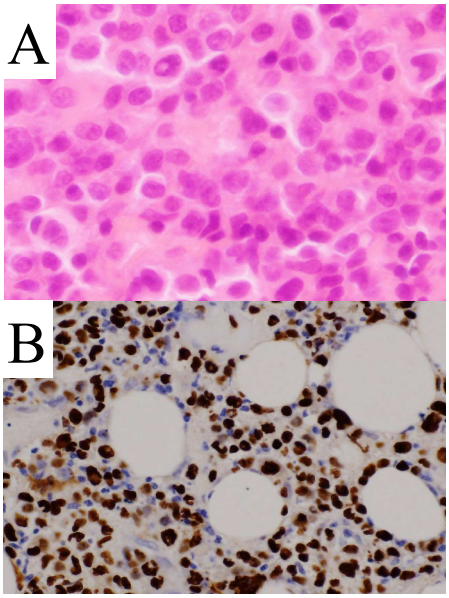

Figure 2. *(A, B) Histopathological findings of the mass. (A) Most of the cells in the infiltrate were large, atypical, transformed lymphoblasts indicating monomorphic type PTLD. The pre-existing lymphatic structure had disappeared. (hematoxyline-eosin staining, x400) (B) EB-encoding region (EBER)-in situ hybridization (ISH) was positive (almost 100% of lymphoid cells) for EBV (x400).*

EBV mainly targets B cells but is also known to infect T cells. The mechanism of infection is not fully understood. In one report, T cells infected by EBV abnormally expressed CD21 [11]. In another report, B, T, and NK cells infected by EBV persistently manifested both CD40 and CD40 ligands, preventing apoptosis and causing proliferation [12]. In general, monomorphic PTLD, especially T-cell related PTLD, is associated with a high mortality rate.

As mTOR inhibitors have immunosuppressive and antivascular effects, the suppression of recurrences and continuing antitumor activity after PTLD therapy may be expected. Two studies suggest that the introduction of TOR inhibitors should be considered in solid organ transplant recipients with PTLD to prevent allograft rejection and potentially inhibit tumor growth [13, 14]. Everolimus may be effective in the treatment of PTLD especially in polymorphic pattern children. De novo everolimus with cyclosporin A treatment was effective against organ rejection after pediatric kidney transplantation and was safe to use [14]. Everolimus has the potential to minimize the dosage of calcineurin inhibitors (CNI), which may lead to lower CNI nephrotoxicity. However, the long-term prognosis of patients with kidney transplantation rejection and PTLD recurrence is not known.

In Japan, the indications for everolimus use covered by the National Health Insurance are angiomyolipoma, subependymal giant cell astrocytoma (SEGA), renal cell carcinoma, neuroendocrine tumor, and breast cancer. Moreover, previous studies have reported improvements in TSC symptoms after everolimus treatment for angiofibroma [15]. These case studies indicate that longer-term everolimus use can mitigate multiple manifestations of TSC. In the present case, we observed improvement in the patient's facial angiofibroma.

4. Conclusions

We describe the effect of everolimus on EBV-positive PTLD after CHOP chemotherapy and Angiofibroma in TSC. We propose that everolimus may be a viable therapeutic option for PTLD and angiofibroma, although this study was based on only one case over a short period of time.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgements

We thank Dr. Kazutaka Ozono (Department of Pathology, Faculty of Life Sciences, Kumamoto University) for providing the pathological diagnosis and findings.

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