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Posttransplant Lymphoproliferative Disorder Following Cytomegalovirus Reactivation in a Lung Recipient

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Abstract

Posttransplant lymphoproliferative disorder (PTLD) is a life-threatening complication after lung transplantation, for which several risk factors including pretransplant seronegativity for Epstein-Barr virus are known. However, the impact of cytomegalovirus on PTLD remains to be determined. Here, we describe a case of Epstein-Barr virus-associated polymorphic PTLD which developed shortly after treatment for cytomegalovirus reactivation in a lung transplant recipient who was preoperatively seropositive for both cytomegalovirus and Epstein-Barr virus.

Key Words

CD20; lung transplantation; rituximab; positron emission tomography

Introduction

Posttransplant lymphoproliferative disorder (PTLD) is a serious complication after lung transplantation with an incidence of 1.8-20% and considerable mortality[1-6]. Several risk factors for developing PTLD are widely accepted, including pretransplant seronegativity for Epstein-Barr virus (EBV) and aggressive immunosuppression. However, there is limited information concerning any correlations between cytomegalovirus (CMV) and PTLD. Here, we report the first case of a lung transplant recipient, who had been both CMV- and EBV-seropositive before transplantation, developed EBV-associated PTLD immediately after CMV reactivation, and was successfully treated.

Case Report

A 52-year-old man underwent single lung transplantation because of emphysema in February 2005. He had received bilateral lung volume reduction surgery in 1996. He was preoperatively both CMV- and EBV-seropositive, while the serostatus of the donor was CMV-positive but not examined for EBV. After lung transplantation, the patient received immunosuppression consisting of prednisolone, azathioprine, and tacrolimus. Trough levels of tacrolimus were maintained between 10 and 15 ng/ml. The patient received prophylaxis for CMV with three-week intravenous and two-month oral ganciclovir treatment and subsequent oral acyclovir with the doses corrected for renal function. The elevation of soluble IL-2 receptor (sIL2R) around postoperative day (POD) 35 was closely followed, also monitoring EBV-PCR, and resolved spontaneously with any evidence of developing acute rejection or infection which both could lead to the elevation of sIL2R in lung recipients[7]. On POD 112, PCR for CMV-DNA became positive, as did CMV pp65 antigen in the peripheral blood (using the CMV antigen test "HRP-C7"; SRL, Tokyo, Japan) with 23 copies/μg DNA and a titer of 5/50000 respectively. At the same time, PCR for EBV-DNA became elevated to 2500 copies/μg DNA. We administered intravenous ganciclovir for three weeks, discontinued azathioprine, and controlled the trough

levels of tacrolimus below 10 ng/ml. Thereafter, PCR for CMV-DNA and CMV antigen rapidly became negative, but the copy numbers of EBV-DNA by PCR were elevated to 17000 copies/μg DNA on POD 132 despite the administration of ganciclovir and the reduction of immunosuppression. The patient also presented with lymphadenopathy in the cervix, axilla, and groin. EBV viremia with lymphadenopathy was treated with intravenous 3-week vidarabin and simultaneous one-week acyclovir. This treatment resulted in decreased copy numbers of EBV, but in elevated sIL2R in the serum and persisting lymphadenopathy. FDG-positron emission tomography (PET) showed multiple foci of hypermetabolism in the left hilus, the mediastinum, the cervix, and the axilla (Figure 1A). A biopsy from the inguinal lymph node showed loss of characteristic architecture and a composition of a majority of small or intermediate-sized lymphocytes including plasma cells (Figure 1B). Infection with EBV and B cell lineage were confirmed by *in situ* hybridization, and the immunohistochemical staining with antibody against CD20 was partly positive. With a diagnosis of polymorphic PTLD, we administered one cycle of rituximab, a chimeric monoclonal antibody specific for CD20, at a dose of 375 mg m^{-2} once a week for four weeks. There were no significant adverse effects. After the therapy, EBV-PCR became negative, the serum level of sIL2 receptor gradually decreased, and the lymph nodes shrunk. A summary of the clinical course is presented including the trend of levels of serum sIL2R in Figure 2. There is no evidence of relapse four years after treatment for PTLD.

Discussion

PTLD is a serious complication following organ transplantation with a mortality rate of up to 40%[5]. PTLD is usually associated with EBV. EBV is readily controlled by T lymphocytes in healthy individuals, but immunosurveillance is impaired in immunosuppressed situations such as after organ transplantation[8]. Therefore, the incidence of PTLD differs according to the type of transplanted organ, depending on the different intensities of immunosuppression required. Risk factors for developing PTLD are reported to be aggressive

immunosuppressive therapy, primary EBV infection, young recipient age, and high rejection frequency[1,9.]

In the present case, prior to development of PTLD, CMV viremia and antigenemia was detected. CMV reactivation and PTLD caused by EBV are both relatively common complications of immunosuppression. The relationship between these phenomena is not clear, but some information is available on possible correlations between CMV and PTLD. In nonrenal transplant recipients, CMV-seromismatch (i.e., a negative recipient and a positive donor) is associated with a six-fold higher risk of developing PTLD in the subgroup of pretransplant EBV-seronegative patients[10]. In another report, CMV disease is significantly associated with the development of PTLD in patients who underwent primary EBV infection after liver transplantation[11]. In a more recent review of a large cohort in one institution, positive CMV serology before transplantation in recipients had a tendency to result in a lower incidence of PTLD, indicating that patients without CMV-seroconversion after transplantation are in a lower risk of developing PTLD in heart and heart-lung transplant recipients[9]. However, as seen in the present case, it should be addressed that even CMV-seropositive recipients can develop PTLD after reactivation of CMV. Rubin suggested several possible effects of CMV on the host after reviewing the impact of CMV on transplant recipients. According to this review, CMV causes a metabolic abnormality in lymphocytes and monocytes that impairs their ability to produce and to respond to some cytokines. In addition, CMV causes an alteration in circulating T cell subsets, with a decrease in $CD4^+$ cells and an increase in $CD8^+$ cells, leading to a decrease in cell-mediated immune function[12]. CMV in our patient might have disturbed the balance of immunity against EBV, resulting in the reactivation of this virus and finally leading to the development of PTLD. According to this hypothesis, when organ transplant recipients need treatment for CMV, it can be important not only to administer anti-CMV drugs and immunoglobulin but also to reduce immunosuppression to prevent superinfection with or reactivation of EBV, which might lead to PTLD, or with other pathogens. In addition, a simple

and reliable method for monitoring the function of cytotoxic T lymphocytes would be desirable, because merely adjusting the trough levels of the administered calcineurin inhibitor might be insufficient in CMV-infected recipients. A study showed the flow cytometry–based assay detected an increase of IFNγ producing EBV-specific $CD8^+$ T cells during reduction of immunosuppression, leading to regression of EBV-associated PTLD in kidney recipients[13]. In addition, one case report described the assay measuring the concentration of ATP from stimulated CD4 T^+ cells for reduction of immunosuppression followed by resolution of PTLD, and thereafter for adjusting the dose of immunosuppression in a kidney recipient[14]. These assays may be also applicable to patients with CMV reactivation or seroconversion. Both CMV reactivation and EBV-associated PTLD are, of course, common in lung transplant recipients and these two entities might have happened sequentially by chance. Further study in a large cohort of patients in a multicenter trial is necessary to elucidate the relationship between CMV reactivation and the development of PTLD.

Conclusion

We report a case of EBV-associated PTLD following CMV reactivation in a lung transplant recipient, who was both CMV- and EBV-seropositive before transplantation.

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Figures and figure legends

Figure 1.

(A)

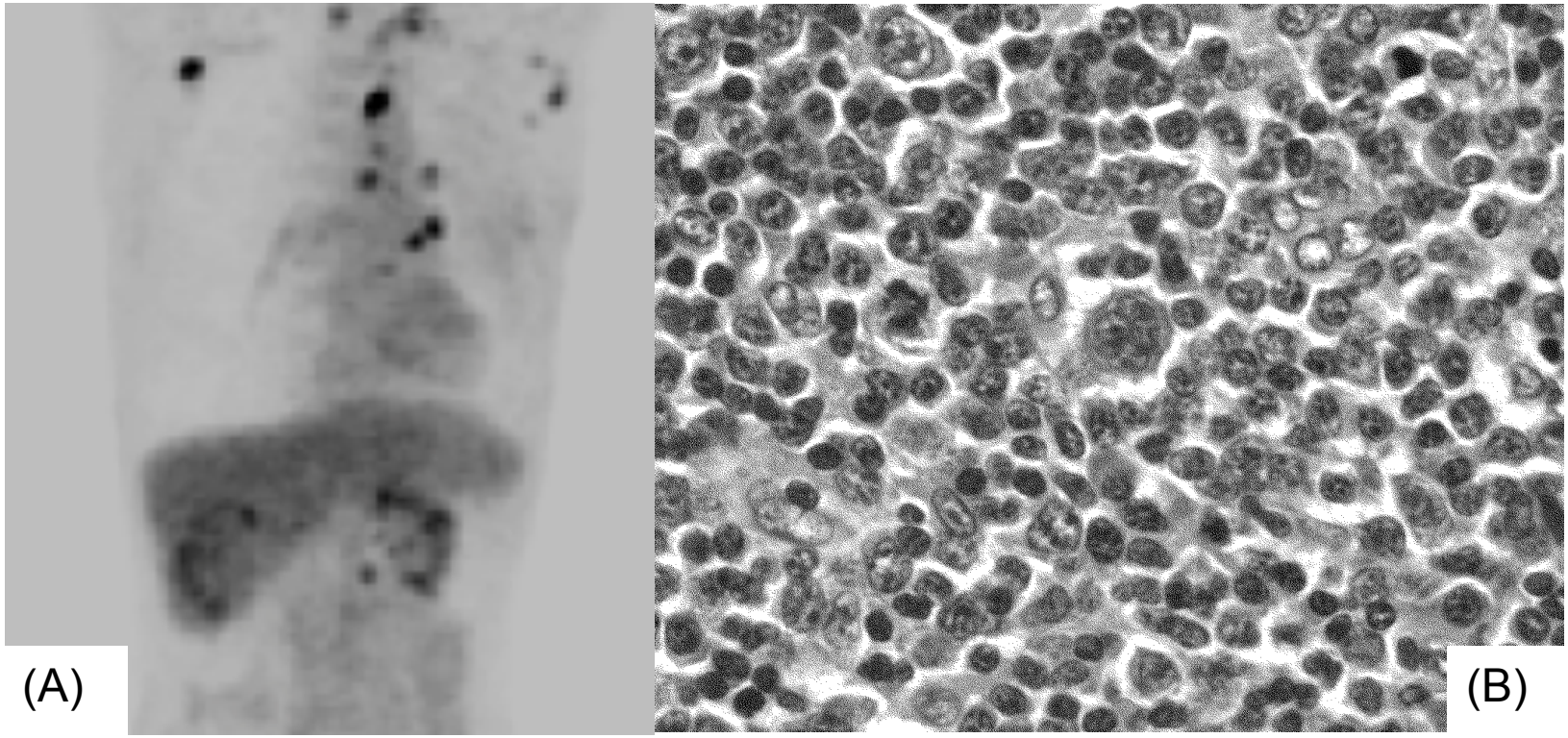
FDG-PET shows multiple foci of hypermetabolism in the left hilum, the mediastinum, the cervix, and the axilla.

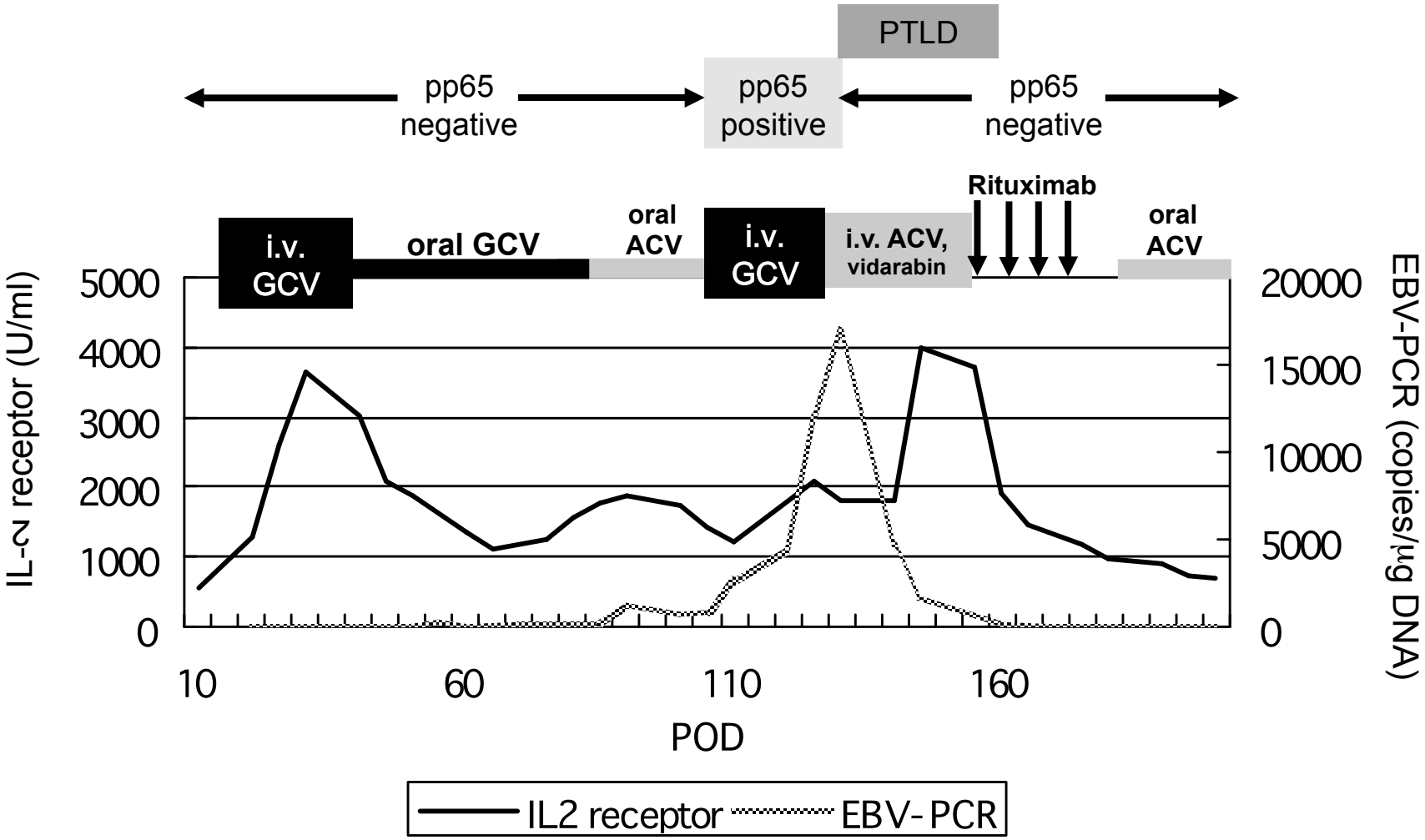
(B)

Photomicrograph of the lymph node shows loss of the architecture of lymphoid follicles, and small and intermediate-sized lymphoid cells and plasma cells. (Hematoxylin and eosin, original magnification x 600)

Figure 2.

The levels of soluble interleukin-2 receptor in the serum, the copy numbers of Epstein-Barr virus by polymerase chain reaction, and summary of the therapy and status of pp65 and PTLD. Modified from reference 15 by permission of Nankodo Co., Ltd. ACV; acyclovir. Other abbreviations as in the manuscript.


(A)
(B)


PTLD
pp65 negative
pp65 positive
pp65 negative
Rituximab
i.v. GCV
oral GCV
oral ACV
i.v. GCV
i.v. ACV, vidarabin
oral ACV
IL-2 receptor (U/ml)
5000
4000
3000
2000
1000
0
20000
15000
10000
5000
0
EBV-PCR (copies/µg DNA)
10
60
110
160
POD
IL2 receptor
EBV-PCR