

# Complete Resolution of Posttransplant Lymphoproliferative Disorder (Diffuse Large B-cell Lymphoma) with Reduction of Immunosuppressive Therapy

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Posttransplant lymphoproliferative disorder (PTLD) is a serious complication of organ transplantation. PTLD is the disorder arising from the combined effects of Epstein-Barr virus associated lymphoid proliferation with the disruption of the normal immune control by the cytotoxic T cells. The treatment for PTLD is one of the most controversial topics in solid organ transplantation. It is well known that the initial management of PTLD is a reduction of immunosuppression. Early diagnosis and the early reduction in immunosuppression are essential even for monomorphic lymphoma. We report here on a case of the complete resolution of PTLD (diffuse large B cell lymphoma) which occurred after a drastic reduction of immunosuppression in a renal transplant recipient.

**Key Words:** PTLD, immunosuppression, reduction, resolution

## INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication of organ transplantation. PTLD represent a wide spectrum of clinically and morphologically heterogeneous lymphoid proliferations, ranging from polyclonal lymphoid hyperplasia to an aggressive monoclonal lymphoma.<sup>1</sup> PTLD is due to the combined effects of lymphoid proliferation induced by Epstein-Barr virus (EBV) infection and the disruption of normal immune control by the cytotoxic T cells.<sup>2</sup>

In general, the treatment of PTLD has been individualized according to PTLD type: the patient with early lesion or polymorphic PTLD has been treated with the reduction of immunosuppression and the addition of antiviral therapy (acyclovir or ganciclovir). But in monomorphic PTLD patients, it is believed that antiviral therapy is ineffective during the monoclonal growth phase and so secondary treatment has been used.<sup>3-6</sup>

We report here on a rare case of the resolution of monomorphic PTLD with a drastic reduction of immunosuppression. To the best of our knowledge, this is the first case in Korea of the complete resolution of PTLD with a reduction in immunosuppression.

## CASE REPORT

A 19-year-old man was admitted in November 2001 to our hospital with a 40-day history of a palpable left submandibular mass. He was diagnosed with end-stage renal disease (ESRD) in November 2000 and he had undergone a renal allograft from his mother in January 2001. Antibody (monoclonal or polyclonal) was not used for induction. He was being given prednisone 10 mg, tacrolimus 10 mg and mycophenolate mofetil (MMF) 1,500 mg daily for the maintenance of immunosuppression.

The physical examination on admission revealed the following: blood pressure 130/80 mmHg; pulse rate 86/min; respiration rate 18/minute and body temperature 37.4C. A movable, non-tender, 10×6 cm-sized mass was palpated on the left sub-

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mandible and also, there was a 2.5×2.5 cm-sized mass on the right submandible. There was no hepatosplenomegaly.

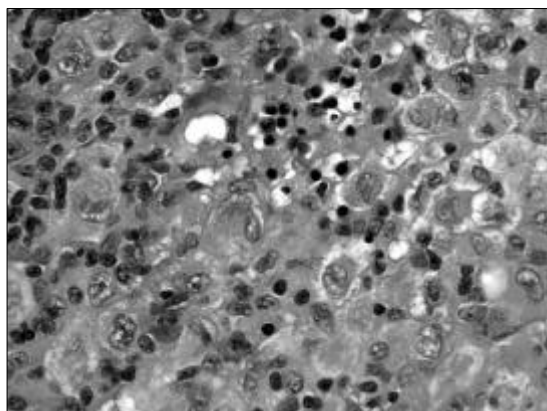
Laboratory tests revealed the following: hemoglobin, 9.5g/dL; hematocrit, 28%; white cell count, 10,500/ $\mu$ L with 75.5% polymorphonuclear cell; platelet count, 390,000/ $\mu$ L; sodium, 137.3 mEq/L; potassium, 4.37 mEq/L; chloride, 103 mEq/L; bicarbonate, 26 mEq/L; calcium, 9.8 mg/dL; phosphate, 3.4 mg/dL; blood urea nitrogen 26 mg/dL; creatinine, 1.8 mg/dL; total protein, 7.3 g/dL; albumin, 3.9 g/dL; total bilirubin, 0.3 mg/dL; alkaline phosphatase, 83 IU/L; AST, 11 IU/L; ALT, 5 IU/L; uric acid, 7.8 mg/dL; erythrocyte sedimentation rate (ESR), 12 mm/hr; lactate dehydrogenase (LDH); 372 IU/L; LDH1, 12.62; LDH2, 28.52; LDH3, 23.65; LDH4, 13.85; LDH5, 21.37;  $\beta_2$ -microglobulin, 5.79 mg/L; EBV Ab IgM, 0.735 (positive); EBV Ab IgG, 0.587 (positive); EBV Ab EBNA IgG, negative.

A needle aspiration biopsy of the left submandibular mass showed a polymorphous population of large transformed lymphoid cells, and this was consistent with PTLD. Excisional biopsy at the right submandible revealed a large cell lymphoma with anaplastic morphology (Fig. 1), and the expression of B-cell marker and EBV positivity on a situ hybridization study was noted (Fig. 2). The bone marrow study revealed no lymphomatous involvement.

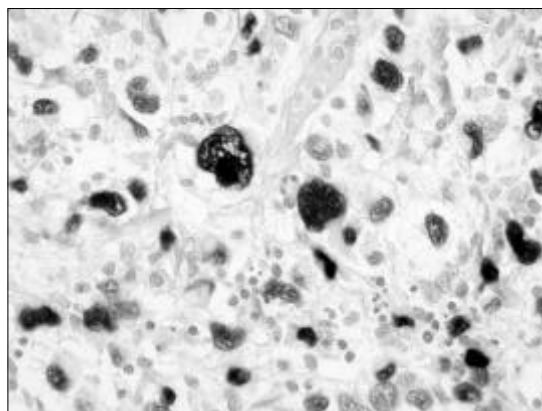
The neck computerized tomographic (CT) scan showed large, low-attenuating, conglomerated lymph nodes measuring 6×4cm in size at the left

level II/III (Fig. 3A). The abdomino-pelvic CT scan showed about a 5×4cm sized well-defined heterogeneous mass at the posterior aspect of the spleen without definite capsule formation, and there was no other abnormal mass seen (Fig. 3B). The chest CT showed bronchiolitis, it was probably infectious such as viral or bronchiolitis obliterans, and there was no evidence of lymphadenopathy in the lungs and mediastium. The whole body bone scan showed no evidence of skeletal metastasis. The positron emission tomography (PET) showed the multifocal areas of increased  $^{18}$ F-FDG uptake in both submandibular areas, the right upper jugular chain and both posterior cervical chains; this was highly suggestive of an active neoplastic process and the spleen was also suggestive of a neoplastic etiology (Fig. 4).

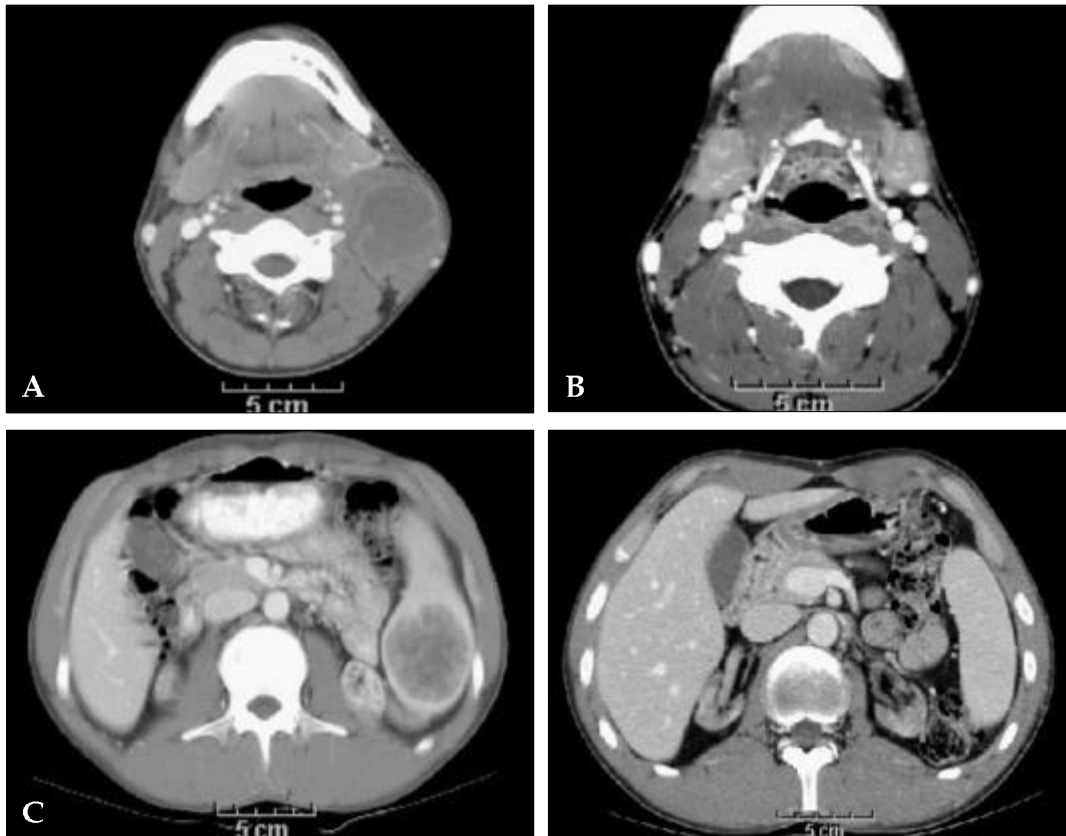
From the second day following hospitalization, he was administered acyclovir 1,200 mg daily intravenously for 14 days. The MMF was discontinued. Tacrolimus was tapered from 10 mg to 3mg for 9 days, maintained at 3 mg for 35 days and then 4 mg for 29 days with the targeting of a 12-hr tacrolimus concentration of around 5ng/mL. His left submandibular mass was observed to gradually decrease on palpation of the mass: on day 20, the mass was 6×4 cm-sized; on day 30, 4×2 cm; on day 40, 3×1 cm; on day 70, 0.5×0.5cm. On day 63 and 64, a magnetic resonance imaging (MRI) of the neck and spleen was taken. The neck MRI showed a markedly decreased lymphadeno-



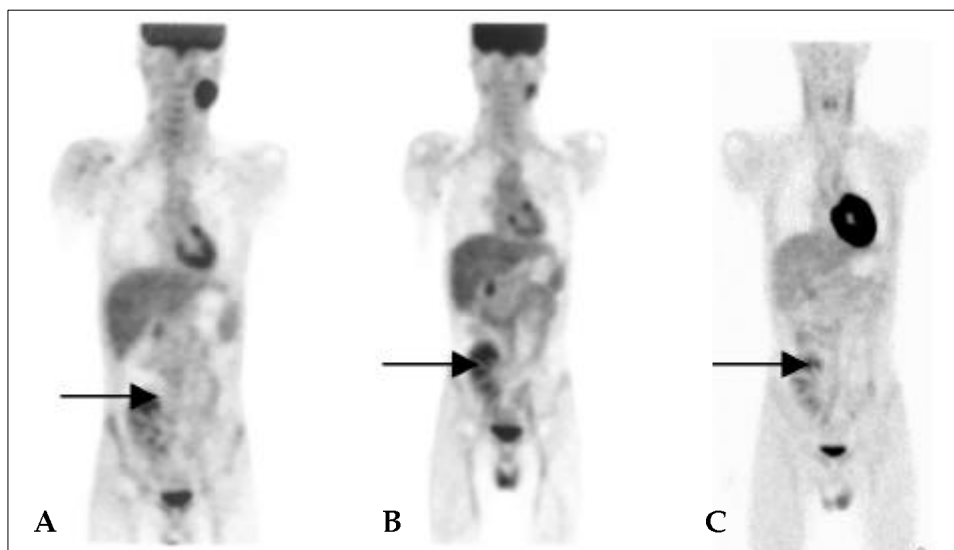
**Fig. 1.** High power view showing large atypical lymphoid cells having the cytologic features of an anaplastic large cell lymphoma (Hematoxylin-eosin,  $\times 400$ ).



**Fig. 2.** EBER1 mRNA in situ hybridization showing intense nuclear signal ( $\times 400$ ).



**Fig. 3.** The initial neck (A) and abdomino-pelvic CT (B) showing conglomerated lymphadenopathy at left level II/III, and about 4cm sized well defined heterogeneous mass at the posterior aspect of the spleen. Seventeen-months later, following neck (C) and abdomino-pelvic CT (D) showing no evidence of cervical lymphadenopathy and no evidence of splenic and other mass or lymphadenopathy in the remaining abdomen and pelvis.



**Fig. 4.** A. The initial PET showing increased  $^{18}\text{F}$ -FDG uptake on both submandibular areas, right upper jugular chain, both posterior cervical chains and spleen. B the following PET 40-days later showing decreased size in the left submandibular, right upper neck lymph node and near complete resolution of the previously noted uptake in the splenic mass. C. Nineteen-months later showing complete resolution of previous uptake lesion in the neck and spleen. Note: arrows indicate transplanted kidney.

pathy (2×2 cm) on Lt. level II/III and the spleen MRI also showed a decreased size of the splenic mass (2×2 cm).

Seventeen-months later, the follow-up neck (Fig. 3C) and abdomino-pelvic CT (Fig. 3D) showed no evidence of cervical lymphadenopathy and no evidence of splenic and other masses, or any lymphadenopathy in the remaining abdomen and pelvis. Nineteen months later, PET showed a complete resolution of the previous uptake lesions in the neck and spleen (Fig. 4C). After he was discharged, the dose of tacrolimus was maintained at 5mg daily and he is alive with complete remission during the last 2 years, but EBV Ab IgM and IgG are still positive (2.655; 1.248) and EBV Ab EANA is positive (1.647). A recent serum creatinine level is around 2.0 mg/dL.

## DISCUSSION

PTLD is a serious complication of organ transplantation, with the mortality rate from PTLD or its related complications reported to be over 50% of the patients. The incidence of PTLD is approximately estimated to vary from 2% for renal allograft recipients, 2% to 4% for liver recipients, slightly higher for heart recipients, and as high as 10% for heart-lung recipients.<sup>6,7</sup> In the period of 1979-2000, among 1,800 allograft recipients, PTLD developed in 4 patients (0.22%) in our Hospital, which shows approximately one tenth the incidence seen in Western countries.<sup>8</sup> This difference implies that the dose of the immunosuppressive agent to the cadaver and living donor may have an influence on the incidence.

PTLD is an EBV-associated disorder that is due to the effects of lymphoid proliferation induced by an EBV infection, and also to the disruption of normal immune control by cytotoxic T cells. In certain immunocompromised patients, the critical T-cell control of B-cell growth is lacking, resulting in the proliferation of EBV-infected B cells, and then hyperplasia or malignancy follows. An inadequate T-cell response results in EBV-related B-cell proliferation.<sup>9</sup> In our case, before transplantation the patient's EBV Ab was negative (IgM, IgG), but the EBV Ab IgM and IgG were converted to positive at the time of admission for

lymphoma management. After the reduction of immunosuppressive therapy, his mass disappeared on palpation and an imaging study showed a complete resolution of the mass, but the EBV Ab IgM remained positive without a decrease of the laboratory value for 2 years. Therefore, he is at risk for relapse of PTLD, depending of course, upon the doses of the immunosuppressive agents.

The treatment of PTLD is one of the most controversial topics in solid organ transplantation. This is a result of the limited understanding of its pathogenesis and the lack of uniformity in the definition. No randomized controlled treatment trials have been performed.<sup>10,11</sup> Furthermore, spontaneous regression of PTLD was reported after the reduction in immunosuppression, and this occurred even in monomorphic lymphoma.<sup>12,13</sup>

It is well known that the initial management of PTLD is achieved with the reduction of immunosuppression. However, the reduction period, the dose of immunosuppressive agents and what choice is the best second strategy after immunosuppression is unclear. Paya et al., suggested a potential algorithm where cyclosporine or tacrolimus and prednisone should be decreased.<sup>10</sup> For limited disease, surgical extirpation, localized radiation therapy is recommended (particularly for localized CNS PTLD) or minor/moderate disease, (e.g., 25%), immunosuppression reduction can be performed. For an extensive disease in critically ill patients, stop all immunosuppression and administer prednisone at 7.5-10 mg/day. For those patients who are not critically ill, decrease cyclosporine or tacrolimus by 50%, discontinue azathioprine/mycophenolate mofetil (MMF), and maintain prednisone at 7.5-10mg/day. If there is no response within the early period (a suggested period of 10-20 days), a second strategy should be considered, such as chemotherapy, antiviral agents, monoclonal anti-B cell antibody (anti-CD20, CD21 and CD24), interferon- $\alpha$  and so on.<sup>13</sup> Bobey et al., reported the successful use of autologous peripheral blood stem cell transplantation in a patient with relapsed PTLD after chemotherapy.<sup>14</sup> In our case, the response to the reduction of immunosuppression was dramatic and rapid. With the cautious observation of mass reduction in response to lowering the dose of the

immunosuppressant, and also the consideration of chemotherapy if there was a poor response, our patient finally achieved a complete remission. On the other hand, Soler et al reported 10 cases of PTLD and he treated each case individually according to PTLD type. Seven patients with monomorphic PTLD underwent a reduction of immunosuppression, or a complete withdrawal of immunosuppression plus chemotherapy: six patients received different regimens of chemotherapy depending on their histopathology, bone marrow involvement and toxicity. They achieved a complete response with a mean follow-up period of 77 months and only one patient with Burkitt lymphoma died less than 1 month after diagnosis.<sup>6</sup>

Certainly, early diagnosis and immunoreduction for PTLD is important. Tsai et al. reported that a reduction in immunosuppression is an effective initial therapy for PTLD. The response to a reduction in immunosuppression alone was 100% for hyperplasia or polymorphic B-cells; on the other hand, it was 52% for all other histologies (monomorphic B cell lymphoma, multiple myeloma, T-cell NHL). With a median follow-up of 147 weeks for Tsai's study, 55% of the patients are alive with 50% of them in complete remission. It was also emphasized that increased age, elevated LDH level, severe organ dysfunction, presence of B symptoms (fever, night sweats and weight loss), and the multi-organ involvement by PTLD at the time of diagnosis are independent prognostic indicators for poor survival.<sup>15</sup> Tsai showed that the reduction of immunosuppression can lead to long-term relapse-free survival when used as an initial therapy for PTLD, and those patients with multiple poor prognostic factors (elevated LDH ratio, significant organ dysfunction, or multiple-organ PTLD) should be considered for other therapies in combination with a reduction of immunosuppression. This means that individualized therapy according to histology or prognostic factors is very important.

In this case, our patient had monomorphic lymphoma with the two poor prognostic factors of an elevated LDH level and multi-organ involvement, and a complete resolution was still possible with only a reduction of immunosuppression; after a follow-up of 2 years he is alive, but with

a decreased renal function. If the dose of tacrolimus is increased due to the patient's decreased kidney function, this case will have an increased risk for PTLD relapse because his EBV Ab is still positive.

PTLD is more common in the first post-transplant year and its incidence decreases in frequency thereafter.<sup>16</sup> In this case, PTLD developed 10 months after transplantation. Therefore, for the effective treatment of PTLD in allograft recipients, the serologic tests such as EBV Ab and LDH with an isoenzyme level should be routinely monitored and imaging study such as PET scan may be done for high risk patients with increased serologic markers or EBV Ab IgM positivity. Considering the poor prognosis of advanced PTLD, early diagnosis and an early reduction in immunosuppression are essential, even in those patients with monomorphic lymphoma. Even for patients with a complete remission, as in our patient, proper management is necessary for maintaining both a continued complete remission and proper kidney function.

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