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## CASE REPORT

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# Post-transplant Lymphoproliferative Diseases: a Case Report and Discussion of Management

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### ABSTRACT

*Post-transplant lymphoproliferative disorders (PTLD) are lymphoid or plasmacytic proliferations that develop in immunosuppressed individuals, particularly in recipients of solid organs, bone marrow, or stem cell allograft. Although rare in the general population, the prevalence of PTLD is increasing among transplant patients, particularly as transplantations have become more frequent procedures in recent years. PTLD are very closely associated with Epstein-Barr virus infection, with up to 80% of all PTLD cases testing positive for Epstein-Barr virus. Histologically, PTLD have three main subtypes as classified by the World Health Organization: early lesions, polymorphic PTLD and monomorphic PTLD, which can be regarded as lying on a pathological continuum. While there are currently no data from phase III clinical trials to guide optimal treatment of PTLD, evidence from phase I and II studies, retrospective analyses and case series, as well as expert opinion, indicate the effectiveness of immediate reduction in immunosuppression as first-line therapy, particularly in early-stage disease. When reduction in immunosuppression is inadequate, the evidence shows that addition of rituximab and / or chemotherapy is a useful and effective option. Radiation has limited indication in PTLD except in localised disease and for palliation. This article describes a case of PTLD in a female patient with end-stage renal failure due to lupus nephritis, who had previously received a cadaveric renal transplant. Her management is discussed with some reference to the published literature and current opinion.*

**Key Words:** Epstein-Barr virus infections; Immunosuppression; Lymphoproliferative disorders; Organ transplantation; Postoperative complications

## 中文摘要

### 移植後淋巴增生性疾病：病例報告及治療方法的討論

陳守仁

移植後淋巴增生性疾病（PTLD）是指出現在免疫抑制病人中的淋巴或漿細胞增生，尤見於異體器官、骨髓或幹細胞移植病人身上。雖然在一般人口中罕見，在移植病人中PTLD的流行率正在上升，尤其是近年間移植手術越趨頻密。PTLD與Epstein-Barr（EB）病毒感染密切相關，在所有PTLD個案中有高達八成對EB病毒測試呈陽性。組織學上，世界衛生組織將PTLD分為三個主要亞型：早期病變、多形性PTLD和單形性PTLD。這三個分類可被視為一個連續體。雖然目前尚未有第三期臨床試驗數據作為PTLD理想治療的指引，但第一及第二期研究、回顧分析、病例系列報告及專家意見指出，即時降低免疫抑制作為一線治療具有療效，尤其在疾病早期。在免疫抑制下降不足的情況下，

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證據顯示加用利妥昔單抗 (rituximab) 及 / 或化療是一個有用而有效的選擇。電療在PTLD中的適應證有限，除非用於局部疾病及紓緩治療。本文報導一個因紅斑狼瘡性腎炎出現末期腎衰竭、曾接受屍腎移植的PTLD女病人個案，並參考過往文獻與專家意見，對個案的治療作出討論。

## INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD) are rare conditions that most commonly affect immunocompromised individuals, such as transplant recipients. The prevalence of PTLD has increased in recent years as a result of the increased and more intense use of therapeutic immunosuppression, and the increased total number of transplantations performed. Here, we describe a case of PTLD in a patient with end-stage renal failure due to lupus nephritis, and discuss the management course according to the current recommended practice.

## CASE REPORT

A 47-year-old woman with end-stage renal failure due to lupus nephritis presented with a 2-week history of right-sided weakness, expressive dysphasia, and easy memory loss in December 2011. She had received a kidney transplant in 1993, following which she had developed acute cellular rejection and chronic allograft nephropathy resulting from the use of calcineurin inhibitor. For this, she was initially treated with a course of high-dose methylprednisolone and her serum creatinine was maintained at around 250  $\mu\text{mol/l}$ . She was subsequently maintained on a low dose of prednisolone 5 mg daily and mycophenolate mofetil (MMF) 750 mg am and 500 mg pm, a common maintenance regimen prescribed to renal transplant patients.

Examination of the patient at presentation showed gross left-sided neurological deficit. Computed tomography (CT) scan of the brain showed a mass over the left frontal lobe. Burr hole drainage was performed for suspected brain abscess in view of the recent history of tooth extraction, but this yielded minimal pus. Thus, formal craniotomy and partial excision of the tumour was undertaken. Subsequent pathological examination enabled diagnosis of monomorphic PTLD with diffuse large B-cell lymphoma, which tested positive for Epstein-Barr virus (EBV)-encoded RNA according to the 2008 World Health Organization (WHO) classification. Pre-treatment assessment and staging were performed, including a whole-body positron

emission tomography-CT scan. These revealed a residual, hypermetabolic left frontal lobe tumour; no other fluorodeoxyglucose-avid lesions were found elsewhere in the body. Bilateral bone marrow aspiration and trephine biopsy showed no evidence of lymphoma in the bone marrow. Blood tests showed elevated level of lactate dehydrogenase (LDH; 317 U/L).

Treatment was initiated with immediate reduction in immunosuppression (RIS), and MMF was substituted with everolimus. The patient also received whole-brain radiotherapy of 40 Gy and 4 weekly doses of rituximab. At the patient's last follow-up, 18 months after treatment, serum EBV-DNA remained undetectable and there was no evidence of relapse.

## DISCUSSION

### Classification of Post-transplant Lymphoproliferative Disorders

The 2008 WHO classification describes PTLD as lymphoid or plasmacytic proliferations that develop in recipients of solid organs, bone marrow, or stem cell allograft as a result of immunosuppression.<sup>1</sup> There is a close relationship between the development of PTLD and EBV, with up to 70 to 80% of all PTLD being due to EBV infection.

EBV infection in childhood is almost universal, but is typically asymptomatic or self-limiting. After infection, the virus persists long term as a latent infection, with the EBV genome being maintained for life in a small fraction of B cell lymphocytes. Systemic reactivation is normally kept in check by a healthy immune system, specifically, by cytotoxic T lymphocytes, which play a key role in controlling EBV proliferation. When T cell immunity is diminished, such as in immunocompromised individuals, EBV infection can progress rapidly and systemically, and significantly increase the risk of PTLD.<sup>2</sup>

Several different types of EBV latency have been described, each characterised by different patterns of EBV gene expression and corresponding differences in immunogenicity.<sup>3</sup> PTLD is a type III latency

malignancy, in which there is unrestricted expression of all latent viral proteins.<sup>2-5</sup> This is in contrast with Hodgkin's lymphoma and Burkitt lymphoma, which are type 2 and type 1 (expression of viral proteins including EBNA-1, LMP1, and LMP2) and type 1 (expression of EBNA-1 only) latency malignancies, respectively.

PTLD can be divided into three major histological subtypes: early lesions, polymorphic PTLT, and monomorphic PTLT.<sup>1</sup> Early lesions are frequently polyclonal or oligoclonal and have two histological patterns — plasmacytic hyperplasia and infectious mononucleosis-like PTLT. Polymorphic PTLT is a heterogeneous mixture of small-to-large lymphocytes and immunoblasts that efface lesional tissue by microscopic examination, and which can progress to monomorphic PTLT. Monomorphic PTLT is a clonal lymphoid disorder characterised by sheets of atypical lymphocytes that mimics one of the conventional histopathological types of B cell malignancy (i.e. diffuse large B cell lymphoma, immunoblastic lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma or myeloma). In practice, a clear separation of these WHO-classified subtypes is not always possible and early lesions, polymorphic PTLT, and monomorphic PTLT probably represent a continuum or spectrum of disease.<sup>6</sup>

Knowledge of the various histological subtypes is important since this can help to guide treatment. For example, early lesions are more likely to regress with RIS alone, whereas RIS alone may not be sufficient to control disease in patients with monomorphic PTLT.

### **Management of Post-transplant Lymphoproliferative Disorders**

There is a lack of data on PTLT treatment from randomised phase III clinical trials, and evidence in this area derives mainly from expert opinion, retrospective analyses and case series, which should be interpreted cautiously in light of case selection bias. In 2010, the British Committee for Standards in Haematology and British Transplantation Society jointly developed guidelines for the diagnosis and management of PTLT in solid organ transplant recipients that provide a useful evidence-based approach to management.<sup>7,8</sup> These guidelines sequentially discuss the evidence for manipulation of immunosuppression, the role of radiotherapy and rituximab (alone or in combination with chemotherapy), and other ancillary (experimental) treatments, such as antiviral therapy and adoptive immunotherapy.

### ***Reduction and manipulation of immunosuppression***

In the case presented here, RIS by around 25 to 50% (i.e. to the lowest tolerable level that is still effective for preventing graft rejection or graft-versus-host disease) was immediately undertaken. Indeed, RIS is considered the essential first step as soon as a diagnosis of PTLT is confirmed, and it should be considered when PTLT is suspected.<sup>8,9</sup> RIS alone may be sufficient to achieve complete remission (CR) in some patients; however, more extensive PTLT will likely require treatment with other modalities in conjunction with RIS. In other words, manipulation of immunosuppression alone is unlikely to be effective indefinitely in these cases.

In the current case, MMF was stopped and replaced with the mammalian target of rapamycin (MTOR) inhibitor everolimus, as there is some evidence of the efficacy of MTOR inhibitors and proliferation signal inhibitors in PTLT. Specifically, in-vitro and in-vivo preclinical studies have shown that these drugs — acting as single agents — can retard tumour progression and possibly even tumour regression (as shown in a mouse model).<sup>10,11</sup> Robust phase III clinical trial data with these agents are awaited to provide more definitive evidence in PTLT.

### ***Radiotherapy***

Radiotherapy may be considered in localised disease following RIS.<sup>8</sup> It is particularly useful in specific sites, for example, in central nervous system lymphomas; thus, the current case was treated with radiotherapy. The other important role of radiotherapy in PTLT is for palliation, when the disease becomes unresponsive to chemotherapy plus rituximab.

### ***Rituximab and / or chemotherapy***

Rituximab is a monoclonal antibody directed against CD20, an antigen expressed on the surface of mature and immature B lymphocytes. Several phase I and II clinical trials have demonstrated the effectiveness of single-agent rituximab in CD20-expressing PTLT, with overall response (OR) rates of 44 to 75% and CR rates of 28 to 75%.<sup>12-14</sup> Some studies of rituximab in PTLT have also suggested that this agent might compensate for the effects of RIS, thereby helping to preserve long-term graft function, especially following renal transplant. Although predictors of response to rituximab vary across studies, a consistent factor appears to be LDH, with elevated levels considered to predict low response to rituximab monotherapy.

In terms of chemotherapy, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) is the preferred regimen for PTLD, globally and in Hong Kong. While increased intensity of chemotherapy is associated with high response rates, this is offset by increased toxicity, including an increased incidence of treatment-related mortality. Against this background, the use of rituximab with CHOP (R-CHOP) has emerged as an effective treatment option for PTLD that is associated with long-term disease-free survival, as well as substantially lower rates of treatment-related toxicity than chemotherapy alone.<sup>15-18</sup> Of note, OR rates reported with rituximab plus chemotherapy were higher than with rituximab alone, ranging from 65 to 100%; high CR rates were also associated with high cure rates and overall survival at 1 year.<sup>8,14-17,19-23</sup> Furthermore, the concern of increased risk of graft loss with increasing intensity of chemotherapy, with or without rituximab, has not been substantiated in the published literature, with existing reports showing very low rates of graft loss.

The positive experience with rituximab plus chemotherapy has been replicated in Hong Kong, as recently reported by Chan et al<sup>24</sup> In a retrospective analysis of 19 consecutive patients with PTLD, the use of rituximab plus chemotherapy was associated with durable response and CR rate of 92%. Interestingly, most of these cases were late-onset PTLD that were EBV-positive, in contrast with western data that indicate most late-onset PTLD to be EBV-negative. Indeed, the case presented here is an example of EBV-positive late-onset PTLD. This difference might be explained by the epidemiological variations in EBV prevalence and infection between western and Asian populations.

## CONCLUSION

In the case presented here, a patient with late-onset PTLD following renal transplant was successfully treated with a regimen of RIS, rituximab monotherapy, and radiation. At her last follow-up (18 months after treatment), serum EBV-DNA remained undetectable and there was no evidence of relapse. PTLD is a distinct lymphoproliferative disorder that arises largely due to reactivation and proliferation of EBV following immunosuppression. Current management of PTLD involves various treatment modalities but, in the absence of data from phase III randomised controlled trials, there is no gold standard for PTLD treatment. Knowledge of the histological subtype may help to guide initial treatment; for example, RIS alone may be sufficient to treat early lesions, but the addition of

rituximab and / or chemotherapy (e.g. CHOP; R-CHOP) may be warranted and prudent in patients with advanced disease to enhance CR and OR rates and improve the durability of response.

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