Native lung pneumonectomy for post transplantation lymphoprolypherative disorder refractory to Rituximab following contralateral lung transplantation

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**Disclosure**

The authors have no conflicts of interest to disclose.

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**Key words:** Lung transplantation, Post transplantation lymphoproliferative disease, Pneumonectomy, Rituximab, Native Lung.

**Abstract**

Post-transplant lymphoproliferative disorder (PTLD), despite rare, is one of the most serious life-threatening complications following lung transplantation. We report a PTLD case of high grade B-cell lymphoma following contralateral single lung transplantation. The disease involved the liver, right kidney and the right native lung. While the PTLD affecting the abdominal organs regressed with Rituximab and chemotherapy, the native lung disease progressed and was treated surgically (right pneumonectomy). Some aspects are unique in this case: a) the different response to medical treatment between lung and abdominal organs; b) the absolute absence of involvement of the native lung; c) the surgical treatment with a pneumonectomy, still very rarely described in the literature. We do not have a full explanation for these aspects, but we hypothesize that a different morphotype of the disease involved the abdominal organs or the penetrance of Rituximab and chemotherapy could have been impaired by the presence of pulmonary fibrosis and bronchiolitis obliterans syndrome.

**Background**

Post transplantation lymphoproliferative disorder (PTLD) is one of the most serious life-threatening complications following lung transplantation, (1) with multiple predisposing risk factors including: Epstein-Barr virus (EBV) infection in naïve patients, (2) high levels of immunosuppression, cystic fibrosis diagnosis, Cytomegalovirus (CMV) infection or old recipient age. In the majority of the cases, EBV infection leads to a transformation of B-cells in conjunction with decreased levels of cytotoxic T-cells, impaired natural killer (NK) cells, decreased colony stimulating factor (CSF-1) and anti-apoptosis pathways. (3) The incidence of PTLD varies between 3-5% in recent reports (4), and the majority of cases are diagnosed under a year following lung transplantation. PTLD was demonstrated to be purely of recipient origin, but not all cases present with concomitant EBV infection. (2)

The paradigm of PTLD treatment has evolved during the last decade, targeting the risk factors such as: EBV naïve status, early diagnosis and immunosuppressant modulation, (5) while surgery is reserved for tumour debulking. The reported mortality ranges between 50-75%, despite the current treatment options.

We report one case of PTLD high grade B-cell lymphoma in the native lung following contralateral single lung transplantation, with concurrent liver and kidney disease. This was treated with pneumonectomy due to the resistance to Rituximab and chemotherapy of the lung PTLD.

**Case report**

A 53-year old female underwent left single lung transplantation from a DCD donor for bilateral pulmonary fibrosis and obliterative bronchiolitis syndrome in January 2014. Past medical history included: osteopenia, steroid-induced diabetes mellitus and diverticulitis. The donor was reported positive for EBV. The immediate postoperative period was precipitated by renal filtration and non-invasive ventilation for two days in intensive care.

In the following 6 months post transplantation, the patient had multiple episodes of A2-A3 rejection, treated with high doses of Methylprednisolone and Anti-thymocyte globulin (ATG). In August 2014, the patient presented acutely with pain and diarrhoea. A CT scan of her chest, abdomen and pelvis identified multiple low density lesions in the liver, bilateral kidneys, pancreas and right lung.

The biopsy of the liver was attempted, but due to an iatrogenic right haemothorax, the procedure was abandoned. According to the presentation and imaging, high suspicion was raised for post-transplant lymphoproliferative disease (PTLD). The immunosuppressive treatment was reduced, additionally to the chemotherapy regime: Cyclophosphamide, Vincristine, Prednisolone and Rituximab (R-CVP). The CMV reactivation was diagnosed and treated with Valganciclovir. An interval CT scan at 2 months showed radiological complete remission of the PTLD in the liver, kidneys and pancreas. Progression of the disease in the right lung consisted of diffusely thickened interstitial spaces and multiple confluent consolidation areas, with the biggest increasing in size from 2.47 to 4.80cm (**Figure 1.**). The CT guided biopsy of the lesion in the right lung revealed a monomorphic high grade B-cell lymphoma, which was positive EBV encoded RNA (EBER). Further chemotherapy was initiated with Cyclophosphamide, Doxorubicin hydrochloride, Vincristine, Prednisolone and Rituximab (R-CHOP) with further disease progression limited to the native lung.

After multidisciplinary discussion between the transplant team, thoracic oncologists and thoracic surgeons, the patient was left with three options for the refractory PTLD in the right lung: 1. Further third line high-dose chemotherapy which would herald high mortality (30-40%); 2. Surgery with curative intent by performing a right pneumonectomy; and 3. Palliative treatment with less than 6 months life expectancy quoted.

In the context of the patient’s young age, relatively preserved lung function, no additional comorbidity, high risks associated with chemotherapy, the patient was offered a high risk surgical right pneumonectomy. The high risk was stratified based on the patient receiving high dosage steroids, immunosuppressive treatment and chemotherapy preoperatively.

An intra-pericardial right pneumonectomy was performed through a muscle sparing lateral thoracotomy. Histology confirmed EBER positive high grade B cell lymphoma in the explant. The patient spent one night in ICU and was discharged home on day 7 without complications. In the six months following surgery, the patient was readmitted with neutropenic sepsis, from which she recovered well. Interval clinical and imaging surveillance were continued for early recurrence detection.

**Discussion**

While a minority of the lung PTLD cases are treated by surgical intervention, we report a case of native lung PTLD B-cell lymphoma refractory to Rituximab and chemotherapy following contralateral lung transplantation, treated by pneumonectomy. Similarly to existing evidence, this patient was diagnosed in the first year following transplantation and was subjected to recognised risk factors as high immunosuppressive treatment, EBV infection and CMV infection. (3)

Some aspects are unique in this case: a) the different response to medical treatment between lung and abdominal organs; b) the absolute absence of involvement of the native lung; c) the final surgical treatment with a pneumonectomy that while described in the literature still remains very rare.

This case intrigues due to the presentation and evolution of PTLD despite optimal medical management. On one side the native lung was affected by the disease, while the transplanted lung was disease free and PTLD affecting the abdominal organs regressed with Rituximab and chemotherapy, while the lung disease progressed. One explanation could be that the disease involving the abdominal organs had a different morphotype of lymphoma when compared to the lung disease. Unfortunately the morphotype and tumour histology could not be compared due to the lack of the liver biopsy. Alternatively, the penetrance of Rituximab and chemotherapy could have been impaired by the peribronchovascular interstitial thickening secondary to pulmonary fibrosis and bronchiolitis obliterans syndrome in the native lung.

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**Legend of Figures**

**Figure 1.** Comparison between CT scan slices of the liver, kidneys and lungs respectively pre- (above images) and post- (below images) chemotherapy showing remission of the PTLD after four cycles of Rituximab based chemotherapy. The interval CT scan shows progression of the PTLD in the right lung with a tumour diameter to 4.8cm from 2.4cm despite treatment with Rituximab and chemotherapy.

**Figure 2.** Photographs of the postoperative right lung explant with lateral view on the left and medial view on the right, demonstrating the tumours.