OMCR

Oxford Medical Case Reports, 2018;8, 237–239

doi: 10.1093/omcr/omy035
Case Report

CASE REPORT

Post-transplant lymphoproliferative disorder presenting on post-transplant Day 35 as a pulmonary parenchymal infiltrate—a case report

Andrew J. Lewis[1,*], Deepa Jagadeesh[2], Sanjay Mukhopadhyay[3], Marie Budev[4] and Atul C. Mehta[4]

[1]Department of Internal Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA, [2]Department of Hematology and Medical Oncology, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA, [3]Department of Anatomic Pathology, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA, and [4]Department of Pulmonary Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA

*Correspondence address. Department of Internal Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA. Tel: +1-216-219-5991; E-mail: lewisa6@ccf.org

Abstract

Post-transplant lymphoproliferative disorder (PTLD), a rare but serious complication of solid organ transplantation, is classified into early-onset and late-onset subtypes. Early-onset PTLD occurs a median of 4–11 months after lung transplantation. It rarely presents in the first 2 months post-transplant. Early-onset PTLD usually presents as a solitary pulmonary nodule. We present a unique case of early-onset PTLD that was diagnosed on post-operative Day 35 and presented as a pulmonary parenchymal infiltrate. This case is also exceptional in that the patient had a significant clinical response to only a single dose of rituximab.

INTRODUCTION

According to the International Society for Heart and Lung Transplantation (ISHLT), over 4200 lung transplants are performed worldwide each year [1]. Indications include idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, alpha-1 antitrypsin deficiency and pulmonary artery hypertension. Complications include primary graft failure, acute cellular rejection, chronic allograft lung dysfunction (including obliterative bronchiolitis), infection, restrictive allograft syndrome and malignancy. A rare side effect of lung transplant immunosuppression is post-transplant lymphoproliferative disorder (PTLD) [2–4].

PTLD following lung transplantation is divided into early-onset and late-onset subtypes. Early-onset PTLD develops within one year after transplantation and is more prevalent. To our knowledge, there are only five reported cases in which PTLD was diagnosed within the first 2 months after transplantation [2]. PTLD typically presents as a single pulmonary nodule on routine imaging. It is less common for PTLD to present as a pulmonary parenchymal infiltrate [5]. We present a case of early-onset PTLD with three unusual features: (i) the lesion presented as a pulmonary parenchymal infiltrate, (ii) the diagnosis was made on post-transplant Day 35 and (iii) the patient had a clinically significant response to reduction of immunosuppression and only a single dose of rituximab.

Received: December 28, 2017. **Revised:** March 24, 2018. **Accepted:** May 10, 2018

CASE REPORT

A 62-year-old man with a past medical history of COPD and pulmonary artery hypertension underwent double lung transplantation. His Epstein-Barr virus (EBV) status was donor positive/recipient positive and his cytomegalovirus status was donor positive/recipient negative. His immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisone. No induction therapy was given.

His hospital course was complicated by failure to wean from mechanical ventilation ultimately requiring tracheostomy. On post-transplant Day 7 he became febrile and a new left-sided lung infiltrate was seen on CT chest. His tacrolimus levels during that time ranged from 4.9 to 7.4 ng/mL (mycophenolate mofetil levels were not monitored). He underwent bronchoscopy with bronchoalveolar lavage (BAL), which yielded normal respiratory flora. An empiric course of piperacillin–tazobactam was administered. He also tested positive for influenza A and was given a 10-day course of oseltamivir. However, his respiratory status remained unchanged. Transbronchial lung biopsy performed 3 weeks post-transplantation showed only minimal acute cellular rejection (A1B0); the specimen was not tested for Epstein-Barr virus encoded RNA (EBER).

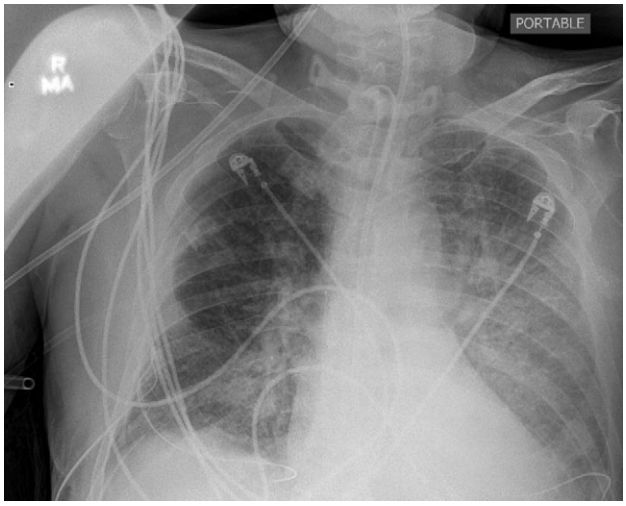

Figure 1: Chest X-ray: diffuse bilateral interstitial and airspace opacities on the left greater than the right with an interval increase in size of the left lower lobe infiltrate

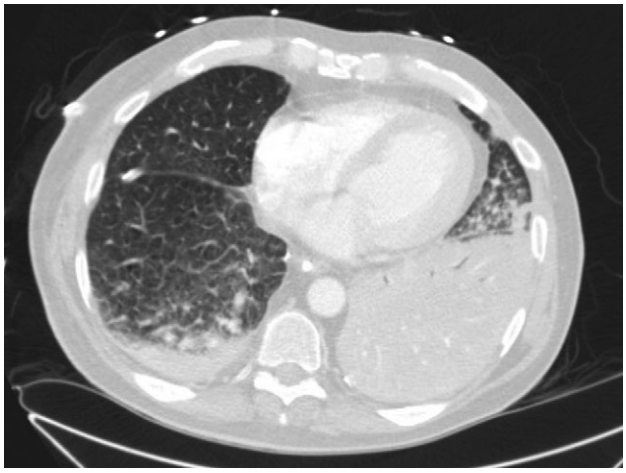

Figure 2: CT chest: interval development of a dense consolidation of nearly the entire left lower lobe

On post-transplant Day 35 he had an acute worsening of his respiratory distress. Chest X-ray and repeat CT chest revealed interval worsening of his left lung infiltrate (Figs 1 and 2). His tacrolimus levels from post-transplant Day 7 to 35 ranged from 8.5 to 18.7 ng/mL. A bronchoscopy with BAL was repeated and transbronchial lung biopsy showed pathologic features diagnostic of PTLD (Fig. 3). The majority of lymphocytes and plasma cells were positive for EBER by chromogenic *in-situ* hybridization (CISH). The polymorphic subtype of PTLD was favored. There was no endobronchial involvement.

CT scan of the chest, abdomen, and pelvis demonstrated that his disease process was confined to the lung. To reduce his net immunosuppressed state, his mycophenolate mofetil was discontinued, goal tacrolimus levels were decreased to 6–8 ng/mL, prednisone was decreased, and treatment with rituximab (once weekly) was administered with a plan to complete four doses. A rapid improvement in his respiratory status ensued. His tracheostomy was capped 11 days after initiating therapy and he was decannulated on post-transplant Day 61. He was discharged on post-transplant Day 78 on tacrolimus (goal of 8–10 ng/mL) and 5 mg prednisone. Repeat lung biopsies at 1, 3 and 6 months after initial diagnosis showed no recurrence of PTLD and a 6-month follow-up flourodeoxyglucose positron emission tomography (FDG-PET) scan showed complete remission.

DISCUSSION

PTLD is a complication of solid organ transplantation characterized by abnormal proliferation of lymphoid or plasma cells, mostly driven by EBV. Definitive diagnosis requires a tissue biopsy. The new 2016 World Health Organization (WHO) classification includes the following subtypes: plasmacytic hyperplasia, infectious mononucleosis, florid follicular hyperplasia, polymorphic, monomorphic and classical Hodgkin lymphoma PTLD. PTLD can affect the lymph nodes, extranodal sites and the

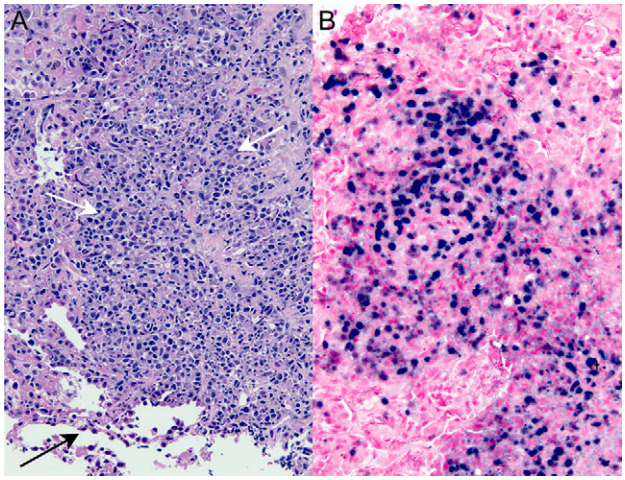

Figure 3: Post-transplant lymphoproliferative disorder diagnosed 35 days following lung transplantation. (**A**) Transbronchial lung biopsy of transplanted lung showing a dense polymorphous lymphoplasmacytic infiltrate (white arrows). Alveolated lung is seen at bottom (black arrow). Scattered large CD20-positive cells were present within the infiltrate (not shown). (**B**) Chromogenic *in-situ* hybridization (CISH) for Epstein-Barr virus-encoded RNA (EBER) is positive within neoplastic lymphocyte nuclei (blue signals). (**A**) Hematoxylin–eosin, original magnification ×200 and (**B**) EBER CISH, original magnification ×200.

Table 1: Patients with PTLD diagnoses in the first 2 months post-transplant, their associated EBV status, histological subtype and immunosuppression therapy (maintenance and induction). Mode of presentation was not disclosed for any of these cases

Patient	Time of onset of PTLD	EBV status at diagnosis	Histological classification	Immunosuppression regimen; induction immunosuppression agent
1	<1 Month	n/a	Polyclonal	Prednisone, AZA, CSA; ATG
2	<1 Month	+	n/a	Prednisone, AZA, CSA; ATG
3	<1 Month	+	n/a	Prednisone, AZA, CSA; ATG
4	1 Month	+	Polyclonal	Prednisone, AZA, CSA; ATG
5	1 Month	n/a	Polyclonal	Prednisone, AZA, CSA; Daclizumab

AZA, azathioprine; CSA, cyclosporine; ATG, anti-thymocyte globulin.

allograft [2, 4–7]. After the pathologic diagnosis is made, a full body scan should be performed for staging. FDG-PET scan or CT scan is commonly used [5].

PTLD in lung transplant patients may also be classified according to the time of onset. Early-onset PTLD occurs within 1 year of transplantation, tends to be a polyclonal B-cell proliferation, is often localized to the graft site and has a more favorable response to treatment. It most commonly presents as a pulmonary nodule or mass [2, 5].

Our case is unique in that PTLD presented as a pulmonary parenchymal infiltrate. The infiltrate first observed on post-transplant Day 7 did not respond to antibiotics and antivirals, arguing against an infectious etiology. Although radiographic signs of pneumonia can take ≥4 weeks to resolve after appropriate therapy, clinical improvement is expected. There being no endobronchial involvement argues against a post-obstructive pneumonia. Also, the initial biopsy did not show signs of acute rejection. While biopsies can miss signs of graft rejection, reducing his immunosuppression would have exacerbated it had it been present.

Another interesting aspect of this case was how early it occurred post-transplant. Only three cases of PTLD arising in the first 31 days and only two additional cases occurring during the second month post-transplant have been reported [2]. In all of these cases, immunomodulation with monoclonal antibodies was used in induction therapy whereas no such therapy was used in our patient (Table 1). It is likely that the PTLD started as early as post-transplant Day 7 in our patient based on the radiographic findings and clinical course, making this case a rare occurrence.

Treatment of early-onset PTLD involves reduction of immunosuppression and initiation of chemotherapy. Single agent rituximab is used in localized disease. CHOP therapy (cyclophosphamide, doxorubicin, vincristine and prednisone) is added if the disease is diffuse or recalcitrant to rituximab [5, 7]. Surgical resection is an option for large lesions or disease refractory to medical therapy [5, 8, 9]. The rapidity of the patient's response to the reduction of immunosuppression and initiation of single-agent rituximab was remarkable.

This case demonstrates that PTLD can present as an infiltrative process and can also occur very early after lung transplantation. PTLD should be considered in patients even in the immediate post-transplant period.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

FUNDING

There were no sources of funding involved in the writing of this case report.

ETHICAL APPROVAL

This case report was conducted in adherence to the guidelines set forth by the Cleveland Clinic Foundation ethics department

GUARANTOR

Andrew J. Lewis, DO.

REFERENCES

1. ISHLT: The International Society for Heart & Lung Transplantation. *International Society for Heart & Lung Transplantation*. http://www.ishlt.org/. (9 October 2017, date last accessed).
2. Kremer BE, Reshef R, Misleh JG, Christie JD, Ahya VN, Blumenthal NP, *et al.* Post-transplant lymphoproliferative disorder after lung transplantation: a review of 35 cases. *J Heart Lung Transplant* 2012;**31**:296–304. doi:10.1016/j.healun.2011.10.013.
3. Lee P, Minai OA, Mehta AC, DeCamp MM, Murthy S. Pulmonary nodules in lung transplant recipients. *Chest* 2004;**125**:165–72.
4. Paranjothi S, Yusen RD, Kraus MD, Lynch JP, Patterson GA, Trulock EP. Lymphoproliferative disease after lung transplantation: comparison of presentation and outcome of early and late cases. *J Heart Lung Transplant* 2001;**20**:1054–63.
5. Neuringer IP. Posttransplant lymphoproliferative disease after lung transplantation. *Clin Dev Immunol* 2013;**2013**:430209. doi:10.1155/2013.430209.
6. Reams BD, McAdams HP, Howell DN, Steele MP, Davis RD, Palmer SM. Posttransplant lymphoproliferative disorder: incidence, presentation, and response to treatment in lung transplant recipients. *Chest* 2013;**124**:1242–9.
7. Muchtar E, Kramer MR, Vidal L, Ram R, Gurion R, Rosenblat Y, *et al.* Posttransplantation lymphoproliferative disorder in lung transplant recipients: a 15-year single institution experience. *Transplantation* 2013;**96**:657–63. doi:10.1097/TP.0b013e31829b0718.
8. Roman M, Parmar J, Goddard M, Piergiorgio S. Native pneumonectomy for post-transplant lymphoproliferative disorder refractory to rituximab following contralateral lung transplantation. *Interact Cardiovasc Thorac Surg* 2016;**23**:841–3.
9. Chang YS, Kim Y, Kim DY, Kim HJ, Ahn CM, Lee DY, *et al.* Two cases of post transplant lymphoproliferative disorder in lung transplant recipients. *Korean J Intern Med* 2004;**19**:276–81.