Lymphoproliferative Disorders after Lung Transplantation: Clinicopathological Characterization of 16 Cases with Identification of Very-Late-Onset Forms

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Key Words

Epstein-Barr virus · Posttransplant lymphoproliferative disorders · Lung transplantation · Histopathology

Abstract

Background: The incidence of posttransplant lymphoproliferative disorders (PTLD) has recently declined, but late cases are increasingly reported in lung transplant recipients. **Objectives:** We present our experience with PTLD after lung transplantation, attempting to examine the distinguishing characteristics of early versus late cases. **Methods:** We have reviewed clinical and pathological data of all cases occurring in our institution between 2001 and 2014. **Results:** Patients, aged 15–63 years, were mostly (12/16) Epstein-Barr virus (EBV) seropositive at the time of transplantation. Eleven early cases, occurring 9.4 ± 5.2 months after transplantation and mostly (9/11) prior to 2010, had EBV+ diffuse large B-cell lymphomas. Lungs and/or thoracic lymph nodes were often involved ($n = 8$). Treatments included reduction of immune suppression ($n = 11$), rituximab ($n = 8$) and chemotherapy ($n = 7$). Two patients are in complete remission at 26 and 216 months. Nine patients died 8.0 ± 6.5 months after PTLD di-

agnosis. Of the 5 cases with late PTLD occurring 4–23 years (mean $\pm$ SD: 10.4 ± 7.7) after transplantation (and 3/5 after 2009), 1 had pulmonary lymphomatoid granulomatosis (only endothoracic case), 1 cutaneous large T-cell lymphoma, 2 had anaplastic large cell lymphomas, and 1 Hodgkin's disease. Two of the 5 cases were EBV–, including one followed by a second EBV+ PTLD after 8 years of complete remission. Two patients were alive and well (follow-up: 44 and 151 months), one having suffered from EBV-related cholestatic hepatitis 6 years after the PTLD. **Conclusion:** Our small experience shows a trend toward (very) late occurrence, associated with more unusual clinicopathologic features, but not with a worse prognosis.

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Introduction

Solid organ and bone marrow transplant recipients have an increased risk of developing lymphoproliferations as a consequence of immunosuppression [1, 2]. These rare lesions are called posttransplant lymphoproliferative disorders (PTLD), and most are Epstein-Barr

virus (EBV) related. PTLD in the setting of lung transplantation has some specificities: a higher incidence as compared with transplantation of most other organs [1, 3], a frequent involvement of the grafted lung [3–6], and the risk of dysfunction or loss of a vital graft if immunosuppression is importantly reduced [4, 7]. PTLD mostly occur in the first posttransplant year [8], but late cases have been increasingly reported in lung transplant recipients [4, 5, 7]. However, published data are scarce. Therefore, we have reviewed our personal recent experience with PTLD, focusing on the frequency and the clinical and pathological peculiarities of late-onset cases compared with the more common early cases.

Materials and Methods

From 1986 (first transplantation) to December 2014, 579 lung transplantations have been performed at Marie Lannelongue surgical center, including 190 before 2001. Most of our recipients suffered from pulmonary hypertension, and cardiopulmonary transplantations were performed in case of Eisenmenger's syndrome or severe right ventricular dysfunction. All cases of PTLD occurring in lung transplant recipients between 2001 and 2014 were reviewed. Past history, signs and symptoms, and follow-up data were obtained by reviewing the patients' hospital files including surgical and pathological reports. The recipient EBV serostatus prior and proximate to transplantation and the donor EBV serostatus were considered positive when serum anti-Epstein-Barr nuclear antigen or anti-viral capsid antigen immunoglobulin G antibodies were beyond normal levels. Since 2005, viral prophylaxis with valganciclovir has been used for 6–12 months, if either the donor or the recipient had a positive cytomegalovirus (CMV) serology, or with acyclovir for 3 months, if CMV serology was negative. Prior to 2009, patients received induction immunosuppressive therapy with antilymphocyte serum during the 5 first postoperative days. No induction immunosuppression was given after 2009. Maintenance immunosuppression regimens only slightly varied during the interval of the study and included prednisone, cyclosporine and either azathioprine or more recently mycophenolate mofetil. The cutoff between early and late occurrences of PTLD was empirically set at 18 months. Extension of the tumor was assessed by CT scan, bone marrow biopsy, and, in recent cases, by positron emission tomography (PET). After PTLD diagnosis, all patients had reduction of immunosuppression with cyclosporine dose reduction and discontinuation of azathioprine and mycophenolate mofetil. Statistical analysis of survival, according to the early or late onset of PTLD after transplantation, was performed by the Kaplan-Meier method, and significance was assessed with the log rank (Mantel-Cox) test, using IBM® SPSS Statistics software 20.0. Survival time was calculated between date of PTLD histological diagnosis and date of death.

Histological slides, including the immunohistochemical study with anti-CD3 (Diagomics® rabbit clone SP7, RBK 024-05), anti-CD20 (Diagomics® mouse clone L26, BSB5195), anti-CD30 (Diagomics® mouse clone Ber-H2, BSB 5216) and anti-LMP1 (Latent Membrane Protein 1, Dako®, mouse clone CS.1–4) monoclonal

Fig. 1. Survival curves of lung transplant recipients after PTLD, according to early (<18 months) or late onset.

antibodies, and in situ hybridization with an EBER (EBV-encoded RNAs) probe (Roche®-Ventana®, Inform EBER probe 800-2842), were reviewed in all but 4 cases. In these latter cases, data were obtained from the detailed pathological reports. The lesions were classified according to the 2008 WHO classification [1].

This study had the approval of the Institutional Review Board of our hospital.

Results

The main clinical data are summarized in table 1. Patients were 8 females and 8 males. Ages at PTLD diagnosis ranged from 15 to 62 years (mean 46.6 ± 14.4). Most patients (12/16) were EBV seropositive at the time of transplantation. Two (18%) of the 11 early cases and 2 (40%) of the 5 late cases occurred after 2009. Mean and median global survival rates after PTLD diagnosis were 64.4 ± 23.2 and 10.0 ± 7.1 months, respectively. Mean survival rates were 50.1 ± 26.8 and 77.4 ± 28.3 months for cases with early and late onset, respectively. The difference of survival was not statistically significant (fig. 1; $p = 0.873$).

Early-Onset PTLD (Cases No. 1–11)

Eleven cases occurred 9.4 ± 5.2 months after transplantation. Lymphopenia ranging from 500 to 1,000/ mm^3 (normal value $>1,000$) was present since transplantation in 8 patients. Five patients had a histologically proven cellular acute rejection 3.6 ± 2.8 months prior to

Table 1. Main clinical data of the 16 patients suffering from PTLD after lung transplantation

Sex/age at PTLD, years	Type, year	Motive of lung transplantation	EBV status	Delay	PTLD location	Diagnostic procedure	Treatment	Follow-up
1 F/43	CP, 2004	Histiocytosis X + PH	R+/D?	3 m	Mediastinal and left pulmonary lymph nodes	Mediastinoscopy	RI, rituximab ChemoT	Dead 3 m
2 F/40	BiP, 1999	Lymphangio-myomatosis	R+/D?	4 m	Right pulmonary (2.5 cm) and mesenteric lymph nodes	Bronchial biopsy	RI, rituximab ChemoT	Dead 5 m
3 M/58	CP, 2001	Sarcoidosis + PH	R+/D+	5 m	2.5-cm left pulmonary mass	Bronchial biopsy	RI	Dead 1 m
4 M/52	BiP, 2004	Emphysema	R+/D-	5 m	Pulmonary middle lobe hilar mass	Thoracotomy	RI, rituximab ChemoT	Dead 4 m
5 F/15	BiP, 2012	Primary PH	R-/D+	7 m	Skin (breast), cervical lymph node and bones	Skin and lymph node biopsy	RI, rituximab	Alive and well 26 m
6 H/40	CP, 1996	Eisenmenger's syndrome	R+/D?	8 m	5.5-cm mass in liver hilum	Surgical biopsy	RI	Alive 216 m Pulm dysf
7 M/56	CP, 2008	Primary PH	R+/D+	11 m	10.5-cm left pulmonary and mediastinal mass	Anterior mediastinotomy	RI, rituximab ChemoT	Dead 5 m
8 F/43	CP, 2005	Eisenmenger's syndrome	R+/D-	12 m	Bronchopulmonary lesion in left upper lobe	Bronchial biopsy	RI, rituximab ChemoT, RxT	Dead 19 m
9 M/60	CP, 2001	Primary PH	R+/D+	14 m	5.2-cm mass around main left bronchus	Bronchial biopsy	RI, rituximab ChemoT	Dead 10 m
10 M/60	BiP, 2008	Primary PH	R-/D+	17 m	Mediastinal, hepatic, retro-peritoneal, splenic masses	Anterior mediastinotomy	RI, rituximab	Dead 7 m
11 M/63	BiP, 2012	Emphysema	R-/D+	17 m	3-cm cerebellar mass	Surgical resection	RI, resection, ChemoT	Dead 18 m
12 M/58	CP, 2009	Emphysema	R+/D+	4 y, 2 m	Ulcerated cutaneous nodules of legs and arms	Cutaneous biopsy	RI, ChemoT, RxT	Dead 9 m
13 F/26	BiP, 1992	Pulmonary fibrosis + PH	R+/D?	4 y, 9 m	10-cm mandibular mass	Gingival biopsy	RI, ChemoT, RxT	Dead 99 m
14 F/33	CP, 1991	Pulmonary fibrosis + PH	R+/D?	8 y, 5 m	Lung, subcutaneous, bone and gingival lesions	Subcutaneous thoracic surgical biopsy	RI, ChemoT	Dead 3 m
15 F/35	BiP, 1991	Primary PH	R-/D?	11 y, 9 m	8-cm cervical lymph node	Lymph node surgical biopsy	RI, ChemoT, RxT	Alive and well 151 m
16 F/62	CP, 1988	Primary PH	R+/D?	23 y	2-cm nodule of middle pulmonary lobe	CT-guided needle biopsy	RI, rituximab	Alive 44 m Pulm dysf

CP = Cardiopulmonary transplantation; BiP = bipulmonary transplantation; PH = pulmonary hypertension; R = recipient; D = donor; ? = unknown; y = year; m = months; RI = reduction of immunosuppression; ChemoT = chemotherapy; RxT = radiotherapy; Pulm dysf = pulmonary dysfunction.

PTLD diagnosis. Patients No. 2 and 8 had been treated for CMV infection, and patient No. 10 suffered from a herpes zoster before PTLD diagnosis. Most tumors (n = 8) involved the lung and/or mediastinal or pulmonary hilar lymph nodes. Three tumors were multifocal (fig. 2), and there was an abdominal involvement in 3 cases. The 11 early PTLD cases were all large B-cell lymphomas (fig. 2). Tumor cells were CD20+ (11/11), CD30+ (2/5) and EBV+ (11/11), expressing EBER (9/9) and LMP1 (7/8). Initial treatment consisted in reduction of immunosuppression (all cases) and rituximab (all but cases No. 3 and 11), or surgery and chemotherapy with methotrexate and aracytine (case No. 11). Because of incomplete response or progression, patients then received chemotherapy with

CHOP regimen (cyclophosphamide, adriamycin, vincristine and prednisone: cases No. 1, 2, 4 and 7) or CHOP combined with rituximab (cases No. 8 and 9). Patient No. 8 suffered from several recurrences that were treated by other chemotherapy regimens, radiotherapy (40 Gy) and ganciclovir. Stenosis of a large involved bronchus occurred under treatment in cases No. 8 and 9 and required endoprosthesis in case No. 9 (fig. 1). Two patients were alive and in complete remission at the time of study completion, one suffering from severe pulmonary dysfunction. Four patients (cases No. 2, 3, 7 and 9) died with active tumor. Other deaths were secondary to postchemotherapy aplasia and infection (cases No. 1 and 8), hemoptysis related to tumor necrosis (case No. 4), pul-

Table 2. Pathologic data of the 5 PTLD with late onset after lung transplantation

Case No.	Histological type	CD20	CD3	CD30	EBER	LMP1
12	Cutaneous large T-cell lymphoma	–	+	+	+	n.a.
13	Anaplastic large null cell lymphoma	–	–	+	–	–
14	Anaplastic large T-cell lymphoma	–	+	+	–	–
15	Hodgkin's disease	–	–	+	+	+
16	Lymphomatoid granulomatosis	+	–	+	+	+

n.a. = Not assessed.

Fig. 2. Early PTLD after lung transplantation. Left: histological features of large B-cell lymphoma with CD20 and EBER positivity (case No. 7). Top right: endoscopic appearances of a bronchial tumor (case No. 6) with initial necrotic obstructive lesion (left), treated by laser resection (center) and leading to stenosis after chemo-

therapy (right). Center right: CT scan showing mediastinal, hepatic, splenic and retroperitoneal locations (arrows) in case No. 7. Bottom right: PET showing hypermetabolism of the mediastinal tumor in case No. 4.

monary dysfunction (case No. 11) or cardiac deficiency (case No. 10). In the latter case, an autopsy showed that the mediastinal mass was totally necrotic.

Late-Onset PTLD (Cases No. 12–16)

The main pathological data are summarized in table 2. The delay after transplantation ranged from 4 to 23 years (mean = 10.4). PTLD occurred in the setting of chronic lymphopenia in patients No. 14 and 16. Patients No. 12, 14 and 15 were CMV-seronegative recipients and had to

be treated (ganciclovir) for CMV infections during the first year after transplantation. Patient No. 12 had been treated for cellular acute rejections 20 and 10 months before PTLD diagnosis. Patients No. 13, 15 and 16 had also suffered from 1–3 episodes of cellular acute rejection, but at a distance from PTLD.

In case No. 12, the tumor appeared as ulcerated cutaneous nodules on the left ankle, thighs, right leg and left arm. The tumor was progressive in spite of a reduction of immunosuppression, chemotherapy (CHOP regimen

Fig. 3. Late EBV-related disease (case No. 9). Top: histological features of Hodgkin's disease with CD30+, CD20- (small B-lymphocytes are positive) and EBER+ Reed-Sternberg cells. Bottom: graphic showing numbers of copies of EBV DNA in the blood by PCR analysis (EBV) and seric values of creatinine, alanine amino-

transferase (ALT), alkaline phosphatase (ALP) and γ -glutamyl transferase (GGT) with their minimal and maximal recorded values, and their normal values (N) between brackets, according to time (initials of the months on the x-axis) during EBV-related hepatitis and nephritis.

followed by asparaginase) and radiotherapy on the main lesions.

Patient No. 13 had suffered from respiratory syncytial virus infection. Treatment of the EBV-PTLD permitted a complete remission that lasted more than 8 years. However, the patient died rapidly from a second different PTLD, an EBER+, LMP1+ Burkitt-like large B-cell lymphoma occurring in the mediastinum.

In case No. 14, chemotherapy (COPADM regimen with cyclophosphamide, vincristine, prednisolone, doxorubicin and methotrexate) led to complete regression of the PTLD on CT scan. However, the patient died from acute febrile pneumonia during the third course.

In case No. 15 (fig. 3), the tumor was asymptomatic. Four courses of ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) and cervical radiotherapy led to a lasting complete remission. However, 5 years after PTLD, the patient suffered from an EBV-related cholestatic hepatitis with nephritis (fig. 3). She recovered after reduction of immunosuppression (cyclosporin and mycophenolate mofetil) and ganciclovir treatment. At her last follow-up, she was well 24 years after transplantation.

In case No. 16 (fig. 4), an asymptomatic pulmonary nodule was discovered on a chest radiogram. PET showed hypermetabolism of the nodule (standardized uptake

Fig. 4. Histological features of a late-occurring lymphomatoid granulomatosis (case No. 10): needle biopsy specimen of a pulmonary PTLD showing the polymorphous cellular infiltrate (**a, b**) with necrosis (**c**) and angioinfiltration (**d**), containing numerous small T-cells (CD3) and large B-cells expressing CD20, CD30, LMP1 and EBER.

value = 10.8) and an associated smaller and less positive lung lesion, without extrapulmonary abnormality. After 4 courses of rituximab and a reduction of immunosuppression, the lesions shrunk and became PET-. Fifteen months after initial diagnosis, the EBV+ lymphomatoid granulomatosis recurred with the same histology on biopsy and with 3 PET+ pulmonary nodules. Complete remission was obtained with additional reduction of immunosuppression. At the last follow-up, the patient suffered from pulmonary dysfunction 26 years after transplantation.

Discussion

The incidence of PTLD is reported to have declined: a Swedish study showed that the relative risk of lymphoma, in nonkidney recipients versus the general population, had decreased from 23 to 17 between the 1990s and

the 2000s [9]. A series of 34 PTLD developing in a cohort of 705 lung transplant patients showed that the annual incidence had decreased from more than 20% to 0–3% between 1991 and 2011 [5]. This trend was suspected to be related to changes in immunosuppression and especially in induction therapy [5, 9]. The routine use of antiviral medication for CMV is also suspected [7, 10], as well as the improvement in cystic fibrosis care allowing transplantation in older and then less likely EBV- patients. We confirm the low incidence of PTLD in our experience, but in recent years, we have also encountered some late-occurring cases. Several series have shown that such PTLD cases occurring late after transplantation (usually after 1 year) were different from early cases [4, 5, 7, 11]. Indeed, in our series, the 5 cases occurring more than 4 years after transplantation contrasted with the 11 cases occurring less than 18 months after transplantation.

Tumor Location

Our early PTLD often affected the lung allograft, or pulmonary and mediastinal lymph nodes. Such a thoracic location of early cases has been observed in other series [4]. In 3 series, the location in the transplanted lung accounted for 12 of 17 (71%) [5], 8 of 9 (89%) [3] and 3 of 3 (100%) [7] of the early PTLD. Generally, the fact that PTLD are often based in the transplanted organ or its vicinity [3, 6] is possibly related to antigenic stimulation by the graft, contributing to local lymphoid proliferation. The gastrointestinal tract has been reported as a frequent site of presentation in PTLD diagnosed in lung transplant recipients after 1 year [4, 5].

Usual Pathological Features

Most PTLD of our series were diffuse large B-cell lymphomas and occurred early after transplantation. Such lymphomas also represented the most frequent type in 2 recent series of lung transplant recipients: 7/10 [7] and 28/32 cases [4]. The early occurrence is in accordance with its higher risk in the first year after solid organ transplantation [12]. This type of PTLD may be CD30+ [13], theoretically with potential therapeutic implications [14].

As in our series, most PTLD are associated with EBV [1]. A large gene expression study suggested that the occurrence of EBV– diffuse large B-cell lymphomas in post-transplant recipients could simply be coincidental [15]. The risk of PTLD has been shown to be related to the EBV donor (D) and recipient (R) serostatus [16], with the risk increasing from R+ to R–/D– and from R–/D– to R–/D+ in kidney transplant recipients. In a series of lung transplant recipients with cystic fibrosis, 7 of the 8 patients with PTLD were R– [17]. However, in our study, all but 1 recipient were adults and most were EBV+, as are more than 90% of normal adults [18]. A systematic monitoring of EBV DNAemia in the follow-up of lung recipients is not recommended [19]. It may not be feasible since the onset of PTLD may be very late and PTLD may occur in the absence of detectable EBV DNAemia [20]. Otherwise, the presence of EBV in the tumor represents a potential target for virus-directed therapies [18].

Late Cases and Unusual Pathological Features

In a report of 15 PTLD occurring 22–156 months (median 79) after solid organ transplantation, the authors found that such late cases showed heterogeneous histological and clinical presentations similar to lymphomas of immunocompetent subjects and were often (9/16) EBV– [11]. In the setting of lung transplantation, late onset ac-

counted for 18 of 35 [5], 7 of 10 [7], 22 of 34 [21] and 24 of 32 [4] cases in recent series of PTLD. Various histological subtypes have been reported [7, 22], but histological data are scant.

Hodgkin's lymphoma, which occurred in 1 of our patients 11 years after transplantation, is a rare form of PTLD [1]. In a series of 135 PTLD, 5 cases of Hodgkin's disease occurred late (median: 9.5 years) after solid organ transplantation [6]. Seventy-three Hodgkin's lymphomas were identified in a cohort of 283,190 solid organ transplant recipients followed for a mean of 3.7 years [23]. These cases were often (79%) EBV+ [23] as are Hodgkin's lymphomas in immunocompetent hosts [18]. In this study, the risk was not elevated in the first 2 years, but increased monotonically over time especially among heart and/or lung transplant recipients [23].

PTLD, showing all criteria for the diagnosis of lymphomatoid granulomatosis, occurred late in our patient No. 16. This rare EBV-associated lymphoma usually affects immunocompetent hosts, who virtually always present with nodules in the lung [18]. One case has previously been reported after lung transplantation in a series of 32 PTLD [4].

T-cell PTLD are rare [1] as are EBV+ T-cell lymphomas [18]. In a French series of 52 late-onset PTLD in kidney transplant recipients, 7 (14%) were T-cell lymphomas including 2 being EBV-related [24]. In a Korean series, 4 of the 10 PTLD occurring more than 1 year after transplantation were peripheral T-cell lymphomas, 3 of 4 being EBV+ [25]. A cutaneous EBV+ CD30+ large T-cell lymphoma, similar to our case No. 12, occurring 111 months after heart transplantation, has been reported [26]. In a recent Swedish series [6] of 135 PTLD, there were 5 (3.7%) cases of anaplastic large T-cell lymphomas, and 4 of 5 were EBV–. Anaplastic large null [11] or T-cell [7, 24] lymphomas are especially known as late forms of PTLD.

Prognosis

Thoracic organ transplantation has been reported as an adverse prognostic factor in PTLD [27]. Two of our patients, with PTLD occurring 11 and 23 years after transplantation, were alive 151 and 44 months after diagnosis, respectively. Another of our 5 patients with late-occurring PTLD remained in complete remission for 8 years. Overall survival between our late and early cases was not significantly different, possibly because of the small number of patients. In a recent series of 52 cases with PTLD with late onset (>1 year) after kidney transplantation, the 5-year overall survival had increased from 33.3 to 69%

after 2000 [24]. This was attributed to multiple changes in clinical practice, including the use of rituximab. A series of 80 solid organ transplant recipients with PTLD has also shown a 3-year overall survival of 73% with early rituximab-based treatment compared with 33% without rituximab [8]. In an Asian series of 19 cases with PTLD diagnosed between 2001 and 2010 and including 17 with late onset, complete remission was achieved in 17 (90%) [28]. Hence, in our view, late onset of PTLD cannot necessarily be considered an adverse prognosis factor [1]. The main causes of death of lung transplant recipients after PTLD vary among different series and include infections (11/24, 46% [4]), tumor progression (9/24, 37% [4]) or fatal chronic rejection developing under treatment (5/10, 50% [7]). In patients with pulmonary dysfunction as in our patients No. 6, 11 and 16, retransplantation may be an option [29]. In our series, chemotherapy was frequently used (11/16), and the prognosis was possibly worsened by treatment-related deaths. As in our patient No. 15, EBV-related hepatitis has been previously reported in liver transplant recipients suffering from PTLD [30]. In immunocompetent patients, hepatic abnormalities are often present during infectious mononucleosis, and in adults, EBV may also rarely induce hepatitis,

which often are cholestatic [31]. Kidney involvement, as in our case, is relatively common but rarely severe in EBV infection [32].

Conclusion

Our experience confirms the shift toward late or very late occurrence of PTLD, possibly because of the reduction in induction therapy and the decrease in global incidence, and because of the increasing number of lung transplant patients with long-term survival. PTLD remains a serious complication of lung transplantation and should be suspected even very late. Late cases display more unusual pathologic features in terms of tumor location and histological type, but do not appear to have a worse prognosis. Our series also shows that even if EBV is less associated with late PTLD, it still remains a threat for the patients.

Financial Disclosure and Conflicts of Interest

None declared.

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