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Case Report

Post cardiac transplantation T-cell lymphoproliferative disorder presenting as a solitary lung nodule

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Abstract: Post-transplantation lymphoproliferative disorder (PTLD) is an infrequent, but serious complication of solid organ and bone marrow transplantations. The vast majority of the cases are of B-cell origin and usually associated with Epstein-Barr virus (EBV) infection. The non-B (T and NK cell) PTLDs account for up to 14% of the PTLD cases in Western countries. We report a case of a 66-year-old man who received an orthotopic heart transplant for cardiomyopathy 7 years prior to presentation. He was referred to our institution with a hypermetabolic solitary right lower lobe lung nodule with an SUV of 9.2 on PET scan. The combined histomorphological and immunohistochemical pattern was most consistent with monomorphic PTLD, peripheral T-cell lymphoma with angioimmunoblastic features. Molecular studies showed clonal T-cell gamma receptor gene rearrangement. Primary pulmonary involvement of T-cell PTLD is extremely rare. This is the third reported case of T-cell PTLD after cardiac transplantation, primarily involving the lung. Further, studies will be required to determine the appropriate treatment and prognosis of this rare entity.

Keywords: PTLD, T-cell lymphoma, lung nodule, heart transplantation

Introduction

The increased incidence of malignancies in transplant recipients is well known. Hematolymphoid malignancies, so called "post-transplantation lymphoproliferative disorders" (PTLDs) are one of the most common ones along with non-melanoma skin cancers in the post-transplantation setting [1]. PTLD is recognized as an infrequent, but serious complication of both solid organ and bone marrow transplantations. The incidence of PTLD after solid organ transplantation depends on the transplanted organ, the immunosuppressive regimen used, the age and the EBV immune status of the recipient at the time of transplantation [2]. A single institutional study showed that Caucasian race and male gender are independent risk factors [3], while grafted organ involvement and monomorphic histology predict short survival [4].

The vast majority of PTLD cases (approximately 85%) are of B-cell origin and out of these, 80% are associated with Epstein-Barr virus (EBV) infection [5, 6]. The non-B (T and NK cell) PTLDs account for up to 14% of the PTLD cases in the Western countries and are more frequent in Asia, where it may be as high as 40% of transplantation related hematolymphoid diseases. The increased Asian prevalence is most likely secondary to the endemic Human T-cell Leukemia Virus (HTLV) [7]. The T-cell PTLDs are typically extranodal with a broad range of clinical presentations, commonly many years after transplantation.

Heart and/or lung transplant recipients have an intermediate to high risk (1-2%) [2], with a 26 fold relative risk for developing PTLD compared to lymphoid malignancies in the non-transplant population [8]. As for PTLD following cardiac transplantation, Draoua and colleagues reported an overall incidence of 3.8% (14% among pediatric patients and 2.1% among adults) [9]. T-cell PTLDs are rare, most of which occurred after renal transplantation. Less than 30 cases of T-cell PTLDs have been reported following cardiac transplantation with only two of these involving primarily the lung [10] (**Table 1**).

Table 1. Comparison of T-cell PTLDs presented as a solitary lung nodule

Case	Age (y)	Sex	Transplanted organ	Time from transplant to PTLD (y)	EBV status	Immunosuppressive therapy	Survival after PTLD	Ref.
1	56	M	Heart	2	pos	CyclosporinA/Azathioprine/Prednisone	>4 years	[20]
2	31	M	Kidney	4	ND	Antilymphocyte globulin	3 months	[18]
3	66	M	Heart	7	neg	Micophenolate/Tacrolimus	8 months	PC

ND: not determined; PC: present case; y: years.

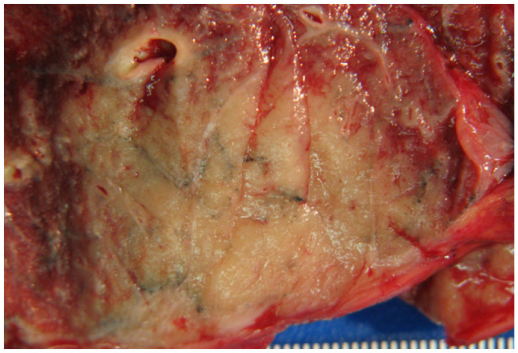

Figure 1. Gross photograph of infiltrating tan white nodule in the lobectomy specimen.

Case report

A 66-year-old man received an orthotopic heart transplant for cardiomyopathy resulting from ischemic heart disease 7 years prior to the current presentation. The patient was referred to our institution when a hypermetabolic (SUV 9.2), enlarging right lower lobe lung nodule was discovered on PET scan. Otherwise, he was asymptomatic with normal routine laboratory studies. Multiple attempts at fine needle aspiration of the mass failed to obtain adequate diagnostic material due to its difficult location. Consequently, a right lower lobectomy was performed.

Gross examination showed a 5.5 x 5.2 x 3.4 cm, white-tan, firm, infiltrating mass (**Figure 1**). Histologically, the nodule was predominantly composed of a monomorphic population of small to medium-sized, atypical lymphoid cells, diffusely infiltrating the lung with loss of architecture (**Figure 2A**, **2B**). Some atypical lymphoid infiltrates were also seen in the bronchiolar epithelium and in the vessel walls as well as at the periphery of the mass expanding into the alveolar septae. Rare lymphoid follicles with germinal centers were also present. The visceral pleura overlying the mass showed fibrous thickening. The atypical cells expressed T-cell markers, CD4, CD8, CD2, CD3, CD5, CD7 and CD43, and co-expressed BCL-6 and CD10 but negative for CXCL13, PD1, CD30 and CD57. CD21 demonstrated the expanded dendritic meshwork (**Figure 2C**, **2D**). A minor component of CD20-positive B cells was also seen. No EBV encoded RNA was detected by EBER in–situ hybridization. The combined morphologic and immunohistochemical pattern was most consistent with peripheral T-cell lymphoma with angioimmunoblastic features, fitting the diagnosis of monomorphic PTLD. Molecular studies showed clonal T-cell gamma receptor gene rearrangement. Staging workup showed no other evidence of disease. The patient was lost to follow up and he expired 9 months after his diagnosis due to unknown cause.

Discussion

PTLDs are lymphoproliferative diseases, which develop secondary to immunosuppressive therapy dampening the cytotoxic T-lymphocyte function to prevent graft rejection. It is a rare but serious complication of solid organ transplantation, representing one of the most frequent malignancies arising in the post-transplant setting [1].

The highest incidence is observed in heart recipients among solid organ transplants (SOT), especially in the first year following transplantation [11]. Although, the likelihood of developing lymphoma following SOT decreases with time, it remains to be higher in heart recipients compared to any other organ recipients. Several reports are available in the literature addressing the incidence, risks, and prognosis in PTLDs [12, 13]. However, the majority of these reports have not accounted for the lineage and histologic characteristics of the neoplasms.

The etiology of PTLD development is not entirely understood. The most widely accepted patho-

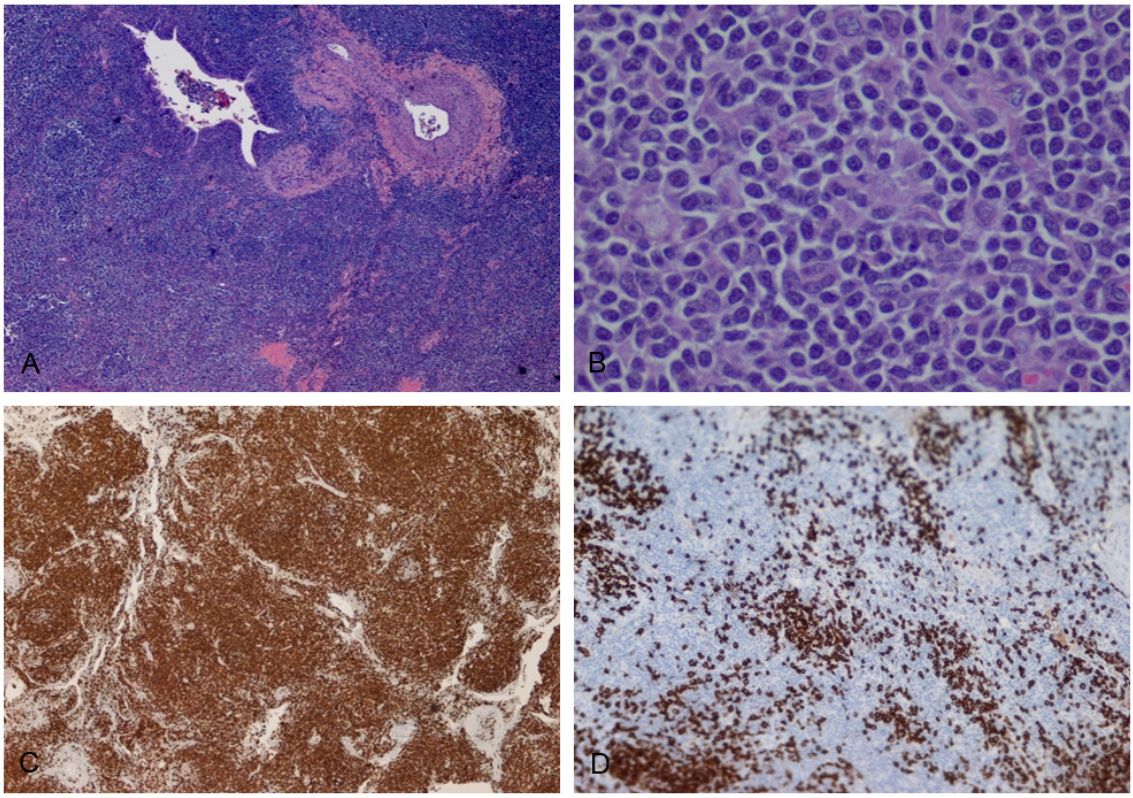

Figure 2. Monotonous proliferation of lymphocytes invading the bronchial epithelium and the lung parenchyma (A). Higher magnification showing diffuse infiltration of atypical small lymphocytes with irregular nuclei (B). CD3 immunohistochemical stain showing the majority of the cells are of T-cell lineage (C). CD20 immunostain highlights scattered B-lymphocytes (D).

mechanism is linked to viral etiologies on the basis of inadequate immune surveillance resulting from immunosuppressive regimes. EBV, but also HTLV (particularly in the endemic areas) are considered the most common causes in early onset diseases. EBV positive cases of PTLDs are usually of B cell lineage. Nevertheless, EBV can be detected in a small proportion of transplantation related T-cell lymphomas. In the meantime, the observation that PTLD commonly presents close to the transplanted organ supports that chronic antigenic stimulation by the graft is also an important factor in the pathogenesis of PTLDs, especially in late onset cases [14, 15].

The precise incidence of T-cell PTLD in cardiac transplant patients is unknown, similarly to the proportion of EBV positivity in such cases. In general, about two third of T-cell PTLDs are not associated with EBV [9, 16-22]. In the meantime, EBV positivity correlates with the epidemiology of these malignancies. The time period between transplantation and the development of lymphoma ranges from 24 days to 7 years with the median of 4 years in EBV positive cases and from 39 days to 26 years with the median of 5.5 years in EBV negative cases [9, 16-22]. The median interval of EBV negative PTLDs has been reported as long as 15 years (4-26 years) after transplantation [22]. Our patient presented 7 years after transplantation.

PTLDs most frequently involve extranodal sites, preferentially the gastrointestinal tract, lung, or liver, which is even more characteristic to the T-cell PTLDs. The largest series of T-cell PTLDs following cardiac transplantation was reported by Haldas, et al. in 2002 [21]. All of the summarized 10 cases had primary extranodal location, including a single case involving the lung [18]. In his study the most common extranodal sites were the kidneys, gastrointestinal tract, skin, bone marrow, spleen, and liver [17, 23].

An interesting observation is that the anatomic region of the transplanted organ is the favored

site for lymphoma development. Despite this remark, primary pulmonary involvement by T-cell PTLD is extremely rare following cardiac transplantation. Only two cases have been reported so far [18, 20]. This is the third presentation of an isolated pulmonary T-cell PTLD. The details of all the three patients are shown in **Table 1**.

Pulmonary nodules are a relatively common complication of SOT, and are diagnostically challenging. Copp and colleagues studied the etiology of pulmonary nodules following SOT. In their study, the majority of the pulmonary nodules was secondary to infection (56%) and presented as lung consolidation [24]. PTLD was identified in 26% of the cases, but it was not further subclassified.

It is still disputed if particular immunosuppressive agents carry an increased risk for lymphoma. Multiple studies showed that therapeutic intensity seems to play a dominant role in the development of lymphoma, rather than individual agents or certain combinations [9, 11]. This conclusion is further supported by the observation that lessening of immune suppressive therapy promoted the regression of T-cell PTLDs in approximately one third of the cases [25].

T-cell PTLD specifically has an aggressive clinical course with poor prognosis. However, rare cases with good outcome have been reported in pediatric patients [22]. Further expanded studies are required to improve early detection and to develop the most optimal treatment strategies for this diverse and typically aggressive disease.

Disclosure of conflict of interest

None.

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