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FULL PAPER

Is there a difference in post-transplant lymphoproliferative disorder in adults after solid organ and haematologic stem cell transplantation? Experience in 41 patients

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Objective: To determine if there is a difference in post-transplant lymphoproliferative disorder (PTLD) in adults after solid organ transplantation (SOT) and haematologic stem cell transplantation (HST).

Methods: In this institutional review board-approved Health Insurance Portability and Accountability Act-compliant study, we reviewed clinical data and imaging at the time of diagnosis in 41 patients (26 SOT and 15 HST) (31 males and 10 females; mean age 51 years) with histopathology-confirmed PTLD seen at our institution from 2004 through 2013. Statistical analysis was performed to assess difference in distribution and survival between SOT and HST cohorts.

Results: SOT: 17 lung/cardiac, 8 renal and 1 liver transplant recipients. HST: 13 leukaemia/lymphoma and 2 patients with aplastic anaemia. Median time to diagnosis: SOT 3.0 years; HST 6 months (Fisher's exact test; $p = 0.0011$).

There was no statistically significant difference in distribution of PTLD after SOT and HST with nodes (15/26; 8/15), lung (10/26; 5/15) and bowel (6/26; 4/15) being the most common sites. Hepatic (3/26) and neurologic (2/26) involvement occurred in only SOT cohort while splenic PTLD (5/15) occurred more often in HST cohort. Death occurred earlier in HST (9/15; 2 weeks) than SOT cohort (12/26; 11 months) (Wilcoxon test; $p = 0.0188$).

Conclusion: PTLD did not differ significantly in distribution between SOT and HST cohorts. PTLD after HST occurred early and had shorter survival.

Advances in knowledge: The most common sites of PTLD were the nodes, lung and bowel. Distribution of PTLD does not differ significantly between patients with SOT and HST. PTLD after HST occurs early and has poor survival compared with PTLD after SOT.

Post-transplant lymphoproliferative disorder (PTLD) occurs secondary to abnormal lymphoid or plasmacytic proliferation subsequent to solid organ transplantation (SOT) or haematologic stem cell transplantation (HST) in the setting of immunosuppression.¹ PTLD typically occurs with Epstein-Barr virus (EBV) infection,² although EBV-negative PTLD can also occur.^{3,4} Per the World Health Organization classification scheme, PTLD is categorized as (1) early lesion PTLD, which includes reactive plasmacytic hyperplasia, (2) polymorphic PTLD, which includes polyclonal and monoclonal subtypes and (3) monomorphic PTLD, which is subcategorized as B-cell lymphomas including diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma, T-cell lymphomas such as peripheral T-cell lymphoma and natural killer lymphomas.¹

Risk for PTLD is dependent on level and duration of immunosuppression and may explain the higher incidence of PTLD in patients with lung transplant and small bowel transplant, who are typically more immunosuppressed.⁵ Incidence of PTLD has also increased with advent of more potent immunosuppressants such as cyclosporine.^{6,7} Other risk factors include EBV seropositive transplant donor, cytomegalovirus (CMV) infection and comorbidities such as Langerhans cell histiocytosis, autoimmune hepatitis and chronic interstitial nephritis.⁸ EBV seronegativity in transplant recipients is also an important risk factor for PTLD.⁹⁻¹² In patients with HST, presence of T-cell depletion, HLA mismatching between donor and recipient, primary immunodeficiency as indication for transplant and antilymphocyte therapy are risk factors for PTLD.^{13,14}

PTLD occurring after SOT and HST are indistinguishable in clinical presentation.¹⁴ However, PTLD after HST is associated with a higher incidence of fulminant and disseminated disease with increased mortality.^{14–17} From an imaging stand point, it is unknown whether PTLD occurring in these two settings differs in any way. Accordingly, the purpose of this article is to determine if there is a difference between PTLD after SOT and HST on imaging.

METHODS AND MATERIALS

Subjects

This retrospective study was approved by the institutional review board with waiver of informed consent and was compliant with the Health Insurance Portability and Accountability Act. We identified 103 patients with PTLD who were either referred to or primarily treated at our adult tertiary cancer centre between July 2004 and July 2013 from the pathology database. 43 patients with equivocal diagnosis of PTLD at histopathology were excluded. Of the remaining 60 patients with unequivocal histopathologic diagnosis of PTLD established either by biopsies performed from at least 1 site of disease or on autopsy, 19 patients were excluded owing to non-availability of imaging at the time of diagnosis. The remaining 41 patients (31 males and 10 females; mean age at diagnosis 51 years, range 20–82 years) who had imaging at the time of diagnosis in our radiology database were included in the study. We retrospectively reviewed electronic medical records to record relevant clinical data including age at time of diagnosis of PTLD, duration of follow-up, organ, type and date of transplantation, EBV and CMV status of transplant donor and recipient before transplant and EBV and CMV status of transplant recipient after transplantation. If patient deceased during follow-up, date and cause of death were also noted.

Imaging

Imaging studies at the time of diagnosis of PTLD in the 41 patients included CT scans in 38 patients (10 with intravenous contrast), MRI in 18 patients (15 with intravenous contrast), positron emission tomography or CT in 20 patients and ultrasound in 14 patients. A total of 140 imaging studies were reviewed (mean number of scans per patient, 3.4; range, 1–6). Of the 41 patients, 39 patients had imaging of at least the chest, abdomen and pelvis. All the 14 patients with ultrasound had cross-sectional imaging of the chest, abdomen and pelvis.

Image analysis

All the available imaging in the 41 patients was reviewed in consensus by two radiologists with 2 and 8 years of experience in radiology under the supervision of a senior radiologist with 14 years of experience in radiology. On each imaging study, the distribution of PTLD was noted. Number of sites of involvement was defined as the number of distinct organs with imaging features concerning for PTLD. When multiple organs were involved in one patient, it was classified as multivisceral disease.

Statistical analysis

Statistical analysis was performed with χ^2 test or Fisher's exact test for categorical variables and Student's *t*-tests or Mann–Whitney *U* test for continuous variables to assess for statistically

significant difference in distribution of PTLD between SOT and HST cohorts. Survival analysis was performed for SOT and HST cohorts using log-rank/Wilcoxon test, and Kaplan–Meier curves were constructed. All the statistical analyses were performed using JMP® Pro v. 10.0.0 (SAS Institute Inc, Cary, NC).

RESULTS

PTLD after SOT and HST

The SOT cohort consisted of 17 patients with thoracic organ transplant (11 lung and 6 cardiac), 8 patients with renal transplant and 1 patient with liver transplant (Table 1). HST cohort consisted of 13 patients with leukaemia/lymphoma and two patients with aplastic anaemia. The median time to diagnosis was 3.0 years [interquartile range (IQR) 1–9 years; mean 6.5 years] among patients with SOT and 6 months (IQR, 3–12 months; mean, 8 months) among patients with HST (Fisher's exact test; *p* = 0.0011) (Table 1).

Among the 26 patients with SOT, 19 (73%) had multivisceral disease and six (27%) had solitary disease (2 patients with solitary bowel, 1 each with isolated cardiac, lung, brain and oropharyngeal involvement). Among the 15 patients with HST, 13 (87%) had multivisceral disease and two (13%) had solitary disease (1 each with isolated oropharyngeal and pulmonary involvement) (*p* = 0.27) (Table 2). We classified PTLD into nodal (*n* = 28) and extranodal (*n* = 55) PTLD according to the distribution (Table 2).

Nodal post-transplant lymphoproliferative disorder

The most common site of PTLD in patients with SOT and HST was lymph nodes. The mean size of the nodes was 2.6 cm (range, 0.8–5.3 cm). There was nodal involvement in 15/26 (58%) patients with SOT and 8/15 (53%) patients with HST (Table 2). The lymphadenopathy was more often thoracic in patients with SOT (12/26; 26%). No lymphadenopathy site predilection was demonstrated in patients with HST.

Extranodal post-transplant lymphoproliferative disorder

The lung was the most common extranodal site of PTLD in patients with SOT and HST, seen in 10/26 patients with SOT (38%) and 5/15 patients with HST (33%). In the SOT group, pulmonary PTLD occurred in only patients with thoracic organ transplantation and often in patients with lung transplant, with 8/11 (73%) patients with lung transplant affected (Figure 1) (seven of nine patients with double lung transplants and 1/2 patient with single lung transplant had pulmonary PTLD).

PTLD involving the bowel was seen in 6/26 (23%) patients with SOT and in 4/15 (27%) patients with HST. The colon was the most common site of gastrointestinal involvement in patients with SOT, with 5/26 (19%) patients affected (Figure 1). Three (11.5%) patients with SOT also had small bowel involvement. Two (8%) patients with SOT had gastric involvement, manifesting as focal intense fluorine-18 fludeoxyglucose (¹⁸F-FDG) uptake in the gastric wall with focal nodular gastric wall thickening and antral wall thickening. Among patients with HST, 3/15 (20%) had colonic involvement and 2/15 patients (13%) had small bowel involvement.

Splenic PTLTD was seen on imaging in 5/15 (33%) patients with HST in the form of splenomegaly. Multiple hypodense splenic lesions on CT in addition to splenomegaly were seen in one patient. Only one patient with SOT (lung transplant) presented with imaging findings concerning for splenic PTLTD, presenting as an ^{18}F -FDG-avid splenic lesion.

Three patients with SOT (14.8%) had radiologic evidence of liver involvement. One patient manifested with ^{18}F -FDG-avid lesions without CT correlate (Figure 1), one patient presented with multiple ill-defined hypodense lesions and one patient had a solitary hypodense hepatic lesion. None of the patients with HST had radiological evidence of hepatic PTLTD. However,

two patients with HST with liver impairment underwent liver parenchymal biopsy and had pathologically proven hepatic PTLTD.

Two patients with SOT (one renal and one lung transplant) presented with central nervous system (CNS) PTLTD, manifesting as multiple ring enhancing supratentorial lesions and solitary enhancing cerebellar lesion, respectively. None of the patients with HST demonstrated CNS involvement. Other less common sites of PTLTD involvement among patients with SOT included kidneys, bone, pleura, peritoneum and heart. Rare sites of PTLTD among patients with HST included adrenal glands and the pleura (Table 2).

Table 1. Clinical and pathological features of post-transplant lymphoproliferative disorder

Clinical characteristic	Solid organ transplant ($n = 26$)	Stem cell transplant ($n = 15$)	p -value ^a
Age (mean $\pm$ standard deviation) (years)	49.9 $\pm$ 18.3 (55.5, 20–82)	51.9 $\pm$ 14.3 (59, 22–69)	0.3537
Time from transplant to diagnosis (years)	6.2 $\pm$ 8.3 (3, 0.25–33)	0.66 $\pm$ 0.51 (0.5, 0.08–2)	0.0011 ^b
Organ transplanted			
Lung	11 (0.42)		
Kidney	8 (0.31)		
Heart	6 (0.23)		
Liver	1 (0.04)		
Pathology			
Hyperplasia	0 (0)	0 (0)	0.3802
Polymorphic	3 (0.12)	3 (0.20)	
Monomorphic	23 (0.88)	12 (0.80)	
Epstein–Barr encoding region (EBER) positive	17 (0.74)	10 (0.67)	
Epstein–Barr virus			
Seropositive donor	10 (0.38)	4 (0.27)	0.5500
Seronegative donor	2 (0.08)	0 (0)	
Unknown donor status	14 (0.54)	11 (0.73)	
Seronegative recipient	9 (0.35)	3 (0.20)	0.0271 ^b
Seropositive recipient	5 (0.19)	11 (0.73)	
Unknown recipient status	12 (0.46)	1 (0.07)	
Cytomegalovirus			
Seropositive donor	8 (0.31)	4 (0.27)	0.0906
Seronegative donor	5 (0.19)	10 (0.67)	
Unknown donor status	13 (0.50)	1 (0.07)	
Seronegative recipient	13 (0.50)	8 (0.53)	0.2238
Seropositive recipient	4 (0.15)	6 (0.40)	
Unknown recipient status	9 (0.35)	1 (0.07)	
Death	46.2%	66.7%	0.1730
Time to death from diagnosis (months)	14.3 $\pm$ 13.1 (11, 0.5–37)	3.1 $\pm$ 4.3 (0.5, 0.25–12)	0.0188 ^b
Death in less than 1 month	3 (0.12)	6 (0.40)	0.0436 ^b

^a χ^2 test or Fisher's exact test for categorical variables and Student's t -tests or Mann–Whitney U test for continuous variables.

^bStatistically significant correlation.

Pathology

Monomorphic PTLD was the most common pathological diagnosis in patients with HST (12/15; 80%) and SOT (23/26; 88%) (Figure 1). Of the 35 patients with monomorphic PTLD, 29 were classified as DLBCL, 4 as plasmacytoid PTLD, 1 as plasmablastic PTLD while 1 case was unclassified. *In situ* hybridization demonstrated positivity for EBV (EBER) in 27/35 (77%). Polymorphic PTLD was seen in 3/26 (12%) patients with SOT and 3/15 patients with HST (20%). No statistically significant difference in pathological type of PTLD was seen between patients with HST and SOT ($p = 0.3802$).

Clinical outcome

Patients in the SOT cohort survived longer than patients in HST cohort [Wilcoxon test; $p = 0.0188$; hazards ratio (log-rank test) HST/SOT, 2.117] (Figure 2). In the SOT cohort, the median duration of follow-up was 23 months (IQR, 8–37 months) during which 12/26 (46%) deceased at a median interval of 11 months (range, 2 weeks to 37 months; mean 14 months) from the time of diagnosis of PTLD (Table 1). 9 of the 15 patients

with HST (60%) deceased during follow-up (median, 5 months; IQR, 0.5–13 months) at a median interval of 2 weeks (range, 1 week to 12 months; mean, 3 months). More number of patients died within 1 month of diagnosis in HST cohort (6/15; 40%) compared with SOT cohort (3/26; 12%) (Fisher's exact test; $p = 0.0436$). There was no statistically significant difference in the outcomes for the three common sites of involvement (nodes, lung and bowel).

Correlation with Epstein-Barr virus and cytomegalovirus status

The EBV and CMV status of the recipients (before and after transplant) and the donors are summarized in Table 1.

Transplant recipients with seronegative EBV status more commonly presented with pulmonary PTLD, although not statistically significant ($p = 0.0695$). 8 of the 15 (53%) patients with pulmonary PTLD had pre-transplant EBV seronegative status compared with five (33%) patients with pre-transplant EBV seropositive status.

Table 2. Distribution of post-transplant lymphoproliferative disorder

	Solid organ transplant ($n = 26$)	Stem cell transplant ($n = 15$)	p -value ^a
Multifocal disease	19 (0.73)	13 (0.87)	0.2730
Number of sites	2.07	1.87	0.2812
Sites			
Bone	3 (0.12)	1 (0.07)	
Kidney	1 (0.04)	0 (0)	
Adrenal	0 (0.00)	1 (0.07)	
Heart	1 (0.04)	0 (0)	
Lymphadenopathy	15 (0.58)	8 (0.53)	
Above diaphragm	11 (0.42)	3 (0.20)	
Below diaphragm	1 (0.04)	3 (0.20)	
Above and below	3 (0.12)	2 (0.13)	
Lymphatic tissue in nasopharynx	1 (0.04)	1 (0.07)	
Lymphatic tissue in oropharynx	2 (0.08)	1 (0.07)	
Lung	10 (0.38)	5 (0.33)	
Brain	2 (0.08)	0 (0)	
Peritoneum	2 (0.08)	0 (0)	
Mesentery	2 (0.08)	0 (0)	
Small bowel	3 (0.12)	2 (0.13)	
Colon	5 (0.19)	3 (0.20)	
Stomach	2 (0.08)	0 (0)	
Liver	3 (0.12)	0 (0) ^b	
Spleen	1 (0.04)	5 (0.33)	0.0185 ^c
Soft tissue	3 (0.12)	0 (0)	

^a χ^2 test or Fisher's exact test for categorical variables and Student's t -tests or Mann-Whitney U test for continuous variables.

^bTwo patients with HST had no imaging findings of PTLD in the liver but had PTLD on liver biopsy.

^cStatistically significant correlation.

Figure 1. 24-year-old male presenting with diarrhoea 6 months after cardiac transplantation. (a, b) Axial non-contrast CT images of the abdomen reveal diffuse nodular pancolonic thickening (arrows). There were multiple nodules as well (not shown). Biopsy of the pulmonary nodules demonstrated post-transplant lymphoproliferative disorder (PTLD). (c) Coronal maximum intensity projection image of fluorine-18 fludeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT performed for staging demonstrates multiple areas of ^{18}F -FDG uptake throughout the body including the neck, both lungs, liver, small bowel, colon, left inguinal region and multiple bones. (d) Axial fused PET/CT image intense ^{18}F -FDG uptake in the small bowel and colon (arrows). Patient was started on chemotherapy but died 1 month after diagnosis of PTLD. (e) Gross specimens of the colon (top) and small intestine (bottom) taken at the time of autopsy show multiple well-demarcated lesions, both mural and polypoid, most with central ulcers. (f) Scanning image of the small intestine showing both a polypoid intraluminal lesion and involvement of the mesentery (lower right) [haematoxylin and eosin (H&E), $\times 1$]. (g) At high magnification, large lymphoid cells infiltrate around intestinal crypts (H&E, $\times 400$). This PTLD was classified as diffuse large B-cell lymphoma.

Seronegative CMV status of transplant donor was associated with more aggressive disease, occurring in 7/9 (78%) patients with aggressive disease ($p = 0.1082$). Additionally, seronegative CMV status of transplant donor was associated with splenic PTLD occurring in all five patients with splenic PTLD ($p = 0.0372$).

DISCUSSION

Knowledge of the anatomic distribution and imaging features of PTLD is important for its timely diagnosis. Although the distribution of PTLD after HST has not been widely reported, several studies have shown that its distribution after SOT varies with the type of transplant: while PTLD localizes to the liver in liver transplant and to the lung in lung transplant, it localizes to organs outside the kidney in renal transplant.^{8,18} A similar observation was made in our study: although lung was the most common site of PTLD in lung/heart transplants, kidney was not involved in any of the renal transplant recipients. The most common sites of PTLD in HST in our study were nodes followed by lung and bowel. However, this distribution was not statistically different from the distribution of PTLD in the SOT cohort. PTLD after HST tends to be often disseminated with 87% of our patients having multifocal disease, although not significantly different from the SOT cohort in our study (73%; $p = 0.68$).

Lymph nodes were the most common sites of PTLD at the time of presentation in both SOT and HST. Nodal involvement limited above the diaphragm was a common manifestation among patients with SOT (46%), consistent with study by Dodd et al,¹⁹ in which 17 of 35 patients with SOT (48.5%) presented with hilar and mediastinal adenopathy. Nodal involvement below the diaphragm occurred less frequently among patients with SOT (15%), which is also consistent with prior study by Pickhardt and Siegel,²⁰ in which eight (22%) of 36 SOT patients with abnormal CT presented with intra-abdominal lymphadenopathy. The higher incidence of thoracic lymphadenopathy in our study is biased because of the higher number of thoracic organ (lung and cardiac) transplants. Unlike patients with SOT, no predilection to nodal involvement above or below the diaphragm was demonstrated in patients with HST. Nodal involvement based on imaging characteristics alone may be non-specific as lymphadenopathy and splenomegaly may occur owing to multiple reasons such as PTLD, reactive enlargement in setting of active infection/inflammation or leukaemic/lymphomatous involvement in patients with HST.^{21,22} For example, Valls et al²² evaluated 19 patients with lymphadenopathy subsequent to orthotopic liver transplantation, and six (31.5%) had PTLD and five (26%) had reactive lymph node hyperplasia. Nevertheless, nodal involvement in PTLD after all types of SOT has been shown to be associated with a favourable outcome in the European collaborative study, although it is unclear whether this refers to isolated nodal PTLD.¹⁸ Correlation of nodal involvement with outcome was difficult in our study as none of the patients had isolated nodal involvement.

Pulmonary PTLD at presentation occurred most commonly in patients with lung transplant, which is consistent with previous

studies.^{23,24} The incidence of pulmonary PTLD after lung transplant in the large European collaborative study was 53%.¹⁸ Our reported 73% pulmonary involvement among patients with lung transplant is higher than reported in the literature.²³⁻²⁵ Pulmonary involvement in PTLD after HST was less common than SOT, occurring in 33% (5/15) of our patients. In the study based on 13 years experience with HST, Hou et al¹⁵ found PTLD in 12/577 patients undergoing HST, eight of whom had pulmonary involvement, four at presentation. Notably, this study concluded that pulmonary PTLD after HST portends poor outcome with aggressive and high mortality in contrast to studies in SOT, which have shown favourable survival.^{15,18}

Gastrointestinal involvement in PTLD (stomach, small bowel and colon) occurred in patients with HST and SOT and manifested as bowel wall thickening, aneurysmal bowel dilatation and bowel perforation, also in concordance with known description of GI PTLD.^{8,20,24,26,27} Similar to the study by Pickhardt and Siegel,²⁰ in which 30.5% of patients with SOT presented with gastrointestinal PTLD, 23% of patients with SOT in our cohort presented with bowel PTLD. GI PTLD was the most common site of PTLD in renal transplant recipients, which is similar to the European collaborative study.¹⁸ No difference in imaging presentation or incidence of bowel PTLD was seen between the SOT and HST populations. Hepatic and CNS involvement on imaging at presentation was noted in only patients with SOT (12% and 8%, respectively). While none of the patients with HST had hepatic or CNS involvement on imaging, liver biopsy showed diffuse involvement in two (13%) patients. By contrast, splenic involvement was more common in patients with HST (33%) rather than patients with SOT (4%).

The aggressive picture of post-HST PTLD in our study is in agreement with known literature.^{14,16,17} PTLD after HST presented earlier than SOT (median, 6 months vs 3 years) (Fisher's exact test; $p = 0.0011$) was associated with shorter median survival (2 weeks vs 11 months) (Wilcoxon test; $p = 0.0188$) and

Figure 2. Kaplan-Meier curves showing modest survival difference between patients developing post-transplant lymphoproliferative disorder (PTLD) after solid organ transplant (SOT) and haematologic stem cell transplant (HST) [Wilcoxon test; $p = 0.0188$; hazards ratio (log-rank test) HST/SOT, 2.117].

greater number of deaths within 1 month of diagnosis (40% vs 11%; $p = 0.0436$).

Limitations of our study include retrospective study design and small number of patients, which is inevitable for a rare condition such as PTLD. The patients in our study were derived from the pathology database and as such the incidence rates of PTLD after specific transplants could not be estimated. Another limitation of our study was the lack of contrast-enhanced CT scans in a substantial number of patients. This was inevitable as these patients often have poor renal function leading to sparing use of intravenous iodinated contrast. Studies have shown that patients with SOT or HST are at increased risk of renal failure.^{28,29}

CONCLUSION

In conclusion, distribution of PTLD did not differ significantly between the SOT and HST cohorts. Most common sites of PTLD at presentation were the nodes, lung and bowel in both SOT and HST cohorts. Hepatic and CNS PTLD occurred in only SOT cohort while splenic PTLD occurred more often in HST cohort. PTLD after HST presented early after transplant and had a poor outcome compared with PTLD after SOT.

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