ISSN: 2755-0206

Journal of Pathology Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Post-transplant Lymphoproliferative Disorders: Single Center Case Series and Literature Review

Sumayyah Altamimi[1], Mohamed Al Shuaibi[1], Mohamed Alnahdi[1], Abdulrahman Altheaby[4], Hanouf Almutairi[5], Moussab Damlaj[123], Ahmed Al Askar[123], Ayman Hejazi[123], Mohsen Alzahrani[123], Khadega A. Abuelgasim[123], Hend Salama[123], Bader Alahmari[123], Abdulrahman Alraiza[123], Haythem Almuhayani[1], Fahad Alanzi[1], Husam Alsadi[1], Giamal Edin Gmati[123]*

[1]Adult Hematology & HSCT divisions, Oncology Department of Oncology. King Abdul-Aziz Medical City. Riyadh. KSA

[2]King Saud Bin Abdul-Aziz University for HeaIth Sciences. Riyadh. KSA

[2]King Abdulla International Medical Research Center. Riyadh. KSA

[3]Organ Transplant Centre and Hepatobiliary Sciences Department, King Abdul-Aziz Medical City. Riyadh. KSA

[4]Nephrology Section, Internal Medicine Department, King Abdul-Aziz Medical City. Riyadh. KSA

ABSTRACT

Post-transplant lymphoproliferative disorders (PTLD) are referred to lymphoid and/or plasmacytic proliferation which occur as result of immunosuppression therapy in patient underwent solid organ or allogeneic hematopoietic stem cell transplantation. Among solid organ transplant recipients, it accounts approximately 20% of all cancers. Epstein-Barr virus (EBV) has been linked to the pathogenesis of PTLD when EBV was identified in the tumor biopsies. In most affected patients, PTLD occurs as a result of proliferation of EBV positive B cell following immunosuppression and impaired Tcell immune activity. EBV negative PTLD has been documented but no clear etiology has been confirmed, however theories of previous exposure to EBV which is completely cleared at the time of PTLD is diagnosed, different viruses or chronic antigenic stimulation all been considered as provoking factors for tumor development. Clinical symptomatology at presentation of patients with PTLD is usually indistinct from de novo lymphoproliferative disorders and chemotherapy protocols in this group of patients are generally similar to the standard of care of lymphoma treatment according to the subtype in addition to cessation or dose reduction of immunosuppressive therapy. We report our experience and outcome analysis in PTLD management among 23 patients from our institution treated between 2011 and 2019.

***Corresponding author**

Giamal Edin Gmati, Adult Hematology & HSCT, Department of Oncology, King Abdulaziz Medical City, Riyadh 11426, KSA; E-Mail: gmatiga@ngha.med.sa

Received: October 27, 2020; **Accepted:** November 03, 2020; **Published:** November 18, 2020

Introduction

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous spectrum of predominantly B-cell disorders, often extra-nodal, with complex distinct pathogeneses and variable clinical presentations determined by pathologic subtype [1]. These disorders involve lymphoid and/or plasmacytic proliferations that occur as a result of immunosuppression in the setting of solid organ or allogeneic hematopoietic stem cell transplantation (HSCT). The World Health Organization (WHO) classification of lymphoid malignancies considers four major diagnostic post-transplant lymphoproliferative disorder (PTLD) categories: early lesions, polymorphic PTLD that could be either polyclonal or monoclonal, Hodgkin lymphoma (HL), and monomorphic PTLD of which diffuse large B-cell lymphoma is the most common [2]. PTLD represents approximately 20 percent of all cancers and is the most common malignancy complicating solid organ transplantation [3,4]. Epstein–Barr virus (EBV) infection is strongly associated with PTLD with approximately 60-80% of PTLD cases are positive of EBV infection [5]. PTLD caused by EBV infected B cell proliferation can originate in the transplant recipient (host) which most commonly occurs in solid organ transplantation or the donor derived PTLD which commonly seen post HSCT [6,7]. EBV-negative PTLD disease is genetically distinct from EBV+ positive and also can be caused by other viruses such as human herpes virus 8 (HHV-8) in post-transplantation primary effusion lymphoma [8,9]. Development of PTLD among solid organ transplanted patients also affected by other factors such as immunosuppressive agents, degree of immunosuppression, EBV serostatus, time post-transplant and age < 25 years at time of transplantation [10-13]. Since the main 2 factors contributing to PTLD are the immunosuppression and viral infections, aggressive tapering of the immunosuppressive therapy found to be associated with lower prevalence of PTLD among renal transplanted patients [14]. Prophylactic antiviral therapy was also shown to reduce the risk of PTLD as shown in a retrospective multicenter case-control study of renal transplant recipients [15]. Treatment strategies in PTLD patients vary according to the recipient graft status, aggressiveness on the lymphoma subtype and patients fitness to tolerate treatment.

However, the general goal of treatment is to balance between tapering immunosuppressive therapy and avoiding graft rejection. Treatment modalities can be immunotherapy where rituximab is the standard of care, chemo-immunotherapy as adding rituximab to CHOP protocol found to be associated with improved complete response (CR), radiation therapy and adaptive immunotherapy by using EBV-specific cytotoxic T lymphocytes (EBV-CTLs) or donor lymphocyte infusion (DLI) [16]. Herein, we report our experience of management and outcome of 23 patients with PTLD over the last 9 years.

Methods

This is a retrospective review of 23 patients diagnosed with lymphoproliferative disorder (LPD) with a previous history of solid organ transplantation mainly renal and liver transplant. The cases of PTLD between January 2011 to December 2019 were captured from Lymphoma database in our institution. Chart review using the electronic medical notes system (BESTCare 2.0). Solid organ transplantation in those patients included in-house and transplantations in other transplant centers in and outside the Kingdom. Histological diagnosis of lymphoproliferative disorder (LPD) was confirmed by our lymphoma pathologist and all cases were discussed in our lymphoma tumor board. Disease staging by computerized tomography (CT) scan, proton emission tomography (PET) scan and bone marrow biopsy. Ann Arbor classification and risk stratification by International Prognostic Index (IPI) were implemented. Treatment plan of PTLD in this group of patients was decided in our tumor board according to the international guidelines. Response to treatment was assessed by end of treatment and classified according to Lugano response criteria [17,18]. Our Institutional Review Board (IRB) approval was granted with approval number RC16-136-R.

Results

A total of 23 patients were diagnosed with PTLD in our institution between 2011 to 2019 with a median follow up of 5 years. Renal transplantation patients represented 60.8 % and liver transplantations patients were 39.2 % .The median duration of immunosuppression is 9 years. Data on viral serology status pre-transplant in recipients and donors were not available in some patients whom underwent organ transplantation abroad or in a different transplantation centers. Patients characteristics and PTLD disease characteristics are shown in **table 1** and **table 2** respectively. Progression free survival (PFS) in 3 years was 57.4% (0.34-0.75) with median PFS 1085 days (36.2months) and overall survival (OS) in the same period of time was 57.4 (0.34-0.75) with median OS 6892 days (229.7 months) (**figure 1**).

Table 1: Patient Characteristic

Variables	Total cohort (23) N (%)
Age	10-78 median age 58
Male	12 (52)
Female	11 (48)
Comorbidities	
DM	14 (60.8)
HTN	9 (39.1)
IHD	2 (8.6)
Others	10 (43.4)
ECOG	
0	11 (47.8)
1	5 (21.7)
3	3 (13.2)
4	4 (17.3)
Organ transplantation	
Renal	14 (60.8)
Liver	9 (39.2)
Duration of transplant (y)	
1-5	3 (13.2)
5-10	5 (21.7)
10-15	6 (26)
15-20	9 (39.1)
Live/Cadaveric transplantation	
Live related	6 (26.1)
Live non-related	4 (17.4)
Cadaveric	7 (30.4)
Unavailable	6 (26.1)
Duration of immunosuppression at the time of LPD diagnosis (Y)	
1-5	6 (26.1)

5-10	5 (21.7)
10-15	5 (21.7)
15-20	6 (26.2)
>20	1 (4.3)
transplant status at time of PTLD diagnosis	
Normal graft function	19 (82.6)
Rejection	4 (17.4)

Table 2: PTLD Disease characteristics

Characteristics	Total cohort (23) N (%)
Type of PTLD	
DLBCL	13 (56.5)
Burkett's	3 (13.1)
Primary CNS lymphoma	2 (8.6)
High grade NHL. NOS	2 (8.6)
MCL	1 (4.4)
MM	1 (4.4)
Extra-nodal NK lymphoma	1 (4.4)
EBV in tissue biopsy	
Positive	7 (30.4)
Negative	10 (43.4)
NA	6 (26.2)
PTLD stage	
1	4 (17.4)
2	3 (13.1)
3	1 (4.4)
4	10 (43.5)
NA	5 (21.7)
Duration between transplantation and PTLD(Y)	
1-5	7 (30.3)
5-10	6 (26.2)
10-15	4 (17.3)
15-20	6 (26.2)
Type of PTLD	
Monomorphic	8(34.7)
Polymorphic	0
NA	15(65.3)
Rituximab	
Yes	17 (73.8)
No	3 (13.1)
NA	3 (13.1)
Chemotherapy	
R-CHOP	8 (34.7)
R-Hyper CVAD	6 (26.2)
MTX only	1 (4.4)
R-CVP	2 (8.4)
VRD	1 (4.4)
Radiotherapy	1 (4.4)
ANHL 0021 protocol	1 (4.4)

NA	3 (13.1)
End of treatment evaluation	
CR	10 (43.6)
Died	10 (43.6)
No show	1 (4.4)
Relapsed	2 (8.4)
SCT	1 (4.3)
Final outcome	
Alive	12 (52)
Dead	11 (48)

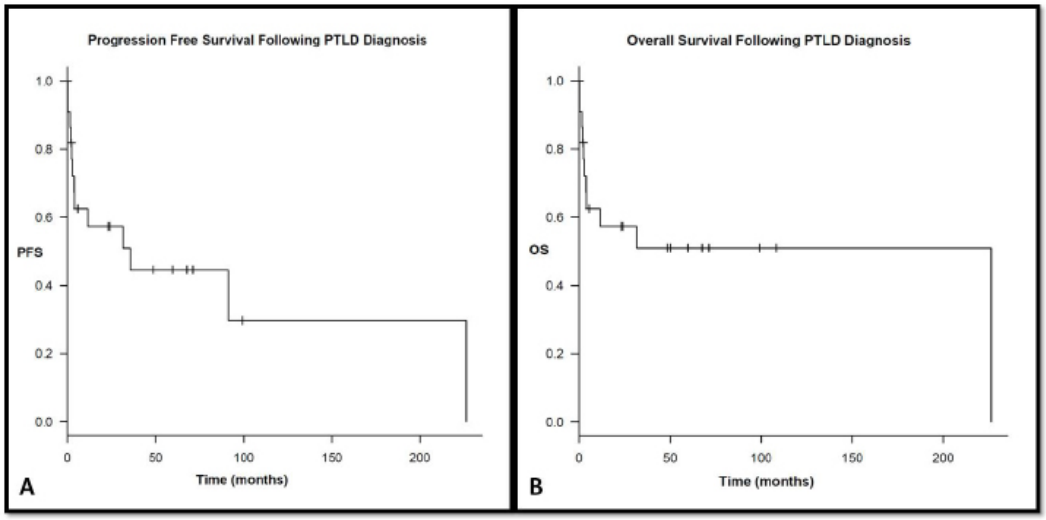

Figure 1: A- 3 years PFS post PTLD diagnosis. B- 3years OS post PTLD diagnosis

Discussion

PTLD is a well-recognized complication of both solid organ transplantation and allogeneic HSCT. It is one of the most common post-transplant malignancies. PTLD may also cause symptoms similar to those seen with organ rejection or similar to side effects from immunosuppressive medications. For decades, PTLD development was attributed mainly to EBV infection, however, recent reports suggest that as many as 50% PTLD in solid organ transplantation are not accompanied by EBV infection [19]. PTLD develops as a result of uncontrolled B cell proliferation due to blunted immunological surveillance. B cells may get infected by Epstein-Barr virus (EBV) either by: (1) Post-transplant viral reactivation; and (2) Primary EBV infection, through the donated organ or via environmental exposure. The majority of PTLD cases (> 85%) are usually observed in the first post-transplant year. On the other hand, PTLD as a result of T-cell proliferation is seen much less commonly and is mostly EBV-negative [20]. In our case series EBV positivity in tissue biopsies was detected in 7 patients (30.4%) and negative EBV in 10 patients (43.4%) while no result was available in 6 patients (26.2%). For EBV-positive transplant recipients, the development of PTLD can be attributed to immunosuppressive-induced decline in the T-cell immune- surveillance. EBV can integrate into normal B-cell program leading to proliferation and transformation of these cells. Normally, these antigens would trigger a T-cell response capable of destruction of most of the EBV-infected B cells. However, this immune defense mechanism has been compromised in transplant recipients leading to unlimited B- cell transformation and the evolution of lymphoma [21]. On other hand, pathogenesis of PTLD in EBV-negative patients is less evident. Several hypotheses have been postulated e.g., CMV or another viral infection, prolonged immunosuppression, allograft-driven persistent antigenic triggering, hit-and-run hypothesis i.e., EBV commences the pathogenic process leading to the development of PTLD and then vanishes. Duration and degree of immunosuppression in transplanted recipients plays an important role in the pathogenesis of PTLD and the median duration of immunosuppression in our study is 9 years. The degree of immunosuppression has long been considered a major determinant of the development of PTLD [22,23]. In particular, the degree of T cell immunosuppression appears to be more important than the degree of immunosuppression overall, due to the impairment of EBV-specific T cell-mediated immunity [24]. Several studies have suggested that higher tacrolimus levels are associated with higher risk for PTLD, and others have reported that the net state of immunosuppression, rather than any individual agent, increases the risk for PTLD [25-27]. Reduction of immunosuppression is the cornerstone of PTLD management. Rituximab therapy is indicated in nondestructive PTLD, polymorphic PTLD, and, monomorphic diffuse large B-cell lymphoma-like PTLD not responding to reduction of immunosuppressive therapy. Chemotherapy is indicated for: Burkett's lymphoma, Hodgkin's lymphoma, peripheral T-cell lymphoma, primary CNS lymphoma, and B-cell PTLD unresponsive to radiotherapy with variable results. However, "risk-stratified sequential" therapeutic approach seems to be promising. Other modalities may include adoptive

immunotherapy and outpatient care. Investigational agents that are currently under trials. Information concerning mortality of patients with PTLD is largely based on case reports and retrospective studies. Although the prognosis varies with clonality and extent of disease, published series suggest overall survival rates ranging between 25 to 35 percent [28]. As shown in (figure 1), in our case series progression free survival (PFS) in 3 years was 57.4% with median PFS of 1085 days (36.2 months). Overall survival (OS) for the same period was 57.4% with median OS 6892 DAYS (229.7 months). Mortality with monomorphic PTLD has been reported to be as high as 80 percent and the T cell subtypes had the worse prognosis [29,30]. Of importance, many of these studies included patients diagnosed with PTLD prior to the availability of rituximab (anti-CD20 antibody), which appears to have improved outcomes in CD20+ PTLD [31,32]. Nearly 3/4 of our case series received rituximab in combination with chemotherapy. The main limitations to our case review are the relatively low number of patients which is mainly due to disease incidence and the difficulty to get enough data on patients whom had the transplantation in transplant centers out of the country.

Conclusion

PTLD is a heterogeneous spectrum of predominantly B-cell disorders and is the most common malignancy complicating solid organ transplantation. Several risk factors have been linked to the development of PTLD such as degree of T cell immunosuppression, the EBV serological status of the recipient and the duration of post-transplant. WHO classified PTLD according to the morphologic, immunophenotypic, genetic and clinical features. Several treatment protocols have been used in PTLD according to the histological subtype but generally they are similar to the standard of care protocols used in de novo lymphoma.

References

1. Allen UD, Preiksaitis JK (2019) Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 33: e13652.
2. Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri S, et al. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC.
3. Penn I (1990) Cancers complicating organ transplantation. N Engl J Med 323: 1767.
4. Adami J, Gäbel H, Lindelöf B, K Ekström, B Rydh, et al. (2003) Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 89: 1221-1227.
5. Ferla V, Rossi FG, Goldaniga MC, Baldini L (2020) Biological Difference between Epstein–Barr Virus Positive and Negative Post-transplant Lymphoproliferative Disorders and Their Clinical Impact. Front Oncol 10: 506.
6. Weissmann DJ, Ferry JA, Harris NL, Louis DN, Delmonico F, et al. (1995) Post transplantation lymphoproliferative disorders in solid organ recipients are predominantly aggressive tumors of host origin. Am J Clin Pathol 103: 748.
7. Ballen KK, Cutler C, Yeap BY, McAfee SL, Dey BR, et al. (2010) Donor-derived second hematologic malignancies after cord blood transplantation. Biol Blood Marrow Transplant 16: 1025.
8. Craig FE, Johnson LR, Harvey SA, Nalesnik MA, Luo JH, et al. (2007) Gene expression profiling of Epstein-Barr virus-positive and -negative monomorphic B-cell posttransplant lymphoproliferative disorders. Diagn Mol Pathol 16: 158.
9. Dotti G, Fiocchi R, Motta T, Facchinetti B, Chiodini B, et al. (1999) Primary effusion lymphoma after heart transplantation: a new entity associated with human herpesvirus-8. Leukemia 13: 664.
10. Bustami RT, Ojo AO, Wolfe RA, Merion RM, Bennett WM, et al. (2004) Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant 4: 87.
11. Opelz G, Henderson R (1993) Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. Lancet 342: 1514.
12. Walker RC, Marshall WF, Strickler JG, Wiesner RH, Velosa JA, et al. (1995) Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis 20: 1346.
13. Smith JM, Rudser K, Gillen D, Kestenbaum B, Seliger S, et al. (2006) Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. Transplantation 81: 175.
14. Shapiro R, Scantlebury VP, Jordan ML, Vivas C, Ellis D, et al. (1999) Pediatric renal transplantation under tacrolimus-based immunosuppression. Transplantation 67: 299.
15. Funch DP, Walker AM, Schneider G,Ziyadeh NJ, Pescovitz MD (2005) Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant 5: 2894.
16. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, et al. (2012) German PTLD Study Group; European PTLD Network. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 13: 196.
17. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, et al. (2014) Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32: 3059.
18. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, et al. (2014) Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32: 3048.
19. Luskin MR, Heil DS, Tan KS, Choi S, Stadtmauer EA, et al. (2015) The Impact of EBV Status on Characteristics and Outcomes of Posttransplantation Lymphoproliferative Disorder. Am J Transplant 15: 2665-2673.
20. Abbas F, El Kossi M, Shaheen IS, Sharma A, Halawa A (2020) Post-transplantaion lymphoproliferative disorders: Current concepts and future therapeutic approaches. World J Transplant 10: 29-46.
21. Thorley-Lawson DA, Gross A (2004) Persistence of the Epstein-Barr virus and the origins of associated lymphomas. N Engl J Med 350: 1328-1337.
22. Swerdlow SH, Campo E, Harris NL, Pileri SA, Harris NL, et al. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127: 2375-2390.

23. Penn I (1990) Cancers complicating organ transplantation N Engl J Med 323: 1767.
24. Lucas KG, Small TN, Heller G, Dupont B, O'Reilly RJ (1996) The development of cellular immunity to Epstein-Barr virus after allogeneic bone marrow transplantation Blood 87: 2594.
25. Shapiro R, Nalesnik M, McCauley J, Fedorek S, Jordan ML, et al. (1999) Posttransplant lymphoproliferative disorders in adult and pediatric renal transplant patients receiving tacrolimus-based immunosuppression. Transplantation 68: 1851-1854.
26. Opelz G, Döhler B (2004) Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 4: 222-230.
27. Höcker B, Fickenscher H, Delecluse HJ, Böhm S, Küsters U, et al. (2013) Epidemiology and morbidity of Epstein-Barr virus infection in pediatric renal transplant recipients: a multicenter, prospective study. Clin Infect Dis 56: 84-92.
28. Savage P, Waxman J (1997) Post-transplantation lymphoproliferative disease QJM 90: 497.
29. Penn I (Ed) (1992) Immunosuppression and Lymphoproliferative Disorders. PRO/COM University of Cincinnati Medical Center.
30. Portell C, Nand S (2008) Single agent lenalidomide induces a response in refractory T-cell posttransplantation lymphoproliferative disorder Blood 111: 4416.
31. Evens AM, David KA, Helenowski I, Nelson B, Kaufman D, et al. (2010) Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol 28: 1038.
32. Ghobrial IM, Habermann TM, Ristow KM, Ansell SM, Macon W, et al. (2005) Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era. Leuk Lymphoma 46: 191.