



Role of Hepatitis C Virus Infection on Lymphoproliferative Disorders after Non-liver Transplantation

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Authors' contributions

This work was carried out in collaboration between all authors. Author HK designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MEGC and MA helped with the literature review and managed the analyses of the study. Author SA helped with the final preparation of report. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The number of reports on HCV positive PTLD patients in non-liver transplantation setting as well as our knowledge on the issue is extremely limited. In this study, we aimed to investigate the impact of HCV infection on non-liver transplant recipients regarding PTLD development.

Study Design: The study is designed as a comprehensive review of the literature.

Place and Duration of Study: The review of the literature was performed at the Department of Internal Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran.

Methodology: A comprehensive search was performed for finding the available data by Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring in non liver organ transplant patients with regard to their HCV test results. P value of 0.05 was considered

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significant.

Results: Data of overall 61 patients was entered into analysis. 9 PTLD patients were HCV positive and the remaining were HCV negative. HCV positive patients were significantly younger at the time of transplantation ($p=0.04$). The same patient group had relatively shorter time from transplantation to PTLD development, but significant level has not been achieved (74 ± 57 vs. 46 ± 38 , respectively; $p=0.06$). No other difference was found.

Conclusion: HCV positivity can reduce the time interval between transplantation and PTLD development which can be interpreted as HCV can enhance the rate of PTLD in non-liver transplant recipients. Our study presents a significant evidence for HCV relationship with PTLD in non-liver transplantation setting. Further studies with prospective designations are needed to confirm our results.

Keywords: Posttransplant lymphoproliferative disorders; PTLD; hepatitis C virus; HCV.

ABBREVIATIONS

PTLD: Posttransplant lymphoproliferative disorders; HCV: hepatitis C virus; EBV: Epstein Barr virus.

1. INTRODUCTION

The organ transplantation practice has witnessed a substantial enhancement in the outcome of organ recipients during the past two to three decades. These advantages have resulted in considerable increase in the survival of transplant patients leading to appearance of hidden complications having been emerged after elongation of transplant patients' survival. Development of the lymphoproliferative disorder post organ transplantation (PTLD) is one of the most prevalent malignancies that develops in organ recipients, and remains a challenging diagnostic and therapeutic problem in the transplantation setting. PTLD is characterized by lymphoid proliferation of B- or T-cell origins which was first discovered by Penn et al. [1] in 1969, in a patient who had undergone living related kidney transplantation. Since then, several reports have been published indicating a high incidence of PTLD among recipients of all types of organs, including the liver. Overwhelming data has demonstrated that the incidence of lymphoma after transplantation is quite higher than that in the general population [2-7]. Reported reasons for this observation include high levels of immunosuppression, antibody induction therapy including OKT3, antilymphocyte globulin (ALG) and antithymocyte globulin (ATG) and viral infections especially Epstein-Barr virus (EBV) infection [5-7].

The association of hepatitis viruses with non-Hodgkin lymphomas (NHL) has been repeatedly

reported. Several studies have reported high prevalence of hepatitis C virus (HCV) [8-10] and/or hepatitis B virus [11,12] infections in NHL patients. HCV reportedly induces clonal proliferation of B lymphocytes and has been suggested as an important player in the pathogenesis of lymphoproliferative disorders [13]. So, there would be no wonder if we realize that HCV can induce PTLD in transplantation setting, as some studies have already suggested, including one of ours [14,15].

Although there is some evidence about the impact of HCV on the development of PTLD in liver graft recipients, however, we found no study in the existing literature that focuses on the impact of HCV infection on the development of PTLD in non-liver transplant patients. In fact, even current data on the HCV and PTLD relationship in liver transplant recipients is based on very limited number of case reports or small series; so the situation on the HCV and PTLD in non liver transplant recipients can be assumed. As mentioned above, HCV can induce B-cell proliferation and may lead to PTLD; so, we could expect a provocative role for HCV infection in the development of PTLD even in non-liver allograft recipients. Moreover, there is no mention that whether PTLD arising in HCV positive patients represents any special features and/or prognosis. Pooling data of PTLD in HCV positive organ recipients from the existing literature, we sought to analyze and compare characteristics, behavior and prognosis of PTLD arising in HCV positive non-liver allograft recipients.

2. MATERIALS AND METHODS

2.1 Approaches to the Study

We conducted a comprehensive search for the available data by Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring in non liver organ transplant patients with regard to their HCV test results. Keywords used for this purpose were "lymphoproliferative disorders + renal/Bonemarrow/heart/lung/ transplantation + hepatitis C". In reports for which we were not able to achieve the full text of the articles, emails were sent to correspondent authors requesting the article. Then we only included studies in which data of each patient was presented separately and excluded others. A standard questionnaire was developed to collect data from different published studies. Finally, data from 10 previously published studies [16-25] were included into the study; two studies were excluded from the analysis due to the very high rate of missing data on the outcome and disease involvement organs. The time between transplantation and PTLD onset was defined as the period between the engraftment and the first signs of PTLD or diagnosis, based on the studies' approaches. Patients who presented with PTLD within the first 12 months post transplantation were considered as "early-onset PTLD" group; and renal recipients representing the disease beyond this time were categorized as "late onset" PTLD patients.

2.2 Study Population

Overall 61 recipients of non-liver graft who developed PTLD through their treatment course were included into analysis. There were 9 cases with HCV positive test result and 55 were HCV negative recipients of non-liver allograft developing PTLD. The controls were recruited from studies in which HCV test has been reported for their reported series or individual subjects. Patients' status regarding EBV infection was documented in 34 (56%) patients; of whom 32 (94.1%) were reported positive. Because data used for this study was from different studies and they had not unique approaches, we were not able to get all the data we needed from the whole included patients. Disseminated PTLD was diagnosed when it was declared by the authors or at least three different organs (Different lymph node areas were excluded from analysis due to lack of knowledge on how to categorize) were involved by PTLD, reported in 3 (10%; 31

missing data) patients. Multi organ involvement defined as involvement of more than a unique organ as well as more than one lymphatic region was available in 13 (43.3%; 31 missing data) patients.

At PTLD diagnosis, all patients were receiving and had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, and antithymocyte/lymphocyte globulin (ATG/ALG) and OKT3. More and less, a rather uniform approach was used to manage all PTLD patients in the included reports. On diagnosis of PTLDs, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; different regimens of chemotherapy with or without surgical interventions were also used for some of patients.

2.3 Response to Treatment

Response to treatment was defined as any favorable change in the PTLD lesional measures as well as patients' clinical condition; data of PTLD response to treatment was reported by authors for only 20 (33%) patients of whom 18 (90%) patients reportedly responded to anti malignancy treatment. However, we developed new criteria for defining remission rates for the study population; while remission episode was defined when patients were alive after their 24th month of PTLD diagnosis (since, all reported cases having this criterion had at least one confirmed remission episode) and no remission was defined when a patient dies within the first month post PTLD diagnosis (because among reported cases there were no patients dying at the first post transplant month and reported to have any remission episodes). According to this criteria, 26 (43%) patients represented data on remission of whom 20 (77%) had at least one response to treatment, irrespective of their future disease course. Overall mortality was 23 (53.5% of the reported cases; 19 missing data) patients; death due to PTLD was defined when 1: if authors state it or 2: when patient dies within 6 months post diagnosis 3: when patients die due to PTLD treatment complications. Overall 18 (78.3% of the whole mortality rate) patients died due to the disease based on the abovementioned criteria.

2.4. Statistical Analysis

Software used for data analyses was SPSS v.13.0. Statistical differences between patients'

subgroups were performed by using χ^2 and Fishers' exact tests for proportions and the Students t test for continuous data. Mann-Witney U test did not change the results. Survival analysis was done with life tables and Kaplan-Meier methods and log-rank test. All statistical tests were performed at the 0.05 significance level.

3. RESULTS

Overall 61 patients with lymphoproliferative disorders after renal (28 patients; 46%), simultaneous kidney-pancreas (1 patient; 1.6%), heart (23 patients; 38%), small intestine (1 patient; 1.6%), lung (6 patient; 10%), bone marrow (1 patient; 1.6%), and peripheral stem cell (1 patient; 1.6%) transplantation were entered into analysis. Mean age at diagnosis of PTLD was 46 ± 16 years. The mean interval between transplantation and the diagnosis of PTLD was 50 ± 42 months whereas follow up time after diagnosis of PTLD was 17 ± 24 months.

Patients and disease characteristics of the HCV positive organ transplant recipients are summarized in Tables 1 and 2. Analysis showed that HCV positive patients were significantly younger at the time of transplantation ($p=0.042$); and relatively had shorter time from transplantation to PTLD although significance level was not achieved ($p=0.064$); Table 3. No other difference was observed between HCV positive and negative transplant recipients developing PTLD in their disease course (Table 3). No priority regarding organ involvements by the PTLD was detected. Due to the low rate of final outcome report, survival analysis was not performed. Table 3 compares characteristics of PTLD patients with positive or negative test results in the study population.

4. DISCUSSION

PTLD represents a potentially fatal disorder that occurs after organ transplantation ranging from early polyclonal lesions to monomorphic high-grade neoplastic disorders with cytologic and histopathologic evidence for a malignant lymphoma. The development of PTLD is described to be associated with an imperfect cellular immune response due to several interfering factors including potent immunosuppressants employed to prevent graft rejection as well as viral infections and most notably EBV. The prevalence of PTLD ranges

from 1% to 20% among all solid-organ transplants. As mentioned above, PTLD is generally considered a life threatening complication for organ transplant recipients for which the mortality rates can raise to as high as 50% to 80% [26-29]. Although the highest incidence of PTLD has been observed during the first year, the risk remains high in the subsequent years. At 10 years, the relative risk is 11.8-fold greater than persons in the nontransplant population [26]. The prevalence of PTLD among renal transplant recipients is reported about 5% [30]. The number of studies reporting HCV positive tests in non-liver transplant PTLD post renal transplantation in the literature is quite limited, so our knowledge on it is incomplete. PTLD.Int. survey was an attempt at gathering international data from PTLD patients to conduct analyses on the largest possible patient population to discover new perspectives on the disease, based on the existing data in the literature. To our knowledge, this report deals with the largest ever PTLD population with HCV positive test results in non-liver transplant recipients to discover various aspects related to PTLD presenting in HCV positive organ transplant patients.

Through our review of the literature, we only found 9 HCV positive non-liver organ recipients; this probably does not only indicate a very low incidence of HCV infection among this population; although, that can be one reason for. However, the more potential reason for this observation is that authors do not report HCV test results in their non-liver transplant study population; because they have nothing to do with it. HCV is supposed to be an important player in inducing morbidity and mortality in liver recipients with or without PTLD. So authors have no intention to report or even examine their non-liver PTLD patients' status regarding HCV. This further limits our knowledge on any potential impact of HCV infection on features, extent and prognosis of PTLD in this patient population. On the other hand, in non-transplant settings, HCV is demonstrated as a provocative agent in inducing B cell line lymphoproliferation and non-hodgkin's lymphoma [13,31-36]. So, we could expect it to play a major role in inducing PTLD or at least to shorten time from transplantation to PTLD development; or may be to worsen the prognosis; as it is demonstrated for EBV, as a confirmed predictor for PTLD, that it shortens PTLD appearance time [37,38].

Table 1. Baseline characteristics of 9 HCV positive recipients of non-liver allograft

No.	Study reference	Induction	IS*	Allograft	Age (Y)	Gender	Time to PTLD (MO)	Histopathology	Organ failure reason
1	[16]	-	-	Renal	55	M	108	Hodgkin like lymphoma	-
2	[17]	-	FK-506	Renal	51	M	97	Diffuse large B cell lymphoma	Nephroangiosclerosis
3	[18]	ATG OR OKT3	-	Heart	65	M	70	Polymorphic lymphoma	-
4	[18]	ATG OR OKT3	-	Heart	19	M	6	polymorphic lymphoma	-
5	[18]	ATG OR OKT3	-	Heart	46	M	76	polymorphic lymphoma	-
6	[19]	ALG + OKT3	AZA	Renal	11	M	72	-	Posterior urethral valves
7	[20]	ALG	AZA	Renal	19	M	192	follicular pattern	chronic pyelonephritis
8	[21]	-	AZA	lung	15	M	46	burkitt lymphoma	Cystic fibrosis
9	[22]	-	-	BM	47	M	3.7	-	Myelodysplastic syndrome

IS, Immunosuppression; mo, months; ATG, antithymocyte globulin; ALG, antilymphocyte globulin; AZA, azathioprine.

Table 2. PTLD characteristics of 9 HCV positive recipients of non-liver allograft

No.	Site of disease	EBV	Treatment strategy	Remission	Outcome	Survival after diagnosis (MO)
1	Bone marrow, Abdominal lymph nodes	Yes	-	-	-	-
2	Thorax wall and retroperitoneal	No	CHOPS; reduction IS	Partial remission	Alive	17
3	Intestine	Yes	VECOP-B; STOP; AZA	-	-	-
4	Intestine	Yes	STOP AZA	-	-	-
5	Lymph node	Yes	VECOP-B; STOP AZA, decrease in CSA; radiotherapy	-	-	-
6	Axillary adenopathy, splenomegaly and bulky right mediastinal	Yes	(ABVD); valacyclovir	-	Alive	120
7	Unilateral cervical only; other organs and BM negative	Yes	Only reduction IS	Partial remission	Alive	12
8	Lytic lesion in 2nd RIB and extrapleural mass	Yes	Chemotherapy	-	Died	-
9	Pulmonary nodules	Yes	Rituximab	Complete remission	Alive	12

EBV, Epstein Barr virus; CHOP, mo, months; cyclophosphamide, doxorubicin, vincristine, and prednisone; IS, immunosuppression; VECOP-B, vincristine, etoposide, cisplatin, epirubicin, cyclophosphamide, bleomycin and prednisone; AZA, azathioprine; CsA, cyclosporine A, ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

Table 3. Characteristics of PTLD patients with HCV positive and negative results

Variables	HCV positive		HCV negative		+Sig.
	Value	Available data	Value	Available data	
Age (yr)*	36.4±20.3	9	49.1±14.6	31	0.042
Gender male (%)	9 (100)	9	21 (75)	28	0.16
Time to PTLD development (mo)*	74.5±56.9	9	46.3±38.5	52	0.064
Multi organ involvement (%)**	3 (50)	6	10 (41.7)	24	1.0
Disseminated PTLD (%) **	0	3	3 (11.1)	27	1.0
Early onset (within first 12 months post TX)	2 (22.2)	9	11 (21.2)	52	1.0
Monomorphic lesions (%)	1 (14.3)	7	9 (39.1)	23	0.515

**Mean±SD; **according to the criteria defined in the methods section; HCV, hepatitis C virus; PTLD; posttransplant lymphoproliferative disorders; mo, months; TX, transplantation; yr, year.*

In the current study, the rate of monomorphic malignant lesions was not different between the two study groups; however, interestingly, in the current study of limited data, we found that time to PTLD development was relatively shorter in the HCV positive PTLD group; although it did not reach significance level. Nevertheless, we found no disparity regarding other PTLD parameters between this study's groups. A younger age for HCV positive patients seemed to be just incidental, or we have no description for it.

Potential criticisms may arise over our study. First, our study population was gathered from different reports with inconsistent approaches. We also believe that this is the unique major limitation for this study leading to substantial missing data for some of study variables and thus, decreasing the power of our analyses. This limitation was most prominent for special data that is not typically included in reports on PTLD patients. Another limitation due to the inconsistencies available between included studies was that results of different studies were not presented in the same way. For example, report of any response to treatment was presented very dissimilarly in different studies; while in one study partial and complete remission was used to translate the results, in another only "response to treatment" was used and in some others no specific terminology was employed. So we ought to invent new methods to cumulate the existing data for analysis.

5. CONCLUSION

In conclusion, we found that HCV positivity has a tendency to reduce the time interval between transplantation and PTLD development which future studies should investigate whether our finding can be interpreted as HCV can enhance the rate of PTLD in non-liver transplant recipients. To the best of our knowledge, our study presents the first evidence for HCV relationship with PTLD in non-liver transplantation setting. However, due to the limited population size of the current study, our findings may not strongly confirm any associations between HCV and PTLD in the mentioned population and future studies with prospective designations are needed to confirm our results.

CONSENT

The article needs no consent document.

ETHICAL APPROVAL

No ethical issue has been arisen in our study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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