Study of Some Lymphoproliferative Clonal Markers Following Renal Transplantation

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Abstract: Post-renal transplant lymphoproliferative disorders (PTLDs) is a well known category among all the other lymphoproliferative disorders. The cause of this complication is mainly due to long term immunosuppression, and infection particularly by Epstein-Barr virus. The aim of this work is the early recognition of clonal changes for early therapeutic intervention as most of these changes are polyclonal. Yet the transition to oligo – and subsequent monoclonal is important for follow up with the other investigation to reach the proper diagnosis. This study compromised sixty post – renal transplantation patients , they were selected from impatient and outpatient clinics of Urology and Nephrology Center, Mansoura Faculty of Medicine. Those patients were compared to (10) de novo Non – Hodgkin lymphoma patients served as a positive control group. These patients were subjected to the following clinical laboratory studies; *full history taking, clinical examination, Routine laboratory investigation and Flow cytometry for CD19, CD20 and light chain immunoglobulin Kappa/Lambda.* There is a high statistically significant increase in CD19 (41.2817 $\pm$ 15.1199 ,21.5000 $\pm$ 2.9533), CD20 (37.9917 $\pm$ 14.7690 , 21.700 $\pm$ 2.7909) in patient compared to healthy group respectively, there is a statistically significant difference in Kappa/Lambda ratio (1.3240 $\pm$ 0.6554 , 2.1210 $\pm$ 0.4968, 1.6310 $\pm$ 1.5354) in patients when compared to both the healthy group and the lymphoma patients. There is statistically significant decrease in CD19, CD20 in patients group in comparison to lymphoma patients (P0.0001), also there is high statistically significant decrease in CD19, CD20 in healthy controls in comparison to lymphoma patients (P0.0001). From these results, we conclude that some of these post – renal transplant patients had abnormal hematological findings in the form of oligoclonality , which may lead to subsequent hematological malignancies. These patients should undergo periodical flow cytometric analysis to reveal if there are any clonal changes.

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Introduction

Post-renal transplant lymphoproliferative disorders (PTLDs) is a well known category among all the other lymphoproliferative disorders[1]. The cause of this complication is mainly due to long term immunosuppression, and infection particularly by Epstein-Barr virus[2][3]. Early recognition of clonal changes is very important for early therapeutic intervention as most of these changes are polyclonal. Yet the transition to oligo- and subsequent monoclonal is important for follow up with other investigations to reach the proper diagnosis[4]. In the case of renal allograft, 6% of patients developed PTLD within 6 months of transplantation, but the mean time was 32 months. It was noted that patients treated with Cyclosporin had a mean time of 5 months to development of PTLD[5]. Survivors were more likely to have a shorter time interval to development of PTLD than those who died, they were more likely to have polyclonal lesions and B-cell hyperplasia, and they were more likely to have involvement of graft or lymph nodes[6]. Several different classification schemes for PTLD have been proposed in order to compare outcomes and determine prognosis. Most of these schemes are based on the following characteristics: clinical, histological, immunologic cell typing, cytogenetic, immunoglobulin gene-rearrangement, and virologic. The different schemes identify either 3 or 4 distinct categories. The classification schemes have common features, including that of benign hyperplasia or mononucleosis as the mildest form, characterized by maintenance of the nodal architecture; malignant lymphoma, with all the features of malignancy, as the most severe form; and polymorphic or polyclonal proliferations (with nodal architecture destruction and local invasion) classified in the intermediate categories,[7],[8] Flow cytometry is a quicker method of analysis and provides more extensive antigen expression information,[9]. This has triggered us to screen patients for lymphoproliferative cell markers after renal transplantation, especially those with long term survival by flow cytometry.

Materials and Methods

This work was carried out at Clinical Pathology Department, Mansoura University Hospital, Mansoura. This study comprised (60) post-renal transplantation patients, they were selected from inpatient and outpatient clinics of Urology and Nephrology center, Mansoura Faculty of Medicine. Those patients were compared to (10) healthy individual served as a negative control group and (10) de novo Non-Hodgkin lymphoma patients served as a positive control group. Written consents were obtained from all the patients & controls subjected to the investigations in this study.

These patients were subjected to the following clinical & laboratory studies:

Full history taking: including name, age, sex, renal problems and manifestations, besides history, date of transplantation, distressing symptoms and signs, immunosuppression regimen.Clinical examination of organomegally and lymphadenopathy. Laboratory investigations: *Routine laboratory investigations, investigations for diagnosis of lymphoproliferative disorders.* Four mls of venous blood were collected from each case & control by clean venipuncture using plastic disposable syringes. Blood was withdrawn slowly without venous stasis and care was taken to avoid frothing. Then, each blood sample was divided into tubes as follows: Two mls of blood were delivered into plastic tube containing dipotassium EDTA solution for performing complete blood picture and immunophenotyping. Two mls of blood were allowed to clot for 30 minutes before centrifugation for 10 minutes and serum was taken for the following: Determination of serum creatinine.

Routine laboratory investigations:

Hematologic; Done for each patient and control person using electronic counter (Coulter) (Onyx, France) and the following parameters were determined Hemoglobin (Hb), total and differential leukocytic count and platelets. Biochemical; Kidney function test (Serum creatinine): Creatinine was done using Jaffe's deproteinization methods (Roche) (Mannheim, Germany)[(10)].

Immunophenotyping:

Different monoclonal antibodies labeled with FITC or PE, B cell markers: CD19, CD20, K and λ light chains.

Method of surface marker antigen staining[(11)]:

100µl of whole blood containing up to $1x10^6$ leucocytic cells with 10µl of monoclonal antibody were put in one tube & 10µl of isotypic control in another tube. Both tubes were incubated in the dark at 4°C for 30 minutes.2 ml of red cell lysis was added then centrifuged for 5 minutes then decant. Both tubes were washed twice with PBS containing 2% bovine serum albumin.300µl of PBS with 0.5% paraformaldhyde was added.Then analyze on a flow cytometer.

Results

Table I shows that there was no statistically significant difference between the three groups regarding the age.

Table I: Age of patient and control groups

	Number of cases	**Age** **Mean and SD**
Patient	60	38.6 ± 9.6
Negative control	10	41.7 ± 7.8
Positive control	10	42.1 ± 8.3
Total	80	39.4 ± 9.2
F test for the age of the three groups		**P value = 0.406**

Table II shows that there was no statistically significant difference between the three groups regarding the sex.

Table II: Sex of patient and control groups

		SEX		Total
		Male	Female	
Patient	***Number***	46	14	60
	%	77%	23%	100%
Negative control	***Number***	6	4	10
	%	60%	40%	100%
Positive control	***Number***	7	3	10
	%	70%	30%	100%
Total	***Number***	59	21	80
	%	74%	26%	100.0%
Pearson Chi-Square test for the sex of the three groups				**P value = 0.519**

Table III shows that there is a statistically significant difference in Hb level (p = 0.002), TLC (p = 0.001) and serum creatinine (p = 0.042) the patient group in comparison to the healthy control group.

Table III: Some routine laboratory parameters in patients and healthy control groups.

		Number	Mean	± S.D.	
S. creatinine mg/dl	***Patients***	60	1.9	1.5972	t test = 2.073 p value = 0.042*
	Healthy controls	10	0.8600	0.2221	
Hb g/dl	***Patients***	60	12.4500	2.2496	t test = 3.178 p value = 0.002*
	Healthy controls	10	14.7500	0.8580	
TLC	***Patients***	60	10201.7	2501.5	t test = 4.556
	Healthy controls	10	6490.0	1399.4	p value = 0.001*

Table IV shows the flowcytometric study of the CD19, CD20 and Kappa/Lambda ratio in the three groups. Regarding CD20, in patients group (37.9917 ± 14.7690), in healthy controls (21.7000 ± 2.7909) and in Lymphoma patients (74.2000 ± 13.1132).Regarding CD19, in patient group (41.2817 ± 15.1199), in healthy controls (21.5000 ± 2.9533) and in lymphoma patients (72.5000 ± 13.3187). Regarding the Kappa/Lambda ratio, in the patient group (1.3240 ± 0.6554), in the healthy controls (2.1210 ± 0.4968) and in lymphoma patients (1.6310 ± 1.5354).

Table IV: Results of CD20, CD19 and the Kappa/Lambda ratio in the three studied groups.

		Number of cases	Mean	± S.D.
CD20				
	Patients	60	37.9917	14.7690
	Healthy controls	10	21.7000	2.7909
	Lymphoma controls	10	74.2000	13.1132
CD19				
	Patients	60	41.2817	15.1199
	Healthy controls	10	21.5000	2.9533
	Lymphoma controls	10	72.5000	13.3187
Kappa/Lambda ratio				
	Patients	60	1.3240	0.6554
	Healthy controls	10	2.1210	0.4968
	Lymphoma controls	10	1.6310	1.5354

Table V shows that there is a statistically significant increase in CD20 in patients group in comparison to healthy group (p = 0.001), while there is a high statistically significant decrease in CD20 in patients group in comparison to lymphoma patients (p=0.0001). Also there is a high statistically significant decrease in CD20 in healthy controls in comparison to lymphoma patients (p=0.0001).

Table V: CD20 in patients, healthy controls and lymphoma patients.

CD20			**Mean**	**± S.D.**	**p value**
	Patients	**Healthy controls**	16.2917	4.6851	0.001*
		Lymphoma controls	36.2083	4.6851	0.0001*
	Lymphoma controls	**Healthy controls**	52.5000	6.1342	0.0001*

Table VI shows that there is a high statistically significant increase in CD19 in patients group in comparison to healthy group (p = 0.0001), while there is a high statistically significant decrease in CD19 in patients group in comparison to lymphoma patients (p = 0.0001). Also there is a high statistically significant decrease in CD19 in healthy controls in comparison to lymphoma patients (p = 0.0001).

Table VI: CD19 in patients, healthy controls and lymphoma patients.

CD19			**Mean**	**± S.D.**	**p value**
	Patients	***Healthy controls***	19.7817	4.7931	0.0001*
		Lymphoma controls	31.2183	4.7931	0.0001*
	Lymphoma controls	***Healthy controls***	51.0000	6.2757	0.0001*

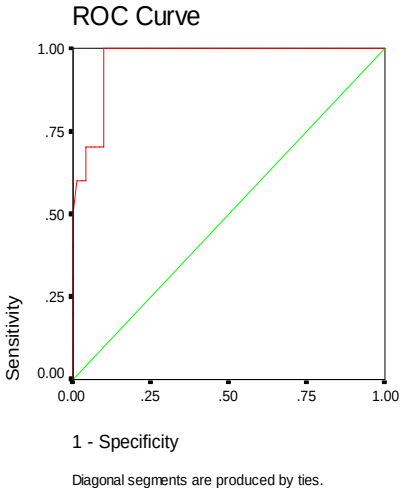
Table VII shows that there is a statistically significant difference in Kappa/Lambda ratio in patients group in comparison to healthy group (p = 0.004), and in comparison to lymphoma patients (p = 0.002). Also there is a high statistically significant difference in Kappa/Lambda ratio in healthy controls in comparison to lymphoma patients (p = 0.0001).

Table VII: Kappa/Lambda ratio in patients, healthy controls and lymphoma patients.

Kappa/Lambda ratio			**Mean**	**± S.D.**	**p value**
	Patients	***Healthy controls***	0.7970	0.2719	0.004*
		Lymphoma controls	0.3070	0.2719	0.002*
	Lymphoma controls	***Healthy controls***	0.4900	0.3560	0.0001*

Figure I shows the specificity and sensitivity of CD19 from which we can assume a cut off point at which the sensitivity of the test is 70 % and the specificity is 96 %, so that all the patients under immunosuppressive drugs should be taken care of specially with repeated flowcytometry of the CD19 together with the light chains Kappa and Lambda every 6 months.

Area Under the Curve

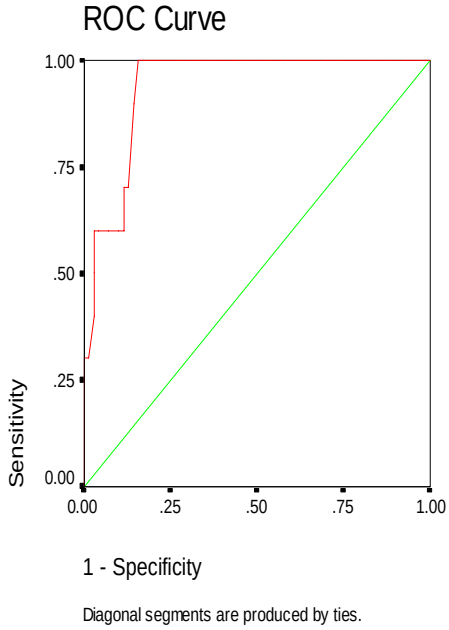


Area	Std. Error	Asymptotic Sig.
0.965	0.020	0.0001

The cut off point = 64.6500

Figure I: Specificity and sensitivity of the CD19.

Figure II shows the specificity and sensitivity of CD20 from which we can assume a cut off point at which the sensitivity of the test is 70 % and the specificity is 89 %, so that all the patients under immunosuppressive drugs should be taken care of specially with repeated flowcytometry of the CD20 together with the light chains Kappa and Lambda every 6 months.



Area	Std. Error	Asymptotic Sig.
0.939	0.028	0.0001

Figure II: Specificity and sensitivity of the CD20. **Area Under the Curve.** ***The cut off point = 60.5***

Data Analysis

Data was analyzed using SPSS (Statistical package for social science) version 9.5. Variability was presented as mean ± SD and percentage data was compared using Student's t – test or Chi square (χ^2) – test as appropriate. A $p \leq 0.05$ was considered to be statistically significant.

Discussion

Renal transplantation is the present-day, state-of-the-art therapy for patients with end-stage renal disease[12] The history of successful renal transplantation parallels the advancement of transplantation immunobiology. Experiments in the early 1900s and continued advances in surgery, nephrology, and immunology helped accomplish this feat ***(Port et al.,).*** Kidney transplantation should be strongly considered for all patients who are medically suitable with chronic and end-stage renal disease (ESRD)[13]. A successful kidney transplant offers enhanced quality and duration of life and is more effective (medically and economically) than chronic dialysis therapy. Transplantation is the renal replacement modality of choice for patients with diabetic nephropathy and pediatric patients. Currently in the US, more than 80,000 persons are living with a functioning kidney transplant. This number represents 27% of the nearly 300,000 persons enrolled in the US ESRD program. In the US: The overall rate of ESRD is approximately 735/1,000,000. As the end-stage population continues to increase, projections estimate that the current population of 372,407 will exceed 660,000 by the year 2010[14]**.** Graft prognosis is directly related to the source of the donor kidney: recipients of cadaveric kidneys generally have more episodes of rejection and lower graft survival rates. The graft survival rate for kidneys from living donors is approximately 95% at 1 year and 76% at 5 years, whereas the graft survival rate for kidneys from cadaveric donors is 89% at 1 year and 61% at 5 years[15]**.** The major causes of morbidity after renal transplantation are hypertension (occurring 75-85% of all renal transplant recipients), hyperlipidemia (60%), cardiovascular disease (15.8-23%), diabetes mellitus (16.9-19.9%), osteoporosis (60%), and malignant neoplasm (14%)[15]**.** The +9 of immunosuppression on the incidence of de novo neoplasms among kidney recipients should be monitored continuously[16]**.** Transplant recipients are at significantly higher risk for cancers than the general population because of (1) chronic immunosuppression, (2) chronic antigenic stimulation, (3) increased susceptibility to oncogenic viral infections, and (4) direct neoplastic action of immunosuppressants. Transplant recipients have a significant overall 2-5 fold higher risk in both sexes for cancers of the colon, larynx, lung, and bladder and in men for cancers of the prostate and testis. Especially high risks, 10-30 fold, exist for cancers of the lip, skin (nonmelanoma), kidney, endocrine glands, non-Hodgkin lymphoma, and, in women, cervix and vulva-vagina[15]**.** Lymphoid malignancies such as post-transplant lymphoproliferative disease (PTLD) are a major complication of solid organ transplantation[17]**.** The incidence of neoplasms among transplanted patients is increasing, being estimated at between 4% and 18% (mean = 6%). The neoplasms were reviewed in 2514 patients who underwent transplantation in Juan Canalejo hospital, Coruna, Spain; between 1981 and 2002 including 1579 kidneys, 418 hearts, 430 livers, 70 lungs, and 17 pancreases. They observed 170 tumors in 117 patients. The most frequent neoplasm was skin and lip carcinoma (30 patients) followed by PTLD (18 patients)[18]**.**In this study the patients were screened for Post-renal Transplant Lymphoproliferative Disorders (PTLD) using the clonal markers useful in the diagnosis of PTLD to evaluate the immunophenotypic patterns by multi-parameter flowcytometric analysis. The present study was conducted on 60 post-renal transplantation patients under immunosuppressive therapy; they were selected from the out-patient clinic of the Urology and Nephrology Center-Mansoura Faculty of Medicine. Their ages ranged from 20 to 64 years (38.6 ± 9.6 years). In addition, 10 healthy subjects were selected to act as a negative control group, their ages ranged from 19 to 61 years (41.7 ± 7.8 years) and 10 patients suffering from de novo Non-Hodgkin lymphoma were selected to act as a positive control group, their ages ranged from 24 to 72 years (42.1 ± 8.3 years).Each patient and control was subjected to full history taking, clinical examination, routine laboratory investigations and the detection of CD19, CD20 and the surface Immunoglobulin light chains Kappa and Lambda by using specific monoclonal antibodies on flow cytometry. We selected the above mentioned markers because the B-cell lymphoproliferative disorders are the commonest among the post transplant lymphoproliferative disorders. In the present study, the routine laboratory investigations show that there are statistically significant differences in HB level, total leucocytic count (TLC) and serum creatinine level between the patients and the healthy control group (table III), and this is because of these patients suffered from renal failure besides they are under immunosuppressive therapy. The present work reveals statistically significant increase in CD19 and CD20 in patients compared to the healthy group, while it shows a significant decrease when compared to the de novo Non-Hodgkin lymphoma patients (table V, VI); also there was a statistically significant difference in Kappa/Lambda ratio in patients compared to healthy

group and the de novo Non-Hodgkin lymphoma patients. From the results obtained by the flow cytometric studies of CD19, CD20 and the light chains κ and λ in the post-transplant individuals and the two control groups, it is clear that there is a significant increase in the expression of the B- lymphocyte surface markers that occur after solid organ transplantation, where we found that there are 6 patients have CD19 and CD20 expression over our proposed cut off value (64.65 and 60.5 respectively). These cut off values are obtained from the ROC curve using all the values of the CD19 and CD20 expression of all the three groups (figures I, II). The same findings were reported by ***Cockfield***[19] who mentioned that the post-transplant lymphoproliferative disorders (PTLD), include a spectrum of disease ranging from benign polyclonal B cell hyperplasia to malignant monoclonal Non-Hodgkin's lymphoma. Overall, the incidence of PTLD is 25- to 100-fold greater than that of Non-Hodgkin lymphoma in age-matched controls. However, the study comprised a large number of cases. Emerging data suggest that certain interventions may be able to reduce the incidence of this potentially fatal complication, particularly during the first post-transplant year when the impact of aggressive immunosuppression and EBV infection is greatest. These strategies include modifications to immunosuppressive protocols, enhanced post-transplant monitoring for EBV activity, and prophylactic or pre-emptive therapy of EBV infection[20]. The risk of PTLD in an individual patient is also strongly influenced by the type of organ transplanted. Although the incidence of PTLD is greatest during the first post-transplant year, the increased risk attributable to the type of organ transplant is not limited to this time period. This is best illustrated by data derived from more than 50,000 transplanted individuals by the Collaborative Transplant Study Group. In this cohort, cardiac allograft recipients experienced a 3-fold greater incidence of PTLD overall when compared to recipients of renal transplants. Although the rate of PTLD declined substantially after the first post-transplant year in both groups, cardiac transplant recipients continued to develop this complication at a rate 7.7-fold that of their renal counterparts. In general, renal allograft recipients experience the lowest incidence of PTLD and recipients of lung or intestinal transplants, alone or in combination with other organs, the highest. Chronic stimulation of the immune system by antigenic differences between the donor-recipient pair may promote polyclonal B cell proliferation and predispose to the development of PTLD. This immunologic imbalance may be amplified by the subsequent allogeneic response. High levels of expression of IL-4, IL-6, and IL-10 have been reported in some individuals with early or aggressive PTLD. These cytokines serve as autocrine or paracrine growth factors for EBV-transformed B cells in vitro and may promote uncontrolled lymphoproliferation or interfere with apoptosis of EBV-infected B cells in vivo. Polymorphisms have recently been identified in certain cytokine genes, including IL-10, IL-6, and IFN-γ. These polymorphisms may dictate inter-individual variations in cytokine expression, potentially influencing both the predisposition to disease and clinical outcome. PTLD was first described in solid organ transplantation in the pre-cyclosporine era, suggesting that any immunosuppressive agent that blunts cellular immunity to EBV constitutes a risk factor. Lymphomas occurring late post-transplant are less predictable; older recipient age and duration of immunosuppression are the only risk factors currently recognized. Therefore the real opportunities for significant intervention appear to be limited to those variables promoting the development of early PTLD. Also ***Opelz and Döhler***[21] published the collected data from 271 centers in 42 countries about 195 938 solid organ transplantation cases, including 145,104 cases of renal transplantation; to clarify the incidence, risk factors, and outcomes of post transplantation NHL, they found that the cumulative 10-year incidence of Non-Hodgkin lymphoma in kidney recipients transplanted between 1985 and 2001, showed that, although the incidence was highest in the first post-transplant year, there was a steady increase in Non-Hodgkin lymphoma cases over 10 years, where the incidence of Non-Hodgkin lymphoma was 11.8-fold, that in a non transplant population matched for age, gender and geographical origin. Also, they found that the incidence, risk factors, and outcomes for post-transplant Non-Hodgkin lymphoma are difficult to assess because results have often been derived from small series or because the duration of follow up was not considered. Their results showed that lymphomas pose a continuing long-term risk after transplantation and underscore the importance of recognizing the changing nature of Non-Hodgkin lymphoma development with time post-transplantation. On the other hand ***Kaleem et al***[22] published that both polymorphic and monomorphic PTLDs show a higher incidence of lack of CD20 and surface immunoglobulin light-chain expression. The lack of CD20 expression in these lesions may be due to therapeutic implications, since anti-CD20 antibody was given to these patients, as it is one of the recent lines of treatment of the B-cell lymphoproliferative disorders, including posttransplant disorders. Transplanted patients receiving immunosuppression have a tendency to develop changes in CD19, CD20 and the surface light chains Immunoglobulins Kappa and Lambda expression. This

could precede the development of lymphoproliferative disorders.

Conclusion

Knowledge of the EBV status of donors and recipients is essential to evaluate individual patient risk and routine viral monitoring is essential to permit early identification of viral activity and Post-renal transplant patients should undergo routine periodical flow cytometric analysis to reveal if there are any clonal changes. If the expression of CD19 or CD20 exceeds the cut off values we stated in this study, these patients should be restrictly followed up every 3 months. Further studies should be conducted on the Post-renal transplant patients to investigate all the suspected risk factors that may predispose to the development of post-transplant lymphoproliferative disorders.

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