Original Research
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Relationship between post-transplant lymphoproliferative disorder and Anti-Thymocyte Globulin or Anti-Lymphocyte Globulin

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Abstract

Background: Lymphoproliferative disorders are among the most serious and potentially fatal complications of chronic immunosuppression in kidney transplant recipients. The principle risk factors for development of PTLD are the degree of overall immunosuppression and the EBV serostatus of the recipient. In this study, the risk of PTLD in kidney transplant recipients who received Anti-Lymphocyte Globulin (ALG) or Anti Thymocyte Globulin (ATG) was evaluated.

Methods: We retrospectively studied 520 patients who underwent kidney transplantation during the period from December 1989 to December 2002, at Taleghani Hospital, Tehran.

Results: 369 patients received classic immunosuppression (prednisolone, cyclosporine, mycophenolate mofetil) and 151 patients (29%) received classic immunosuppression with ALG or ATG. Eight patients had developed PTLD, 5 cases of which (62.5%) received classic immunosuppression without ALG or ATG. Incidence of PTLD was 3.3 percent in patients who received ALG or ATG and 0.8 percent for those patients who did not receive ATG or ALG. This difference is very significant ($p < 0.05$).

Conclusion: ALG or ATG therapy could act as a risk factor for PTLD.

Keywords: PTLD (Post-transplant lymphoproliferative disorder), ATG (Anti-Thymocyte Globulin), ALG (Anti-Lymphocyte Globulin)

Introduction

Malignancy is the fourth main cause of death in kidney transplant recipients within long-term and 26% of deaths in patients whose transplanted kidney has been functional for more than 10 years are due to malignancies [1]. Overall, the risk of malignancy is 3-5 times more than the general population [2]. Post-transplantation lymphoproliferative disorders (PTLD) are the most common form of malignancy after skin and lip malignances and constitute 21% of all malignancies, comparing to 5% of malignancies in the normal population [3,4,5].

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In recent years the incidence of PTLD is increasing which is concurrent with the increasing use of more potent immunosuppression regimens especially cyclosporine and Anti-lymphocytic Antibody (Anti-LyAb) [1,6]. Countries like the US in which the above mentioned medications are being used more have a higher incidence of PTLD than Europe in which substances like ALG are rarely used [1].

Higher doses of ATG or ALG and repeated courses of these agents apparently cause higher rates of viral infection and PTLD [1].

Overall, the incidence of PTLD is about 1-3%, which is 30-50 times more than the general population and recently its incidence is growing. In patients with more intensive immunosuppression the risk of PTLD is higher [5]. Decreased immunity reduces the ability to confront with various carcinogens. Infections due to various viruses are common in immunosuppressed patients. For example, EBV infection may end up in non-Hodgkin and occasionally Hodgkin's lymphoma. Other risk factors include CMV sero-mismatch, HHV8 (Human Herpes Virus8) and Helicobacter pylori [5].

The aim of our research was to study the relationship between post-transplantation lymphoproliferative disorders and the level of immunosuppression including the use of ALG or ATG.

Methods

Our study involves kidney transplant recipients in Taleghani Hospital from December 1989 until December 2001 (when this study was conducted). It is a retrospective descriptive study and is based on the data available from patients' charts. First, the number of patients who had used immunosuppression regimens including Im-

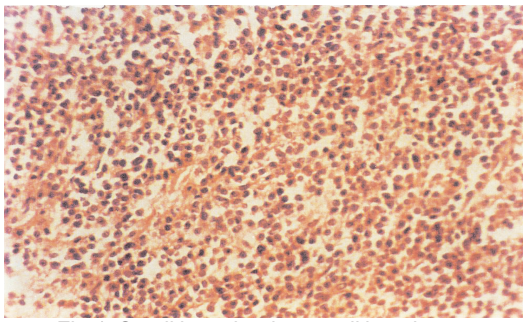

Fig.1. Small intestine-large cell lymphoma

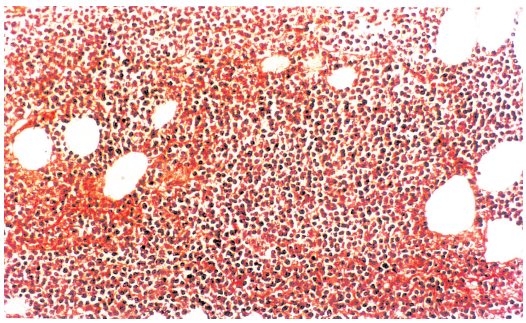

Fig. 2. Small intestine-large cell lymphoma

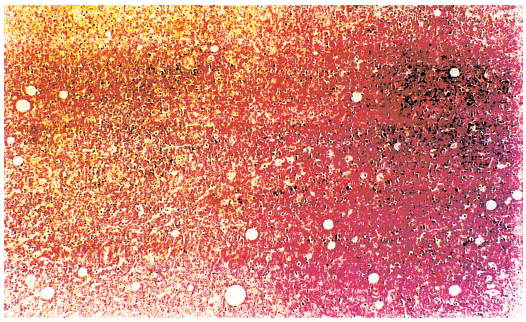

Fig. 3. Omentum-Burkitt's lymphoma (×25)
(a 17 year old boy with vomiting and diarrhea)

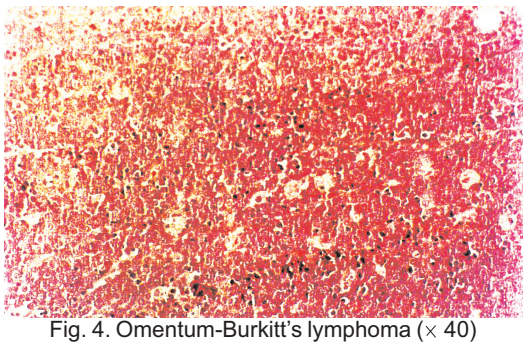

Fig. 4. Omentum-Burkitt's lymphoma (× 40)
(a 17 year old boy with vomiting and diarrhea)

muran, prednisolone and cyclosporine without ALG or ATG as well as the number of patients who had received ALG or ATG for rejection was determined. Then the number of patients who developed PTLD was determined. These patients were divided in to two groups based on their immunosuppression regimen. The first group consists of patients with PTLD whose immunosuppression regimen did not include Anti-LyAb and the second involves patients with PTLD who had received Anti-Lymphocytic Antibody as part of their immunosuppressive regimen.

Data were collected from available information recorded in patients' charts and statistical files in the Transplantation ward. In this study, we considered pathologically proven PTLD cases only. In other words patients whose PTLD diagnosis was based on pathologically studied tissue biopsies were included and those, even with a clinical diagnosis of PTLD, who had been deceased before pathology verifications could be obtained, were excluded from this study.

The diagnosis of PTLD in studied groups was based on tissue diagnosis and those patients who expired before having a tissue diagnosis were excluded from the study.

Also, the relationship between clinical manifestations and the diagnosis of PTLD as well as the type of organ involvement like GI, CNS, LN, FUO or transplanted kidney function disorder have been discussed. Excel 2000 software and the test of comparison proportions were used for statistical analysis.

Results

Overall, from December 1989 until December 2002, 520 patients (212 women and 308 men) underwent kidney transplantation in Taleghani Hospital. From this total, 151 patients (56 women and 95 men)

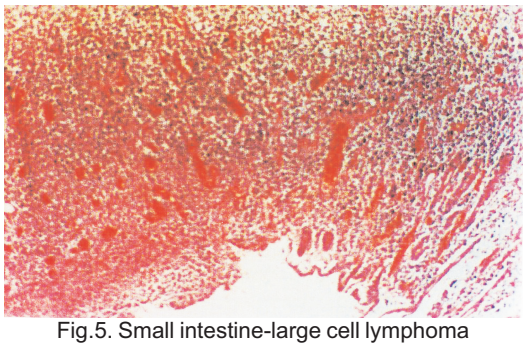

Fig.5. Small intestine-large cell lymphoma (a 47 year old female with peritonitis)

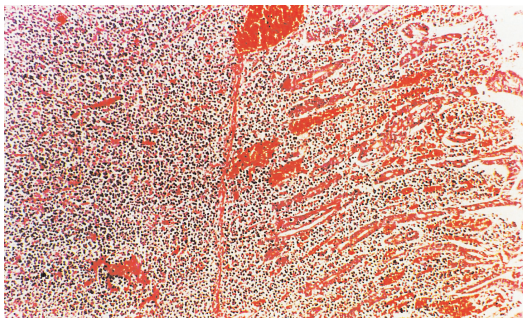

Fig. 6. Small intestine-large cell lymphoma (a 47 year old female with peritonitis)

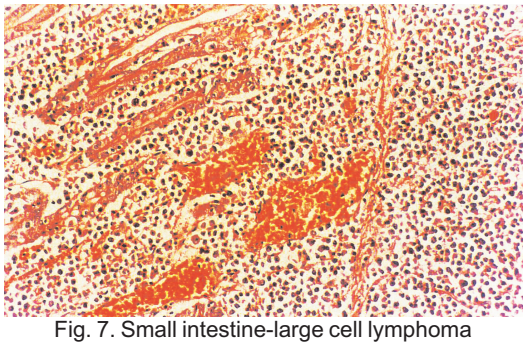

Fig. 7. Small intestine-large cell lymphoma

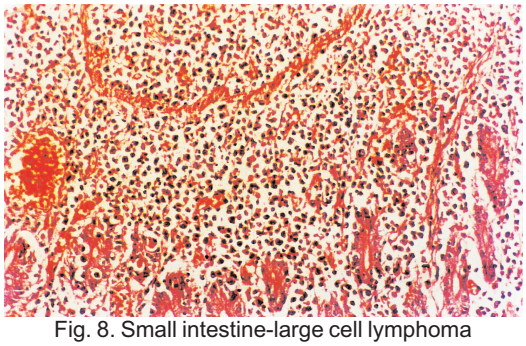

Fig. 8. Small intestine-large cell lymphoma

received Anti-LyAb (ALG or ATG) for acute rejection, in which ALG was given to 84 patients and ATG to 67 patients.

From 520 patients, 8 persons consisting of 6 females and 2 males developed PTLD, in whom the disease was pathologically confirmed. Thus, the prevalence of PTLD in 520 patients was 1.5%. The immunosuppression regimen of five out of eight patients consisted of prednisolone, Immuran, cyclosporine and ALG or ATG.

Therefore, from the 151 out of 520 patients who had received Anti-LyAb, 5 patients, i.e. 3.33% of cases, developed PTLD. Meanwhile in the second group that included 369 patients who had not received Anti-LyAb, 3 patients, i.e. 0.8% of cases were affected with PTLD. This difference was shawn to be statistically significant ($p<0.05$) meaning that in the PTLD patients the use of polyclonal antibody had a higher prevalence. Prevalence of PTLD was 3% in the group that had received ATG and 3.6% in the ALG group. Their difference was not statistically significant. The average age duration between transplantation and developing PTLD was 60 months (5 years), ranging from 6.5 months to 110.5 months.

The average age of patients developing PTLD was 35 years, ranging from 17 to 44 years. Clinical symptoms at the beginning of the disease presentation involved GI problems (50%), FUO (25%), infectious mononucleosis-like syndrome (12.5%) and CNS symptoms (convulsion) (12.5%), consecutively.

Organs from which tissue diagnosis was obtained included GI (jejunum and omentum 62.5%), biopsies from two organs simultaneously (GI and ovaries), tonsils (12.5%) and bone marrow (12.5%), consecutively. Therefore, the most common site that has helped in PTLD tissue diagnosis has been the GI tract.

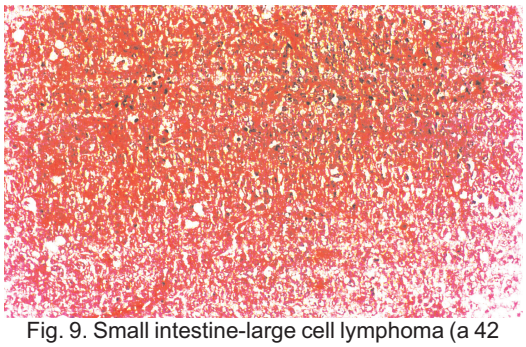

Fig. 9. Small intestine-large cell lymphoma (a 42 year old female with abdominal pain)

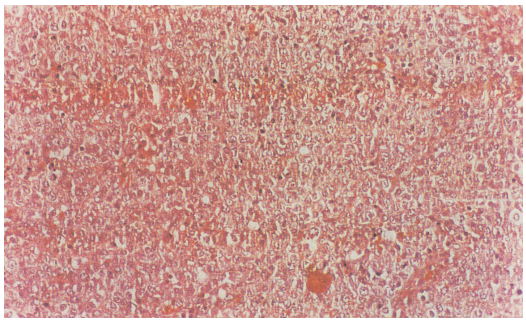

Fig. 10. Small intestine-large cell lymphoma (a 42 year old female with abdominal pain)

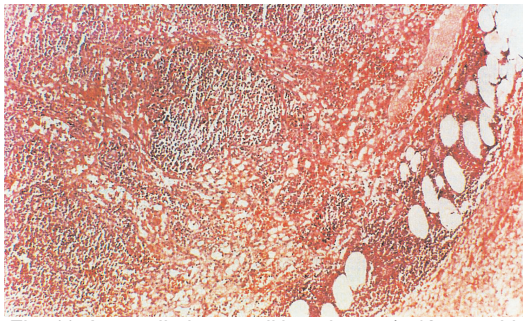

Fig. 11. Appendix-large cell lymphoma (a 42 year old female with GI, ovary and Appendix lymphoma)

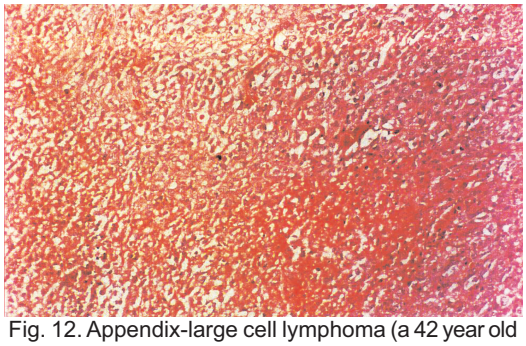

Fig. 12. Appendix-large cell lymphoma (a 42 year old female with GI, ovary and Appendix lymphoma)

One patient was suffering from CNS symptoms (convulsion) at the beginning of the disease and his brain CT scan showed a large hypodense para-ventricular lesion around the third ventricle. Three other patients developed CNS symptoms (convulsion) during the course of their disease.

Thus, 87.5% of the cases had an extranodal presentation. All 8 cases of lymphomas' were non-Hodgkin's type. Pathologically, 7 out of 8 (87.5%) cases were large cell lymphoma. One patient had received his transplanted kidney for the second time and the other 7 patients had undergone kidney transplantation for the first time.

No paraclinical signs other than pathology study of the biopsied tissue have been helpful in diagnosing PTLD. For example, none of the patients had a high ESR. Four of them had high LDH, 5 cases were hyperuricemic, 4 were pancytopenic and 2 patients had abnormal LFT .

Mean patient survival after diagnosing PTLD, despite discontinuing immunosuppression medications and receiving chemotherapy was 4 months, ranging from less than one week to 15 months.

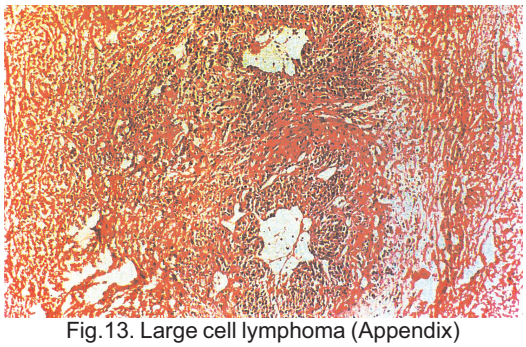

Fig.13. Large cell lymphoma (Appendix)

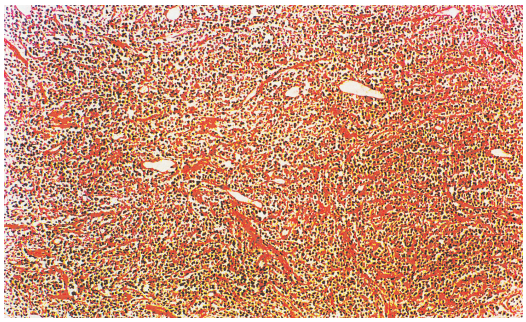

Fig.14. Large cell lymphoma (Appendix, × 25)

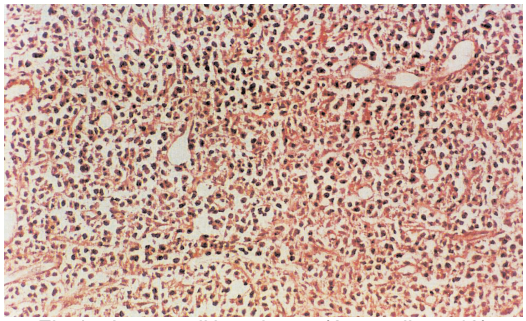

Fig.15. Large cell lymphoma (Appendix, × 40)

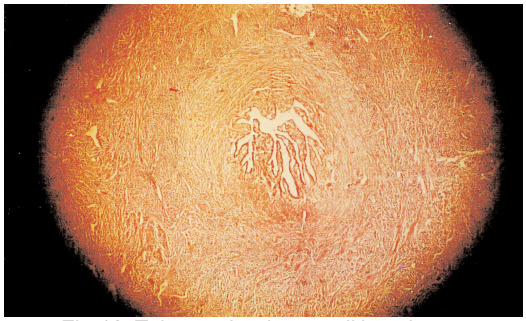

Fig.16. Tuboovarian-large cell lymphoma

Conclusion

The prevalence of PTLD after kidney transplantation is reported to be 1-3%. In this study the prevalence of PTLD appeared to be 1.5%. Prolonged use of thymoglobulin in association with other immunosuppressive agents may cause excessive immunosuppression resulting in severe infections and may increase the incidence of lymphoma or post-transplant lymphoproliferative disease (PTLD) or other malignancies [12].

Although several risk factors for PTLD after solid organ transplantation have been identified, the immunosuppressive regi-

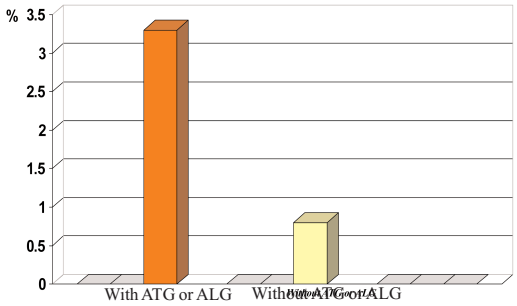

Fig.17. Prevalence of PTLD based on immunosuppression.

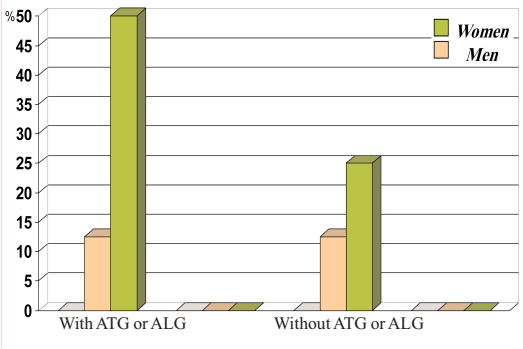

Fig.18. Prevalence of PTLD by immunosuppression and sex.

men probably is the most important one, and both forms of anti T-cell antibody therapy were independently associated with the development of PTLD [13].

Several polyclonal and monoclonal antibodies have been developed for induction therapy in the early post solid-organ transplantation period. The use of these antibodies has been associated with a simultaneous rise in infectious complications, particularly in the incidence of PTLD [14].

There is a higher adjusted relative risk for PTLD after kidney transplantation with ALG [15].

This research has answered the following questions:

1. Receiving ALG or ATG in transplant recipients could act as an important factor for increasing PTLD prevalence by intensifying immunosuppression. These immunosuppressive agents include cytotoxic antibodies against a number of T-cell markers. After their use, other than a transient leucopenia which occurs, CD4+ would be suppressed for many years. Their long-term immunosuppressive effect explains the infrequent numbers of acute rejection relapses and increased prevalence of PTLD.

2. The most important clinical indices that help in diagnosing PTLD are GI symptoms and FUO.

3. The prevalence of using ALG and ATG among PTLD patients is about 62.5% and in all patients who had received these agents PTLD occurred after one year from transplantation. There were no statistics indicating PTLD prevalence and ALG and ATG consumption in the literature for comparison.

4. The most common form of lymphoma is non-Hodgkin's lymphoma. In this study, 100% of PTLD cases were non-Hodgkin's lymphoma. About 70% of PTLD presented in extra nodal sites. In this study about 87.5% of cases were extranodal. Clinical symptoms of PTLD were different in various countries. For example in Mexico, the GI tract was reported to be the most common site involved. But in some European countries fever has been mentioned as the most common symptom [1,5,8,9]. In our country, the GI tract is probably the most frequent site involved.

5. In case of clinical suspicion of PTLD despite normal laboratory tests like LDH, uric acid, ESR and CBC and even normal biopsy results from suspected organs diagnostic evaluations should be continued thoroughly, as biopsy from one site may show polyclonal and reactive changes while biopsy from another site could show

monoclonal and totally malignant changes [10].

Considering that the majority of PTLD cases are extranodal, normal CBC and bone marrow biopsies are expectable. Taking into account that in our country the most common site of PTLD probably is the GI tract and GI lymphoma is symptom-free in early stages, in the case of clinical presumption of GI lymphoma endoscopic ultrasonography (EUS) together with endoscopy and biopsy can be helpful for diagnostic precision [11]. Findings observed in EUS include thickening of mucosal folds, mucosal nodularity, or multiple polypoid masses. Occasionally, for definite diagnosis laparotomy and deep tissue and whole thickness biopsy from GI tract wall is needed.

In conclusion, treatment with ALG or ATG could be a risk factor for PTLD. Therefore, induction therapy with IL-2 receptor blocking antibodies such as Basiliximab or Daclizumab may be better than ALG or ATG in high-risk patients for acute rejection.

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