Original Article

Post-transplantation Lymphoproliferative Disorder after Liver Transplantation: Report of 5 Cases among more than 550 Liver Transplants in Iran

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Abstract

Background: Post-transplantation lymphoproliferative disorders (PTLD) are a spectrum of diseases defined as polyclonal or monoclonal proliferations of lymphocytes which occur after solid organ transplants. In this study, we report our first experiences with PTLD following liver transplantation in Iran.

Patients and Methods: We retrospectively analyzed five cases of PTLD which followed liver transplantation among more than 550 liver transplants in our center. Of these, three were pediatric cases and two were adults. The underlying causes were tyrosinemia, autoimmune hepatitis, and progressive familial intrahepatic cholestasis (PFIC) in the three pediatric cases. HCV hepatitis was the primary cause for cirrhosis in one of the adults and the other adult was labeled as cryptogenic cirrhosis.

All cases, except for one, developed PTLD during the first year following liver transplantation.

Results: Patients were diagnosed as PTLD, B-cell, MALT and Hodgkin-like (according to the WHO classification of PTLD). The three pediatric patients died despite discontinuation of immunosuppressive drugs and chemotherapy. Fortunately both adult patients, until now, are still alive.

Conclusion: The incidence of PTLD in our center is lower than previous reports from other centers (0.9%), with a 60% mortality rate and worse prognosis in the pediatric age group.

Keywords: liver, post-trsnaplantation lymphoproliferative disorder

Introduction

Post-transplantation lymphoproliferative disorders (PTLD) are a family of closely related diseases associated with polyclonal or monoclonal proliferations of B-cells, T-cells, or null cells, which occur after solid organ transplantation.[1,2]

The reported incidence of PTLD varies in different reports among all solid organ transplants.[2] Among liver transplant (LT) recipients, the prevalence of PTLD ranges from 2 to 20% in adult and pediatric patients.[3] Herein we report five LT patients who developed PTLD during the early post-transplant period.

All information was obtained from the patients' medical records.

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Patients and Methods

Among more than 550 patients who underwent Orthotopic liver transplantation (OLT) since 1993 in our center, 427 were adults and 123 were pediatric patients. Of these, there were five cases of pathology confirmed PTLD.

Case reports

In the first case, a 16-year-old female patient underwent LT for cirrhosis secondary to autoimmune hepatitis. The immunosuppressive regimen consisted of Cyclosporine A (CsA), prednisolone and

Table 1. Characteristics of 5 patients diagnosed with PTLD following LT

Patient No.	Age (yr)	Sex	Primary disease	Immunosuppressive regimen	Months after transplant to PTLD	Site of lymphoma	EBV status of PTLD	PTLD type	Cause of death
1	16	F	Autoimmune hepatitis	CsA, prednisolone	3 months	Small intestine	Negative	MALT	Sepsis
2	2	M	Tyrosinemia	Tacrolimus, prednisolone, Cellcept	2 months	Lymph node	Negative	B cell monomorphic	Sepsis
3	42	M	HCV	CsA, prednisolone	12 months	Lymph node	Positive	Hodgkin's- like	Alive
4	1.5	M	PFIC	Tacrolimus, Cellcept, prednisolone	3 months	Lymph node	N/A	B cell monomorphic	Sepsis
5	42	M	Cryptogenic	CsA, prednisolone	60 months	Lymph node	Negative	B cell monomorphic	Alive

Cellcept. She was admitted to the Namazi Hospital, Shiraz, Iran three months following transplant with intractable diarrhea. A small intestinal biopsy was performed which showed MALT-type PTLD that was confirmed by immunohistochemistry. CsA was discontinued but the patient failed to respond. She was subsequently treated with cyclophosphamide, vincristine, and prednisolone (Table 1).

The patient was unresponsive to chemotherapy and died one month later from sepsis.

The second case was a 2-year-old male diagnosed with tyrosinemia who underwent LT. The patient developed prolonged fever, cervical lymphadenopathy, and diarrhea two months after LT. At that time, he was under immunosuppression with oral Tacrolimus, Cellcept, and steroids. The pathology of a cervical lymph node biopsy showed monomorphic PTLD, B-cell type. Immunosuppressive therapy was discontinued, and a regimen of cyclophosphamide and prednisolone was initiated. Unfortunately he died from sepsis (Table 1).

Case number 3 was a 42-year-old HCV positive white male who underwent LT because of HCV-induced cirrhosis. He was on CsA and prednisolone when he developed a low-grade fever one year after transplantation. Physical examination showed a small deep lymph node in the lateral part of his neck which measured 1.5×1.5 cm. Immunohistochemical analysis of the excisional biopsy revealed Hodgkin-like PTLD with EBV antigen in the tissue. Immunosuppressive therapy was decreased and the patient had a good response. After two years he is doing well (Table 1).

The fourth case was a 1.5-year-old boy, known case of PFIC, who developed cervical lymphadenopathy three months after LT. His immunosuppressive regimen was Tacrolimus, Cellcept, and steroids. Lymph node excisional biopsy revealed diffuse large B-cell lymphoma. Unfortunately, adequate tissue was not available to test for EBV status in the PTLD tissue. Despite decreasing immunosuppressive drugs he died 20 days later.

Case number five was a 42-year-old man who underwent LT and developed cervical lymphadenopathy five years following LT. His immunosuppressive regimen was CsA and steroids during the previous five years. Histology and IHC findings showed non-Hodgkin's lymphoma, diffuse large B-cell type. Immunohistochemistry (IHC) for EBV was negative. The dose of immunosuppressive drugs was decreased and he received a chemotherapeutic regimen that consisted of cyclophosphamide and prednisolone. After six months, the patient is doing well and symptom-free.

Four patients were EBV viral capsid antigen (VCA) IgM negative, early antigen (EA) and Nuclear antigen (NA) IgG positive, and PCR negative both at the time of PTLD diagnosis and prior to their transplants. These findings were the same for the pre-transplant status of patient number 4, however, he referred to another center at the time of his PTLD diagnosis; therefore specimens were not available to test for the presence of EBV at that time.

Discussion

According to the literature, PTLD occurs in 2 – 4% of LT patients with the highest incidence more than a year after transplantation.[4] In our center the incidence is much lower (0.9%). The reported mortality

is high, ranging from 40 – 60%, which is the same for our patients (60%).

Earlier studies have reported a much higher frequency of EBV positive PTLD[5] and recent studies report an increasing frequency of EBV negative PTLD.[6] Only one of our patients (case 3), who had a good prognosis, was positive for EBV antigen in PTLD tissue.

EBV pre-transplant serostatus, particularly an EBV positive donor and the negative status of a recipient, is a significant risk factor for EBV positive PTLD.[7] All of our patients had previous EBV exposures and were positive for EBV antibodies. However, the limitation in this study was the unavailability of donor EBV serology.

Controversial results exist regarding the different prognoses in early and late PTLD,[8] however, in our patients, early PTLD in the pediatric age group had the worst prognosis.

The primary immunosuppressive regimen in our center is the combination of a calcineurin inhibitor and prednisolone with or without mycophenolate mofetil. The calcineurin inhibitor has primarily been cyclosporine in the past, however, currently tacrolimus is used. Although recently there have been reports that stated a lack of effect of any drug regimen for developing PTLD, with the exception of a high dose steroid and OKT3.[9,10] This was most likely true with our patients in that no relationship was found between the development of PTLD and a specific drug regimen.

In conclusion, according to our experience with 550 LT patients in our center, it was determined that the incidence of PTLD was lower than previous studies and more common in pediatric patients. A worse prognosis with early PTLD was also seen.

Generally, most of our patients had previous EBV exposures prior to transplantation. This has been proven in our study with 116 renal transplant patients.[11] Primary infection of EBV after liver transplantation increases the risk of PTLD.[12] This may be one of the reasons for a low incidence of PTLD in comparison to other centers. However, it is just 16 years after the first LT in this center (median follow-up of 30 months); thus our follow-up for LT patients is brief and the incidence of PTLD should increase with additional follow-up for patients. It has been shown that with a longer follow-up period, the expected rate of PTLD will be higher.[5]

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