Introduction

Post-transplantation lymphoproliferative disorders (PTLD) are a family of closely related diseases associated with 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.

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

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...
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).

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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. In our center the incidence is much lower (0.9%). The reported mortality

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

Table 1. Characteristics of 5 patients diagnosed with PTLD following LT
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 PTLD5 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, 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

References