Pediatrics Grand Rounds
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Post-transplant Lymphoproliferative Disorder
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I have no financial interests to disclose

Learning Objectives
• Review the pathology of PTLD
• Understand risk factors for the development of PTLD
• Summarize evidence and recommendations for screening high risk patients
• Review treatment strategies and supporting evidence
• Discuss the importance of a multidisciplinary approach to management

Overview
• Historical Perspective
• Description and Epidemiology
• Pathology
• Risk Factors for development
• Screening - EBV quantitation
• Treatment
• PTLD management at Christus Santa Rosa

Historical Perspective
First described in 1969

Malignant Lymphomas in Transplantation Patients
I. Peto, W. MacManus, L. Beshai, and W. J. Shaw
From the Departments of Surgery and Pathology, University of Colorado School of Medicine and the National Institutes of Health, Bethesda, Maryland

A precipitator for success in clinical organ transplantation is the intricate ablation of the host immune apparatus. A coincidental effect might be predicted to be an increased incidence of neoplasms. This possibility is supported by the present communication, which describes the development of malignant lymphoid masses in 5 recipients of renal homografts, treated with differing immunosuppressive regimens in 3 widely separated transplant centers (Table 1).

A brief summary of the cases has already been reported. The complete follow-up of these patients will be published in detail. (Ann Intern Med. 67: 1–12, 1967–1968.)

Historical Perspective
1985 - Identification of EBV as a cause

Epstein-Barr Virus Infection and DNA Hybridization Studies in Posttransplantation Lymphoma and Lymphoproliferative Lesions
The Role of Primary Infection

• Authors reported findings of 14 organ transplant patients with B-cell lymphomas or lymphoproliferative disease
• All 14 patients had EBV infections
• Proposed EBV played etiologic role in development of lesions in these 14 patients
Description

- Lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in a recipient of a solid organ or bone marrow allograft.
- PTLDs comprise a spectrum ranging from early EBV-driven polyclonal proliferations resembling infectious mononucleosis to EBV(+) or EBV(-) lymphomas of predominantly B-cell or less often T-cell type.

Characteristics

- Typically B-cell and Epstein-Barr virus driven, but not always
- Sometimes reversible with reduction in immunosuppression, hence "semi-malignant condition"

Incidence

- Between 1-20% in transplant recipients
  - Patient age at time of transplant
  - Type of organ transplanted
  - EBV status of donor and recipient
  - Intensity of immunosuppression
- High rate of associated morbidity and mortality in organ transplant recipients
  - Mortality rates from 50% to 70% in most studies

Prognostic Factors

- Morphology and clonality- higher the degree, worse the prognosis
- Early and EBV positive PTLDs respond better
- Location
  - Central nervous system worse
  - Allograft PTLD better
- Multiple site worse than single site
- In general, survival post-PTLD better in kidney transplant patients

Pathology

Who Classification for PTLD

1997 Society for Hematopathology Workshop
Early Lesions

- Reactive plasmacytic hyperplasia
- Infectious Mononucleosis-like
- Possibly these are overlapping syndromes
- No treatment

Polymorphic PTLD

- Destructive lesions composed of immunoblasts, plasma cells, and intermediate forms that efface the architecture.
- Full range of B-cell maturation.
- Clonal proliferations.
- EBV +
- Some will regress with reduction in immunosuppression.

Monomorphic PTLD

- Can be diagnosed as lymphoma on morphologic grounds, and are classified accordingly (T- vs. B-cell).
- Most are EBV positive.
- Clonal proliferations.
- Tend to progress and require chemotherapy.

Risk Factors

Age at Transplantation

- Younger patients are at more risk for the development of PTLD
- Likely related to inverse relationship between age and EBV serostatus

Risk Factors - EBV Serology

- Assessed EBV status in 381 consecutive non-renal transplant recipients
- Incidence of PTLD was 24 times higher in recipients with negative EBV serostatus at time of transplant
### Risk Factors- Organ Type

**Incidence of PTLD Development**

- Small Bowel- 20%
- Lung- 8%
- Heart- 5%
- Liver- 3%
- Kidney- 1%
- Bone marrow- <1%

*May result from type of immunosuppression used or from differences in amount of EBV-infected B cells in allograft*

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### Immunosuppressant Choice

- The more T-cell specific the immunosuppression used the higher the incidence of PTLD
- Common agents in decreasing order of immunosuppression
  - anti T-cell antibodies (ATG and OKT-3)
  - Calcineurin inhibitors
  - Mycophenolate mofetil
  - Rapamycin

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### Screening High Risk Patients

**Screening- EBV**

- Development of EBV-associated PTLD is usually preceded by an increase in the number of latently infected B cells
- Levels of EBV DNA in peripheral blood or plasma can be quantitated and correlate with subsequent development of PTLD
- EBV DNA load increases from 2-16 weeks preceding development of PTLD
- Primary infections generally carry higher EBV DNA load than reactivation

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### Guidelines for Screening EBV

- Monthly to biweekly monitoring for the first three months following transplant
- Monthly monitoring for up to a year for EBV-mismatched transplants
- Because of the risk of late-onset disease EBV monitoring every 3 months is recommended

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### Chronic High Viral Load

- A subset of patients with primary EBV infections will develop persistently elevated viral loads
- The long-term clinical significance is unknown
- Development of late onset PTLD appears to be specific to the type of allograft
Chronic high Epstein-Barr viral load carriage in pediatric liver transplant recipients

- Retrospective review of chronic high EBV load carriers at Children’s Hospital of Pittsburgh
- 196 pediatric liver transplant patients
- 36 (18%) deemed chronic high load carriers

### Treatment Algorithm

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<thead>
<tr>
<th>Reduce Immunosuppression</th>
<th>Risk of allograft rejection</th>
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<td>Antivirals?</td>
<td>Organ specific</td>
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<td>Rituximab</td>
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### Treatment

**Immunosuppressant Withdrawal**

- Retrospective review 335 pediatric liver transplant patients between 1998-2002
- 50 developed PTLD
- IMS stopped in all patients
- 1 patient received chemotherapy
- 1 patient received rituximab
- Mortality 31.6% in PTLD and 6% with EBV
- No patients died from graft loss

**Antiviral Therapy**

- Lack of evidence indicating efficacy of antiviral therapy
  - Studies often have confounding factors and attributing treatment success to antiviral therapy is often difficult
- Could theoretically result in increased B-cell proliferation by inhibiting replication of lytic phase virions

**Chemotherapy**

- Reserved for aggressive disease or disease not responding to withdrawal of immunosuppression
- Adult organ transplant patients with PTLD have higher rates of toxicity, infection, and treatment related mortality (35%)
- PTLD is not clinically identical to lymphomas arising in immunocompetent patients
Postulated reduced chemotherapy regimen could be equally effective, but less toxic
- Devised protocol that dropped vincristine and daunorubicin from CHOP
- Patients received cytoxan and prednisone
- Failure-free response rate was 73%

Rituximab
- Chimeric monoclonal antibody directed against CD20-anti B cell agent
- Used extensively in management of PTLD
- Indications for treatment range from preemptive use to combination regimens
- No randomized controlled trials have been completed that assess its efficacy in PTLD treatment

80 adult patients with PTLD treated from 1998-2008
- All patients had reduction of immunosuppression
- 59 patients received rituximab, 21 did not
- PFS and OS was 70% and 73% for patients receiving rituximab, compared to 21% and 33% who did not

Multivariate regression identified three factors associated with progression and survival: bone marrow involvement, CNS involvement, and hypoalbuminemia

Use of rituximab resulted in significant reductions in the cumulative dose of anthracyclines and alkylating agents.
**Multidisciplinary Management**

- PTLD is a good example of a disease that requires multiple subspecialists for optimal treatment.
- For example:
  - Transplanters very comfortable with immunosuppressant management but have little experience with chemotherapy.
  - Oncologists experienced with chemotherapy and managing its toxicities, but not immunosuppressants and nuances of organ transplantation.

**PTLD at Santa Rosa**

- Historically there has been a multidisciplinary effort to care for PTLD patients.
- Plans to revive and extend this approach.
- Working to develop a systematic step-wise approach which will incorporate perspectives of both transplanters and oncologists (Institutional Approach).
- Development of comprehensive database to track patients and outcomes.

**Summary of PTLD**

- Significant source of morbidity and mortality in transplant patients.
- Often driven by EBV.
- Clinically distinct from lymphomas in immunocompetent patients.
- Reduced chemotherapy regimens and rituximab achieve good response rates.
- A step-wise multidisciplinary approach to treatment is necessary.

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