Nephrology Grand Rounds

PTLD in Kidney Transplantation

Charles Le
University of Colorado
6/15/12
Objectives

- Background
- Pathogenesis
- Epidemiology and Clinical Manifestation
- Incidence
- Risk Factors
- CNS Lymphoma
- Prevention and Prognosis
- Treatment
Background
First described in 1969 at University of Colorado by Dr. Penn.

“A coincidental effect might be predicted to be an increased incidence of neoplasia. This possibility is supported in the present communication, which describes the development of malignant lymphoid tumors in 5 recipient of renal homografts, treated with differing immunosuppressive regimens”
Background

- PTLD ➔ Post-Transplant Lympho-proliferative Disorders.

- PTLD are the most common malignancies complicating organ transplantation (excluding non-melanoma skin cancer and in situ cervical cancer).

- Accounting for 21% of all malignancies vs 5% in the general population.

- Develops as a consequence of immunosuppression in a recipient of a solid organ or bone marrow allograft.

Penn, I. et al. NEJM 1990
PTLD

- Lymphoproliferative disorders occurring after transplantation have different characteristics:
  - Non-Hodgkin lymphoma (NHL) accounts for 93% vs 65% of lymphomas in the general population.
  - Mostly large-cell lymphomas, (90% B-cell type).
  - Extra-nodal involvement is common, (30-70% of cases).
  - 90% to 95% are driven by the Epstein-Barr virus (EBV).

- Very few cases of T cell PTLD had been reported in kidney transplant recipients.
Pathogenesis
Epstein-Barr Virus (EBV)

- Herpes Virus Family

- In the US, ~95% of adults have been infected, +IgG Ab.

- Infection with EBV occurs during adolescence or young adulthood, it causes infectious mononucleosis 35%-50% of the time.
**Characteristics**

- Most patients appear to be related to infection with Epstein-Barr virus (EBV) in the setting of chronic immunosuppression (90-95%).

- 2/3 PTLD cells observed in patients with solid organ allografts are of host (recipient) origin & presents as multisystem disease. (mean 76 months post-transplantation).

- PTLD of donor origin is an uncommon occurrence; however, at least in renal transplantation, PTLD of donor origin occurs in the allograft. (mean 5 months).

Petit, B. et al. Transplantation 2002
Normal Immune Control

Hsieh WS et al. Transplant Infectious Disease 1999
Compromised Immune System

- Organ Transplant
- EBV-infected cells proliferate
- Polyclonal lymphomas
- Intensive Immunosuppression
- Loss of Virus-specific CD8+ T cells
Epidemiology and Clinical Manifestation
Epidemiology - 3 types of EBV related PTLD

I. Benign polyclonal lymphoproliferation is an infectious mononucleosis-type acute illness that develops 2-8 weeks after immunosuppressive therapy begins.
   - polyclonal B cell proliferation with no evidence of malignant transformation. (55% of cases)

II. The second EBV-induced disorder is similar to the first in its clinical presentation.
   - polyclonal B cell proliferation with evidence of early malignant transformation. (30% of cases)

III. The last disorder is usually an extranodal condition presenting with localized solid tumors
   - monoclonal B cell proliferation with malignant cytogenetic abnormalities and immunoglobulin gene rearrangements. (15% of cases)

EBV and PTLD

- 95% of population is EBV IgG+
- ~5% of KTx recipients are EBV- recipients of EBV+ kidneys
- PTLD occurs in ~1% overall
- 80% of PTLD occurs in EBV- recipients
- Incidence of PTLD in EBV- recipients is as high as 20%!

1000 Transplant Recipients

- 50 EBV D+R-
- 950 EBV D+R+

Induction + IS

- 8 EBV D+R-
- 2 EBV D+R+

10 patients with PTLD
PTLD: EBV vs non-EBV Related

- PTLD not directly associated with EBV appear to differ clinically from EBV-related tumors

- In one study, the clinical presentation and survival of 32 transplant recipients:
  - Tumors not due to EBV presented much later (2,324 vs 546 days post-transplant),
  - suggesting that their incidence may increase with time, and were much more virulent (mean survival of 1 vs 37 months)

Clinical Manifestations

- >50 % of patients with PTLD present with extra-nodal masses.

- Involved organs include the GI tract (stomach, intestine), lungs, skin, liver, CNS, and the allograft itself.

- 20-25 % have CNS disease (rare in the general population), and a similar proportion have infiltrative lesions in the allograft [29].

- Other symptoms: mononucleosis-like syndrome, unexplained fever, and GI obstruction.

Incidence of PTLD
Higher Risk for Malignancy in KTx Recipients

Kasiske et al. performed a retrospective database analysis of 35,765 kidney recipients from 1995-2001

- Non-Hogkin’s lymphomas were more than 20-fold increased than in the general population.

- Compared with patients on the waiting list, there is an increases risk of non-Hodgkin’s lymphoma (3.3-fold), and cancer of the kidney (39% higher).

Cumulative incidence was 1% after 5 years, 2.1% after 10 years.
Incidence of different types of PTLD

Figure 2: Ten-year cumulative incidence of PTLD as a function of the location of PTLD: graft, cerebral and digestive lymphomas.
## Incidence of PTLD in SOTs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Number of Transplants</th>
<th>Number of PTLD cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine</td>
<td>319</td>
<td>19 (6.0%)</td>
</tr>
<tr>
<td>Heart-lung</td>
<td>532</td>
<td>28 (5.5)</td>
</tr>
<tr>
<td>Heart</td>
<td>24,100</td>
<td>950 (3.9%)</td>
</tr>
<tr>
<td>Lung</td>
<td>6207</td>
<td>228 (3.7%)</td>
</tr>
<tr>
<td>Liver</td>
<td>39,974</td>
<td>375 (0.9%)</td>
</tr>
<tr>
<td>Kidney-pancreas</td>
<td>7719</td>
<td>59 (0.8%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1625</td>
<td>13 (0.8%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>124,638</td>
<td>692 (0.6%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>205,114</td>
<td>2365 (1.2%)</td>
</tr>
</tbody>
</table>

Dharnidarka VR. et al. Transplantation 2001
Risk Factors for Developing PTLD
Risk Factors for PTLD

- Degree of immunosuppression
- EBV status of donor/recipient
- Time post-transplant
- Recipient age and ethnicity
- OKT3 for rejection and CMV seromismatch
Degrees of overall Immunosuppression

- Higher degree = higher risk
- **Agents with Increase Risk for PTLD**
  - Anti T-cell antibodies
    - (ATG, Thymo [21.6%], OKT-3 [21.5%], anti-IL-2 [7.8%] vs gen population)
  - Calcineurin inhibitors (Tacrolimus > CSA)
  - Balatacept (anti-CTLA4 ab) – especially EBV- Recipient
  - ?Sirolimus
- **Agents that *does not* Increase Risk of PTLD**
  - Alemtuzumab (Campath 1H) – use to treat lymphomas
  - Mycophenolate Mofetil
  - Everolimus

Opelz, G. et al. Transplantation 2006
Lymphocyte-Depleting Induction Increases Risk of PTLD

- Cumulative incidence of PTLD per 100,000 recipients of deceased donor kidneys

Opelz, G. et al. Transplantation 2006
CNIs Pro-Cancer Pathways

Guba et al. Transplantation 2004
mTOR-Is: Anti-Cancer Pathways

Guba et al. Transplantation 2004
Controversial whether mTOR-Is is protective for PTLD?

- Everolimus shows *in vitro* activity against EBV+ B cells
  - Inhibition of cell growth
  - Inhibition of cell cycle progression
  - Promotion of apoptosis

- Case reports describe CNI → SRL conversion as a successful strategy for PTLD therapy
  - 4 case reports with complete remission in 20/25 described patients.

(Majewski et al. PNAS 2000)
mTOR-Is: Conflicting data

- Large retrospective registry study of OPTN/UNOS database (2000-2004) shows *increased* risk of PTLD in patients treated with mTOR-Is at discharge (RR=2.047)

- No multivariate analysis to account for differences in population (pediatric vs. adults), induction, EBV status, etc. between groups

Kirk et al. *AJT* 2007
Sirolimus increases risk of PTLD

PTLD in a retrospective cohort of 53,719 patients who underwent transplantation from January 2000 to September 2006 and followed up through December 2007.
EBV Serology

- Highest risk D (+) R (-)
  - 24-fold increased rate of PTLD
  - Primary infection with EBV is much worse than reactivation
  - D (-) R (+) at risk for reactivation

Shahinian. et al. Transplantation 2003

Caillard. et al. Transplantation 2005
PTLD risk stratify by Age

Caillard. et al. Transplantation 2005
Younger Age and Caucasian Race Increases risk of PTLD

- Analyzed data from the Scientific Registry of the (UNOS) database (from January 1988 to December 1999)

- In the UNOS database, PTLD was reported in 2,365 of 205,114 organ-transplant recipients (1.2%).

- Young Caucasian males are at highest risk for PTLD development among solid-organ-transplant recipients.

Dharnidarka VR. et al. Transplantation 2001
# Relative Risks PTLD Development

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>% Developing PTLD</th>
<th>Odds ratios (95% CI)</th>
<th>Relative risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;18 years</td>
<td>2.63%</td>
<td>2.81</td>
<td>2.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>1.02%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.38%</td>
<td>2.22</td>
<td>2.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>0.64%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.29%</td>
<td>1.40</td>
<td>1.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.94%</td>
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</tr>
</tbody>
</table>

- The combination of all three risk factors increased the OR to 8.78.

*Dharnidarka VR. et al. Transplantation 2001*
Time to Development of PTLD

Caillard, S. et al. AJT 2012
Treatment of Rejection Increases risk of PTLD

Caillard. et al. Transplantation 2005
Pre-Transplant Malignancy and CMV status Increases PTLD risk

Caillard. et al. Transplantation 2005
CNS PTLDs
CNS PTLDs

- Primary CNS PTLD is uncommon and its diagnosis and treatment are difficult.

- The diagnosis is suspected in transplant recipients with mental status changes or new neurologic findings.

- The median time from transplantation to diagnosis of PCNS-PTLD was 4.4 years.

- Most patients had monomorphic, EBV+ disease of B-cell origin.
Diagnosis of CNS PTLDs

- Diagnostic tests include
  - MRI + gadolinium of the head,
  - CSF analysis for EBV by PCR and cytology with cell markers by flow cytometry
  - peripheral titration of circulating EBV load in plasma

- Confirmed either by the presence of malignant lymphocytes in the CSF or by direct biopsy of the lesion.
Prognosis of CNS PTLD

- Untreated PTLD has a rapidly fatal course, with survival of approximately 1.5 months from the time of diagnosis.

- Survival after whole brain radiation therapy ranges from 10-18 months, but increases to an average of 44 months following chemotherapy plus radiation.

- Although currently available therapeutic regimes prolong survival, they are not curative in most patients.

- The disease therefore tends to recur and is eventually fatal.
Prevention and Prognosis
Prevention

- Follow EBV by NAT (K-digo) in EBV (D+R-)
  - Once in the 1st week after transplantation then least monthly for the first 3–6 months after transplantation.
  - Followed by every 3 months until the end of the first post-transplant year.

- Limiting patient exposure to antibody-depleting induction, rapid withdrawal and tapering of IS, and ?anti-viral prophylaxis with ganciclovir.

- Consider using Alemtuzumab (Campath 1H) for induction.
Patient survival after diagnosis of PTLD, overall survival and risk factors for death

Caillard. et al. Transplantation 2005
Therapy for PTLD
Treatment

- Reduction in Immunosuppression
- Antiviral therapy?
- Chemotherapy
- Rituximab?
Treatment by type of EBV-related PTLD

I. Polymorphic PTLD - Mono-like syndrome, normal cytogenics
   - Reduction of immunosuppression +/- anti-viral

II. Polymorphic PTLD - Early evidence of malignant transformation
   - Reduction of immunosuppression → chemotherapy

III. Monomorphic PTLD – Malignant, often extra-nodal
    - Reduce immunosuppression + chemotherapy/immunotherapy
      +/- surgical resection
Reduction in Immunosuppression

- 1st line option in early PTLD
- 2/3 of patients will respond to reduction or withdrawal of immunosuppressive medication
- Convention is to stop either CNI or anti-metabolite and reduce the other

- Severely ill -> only prednisone 7.5-10mg/day
- Less ill -> reduce CNI by 50% and pred. d/c antimetabolite

- Change to everolimus? No good data. Jury still out.
- Must monitor closely for organ rejection
Role of Antivirals in PTLD

- There is currently no good evidence of the efficacy of antiviral therapy for treatment of PTLD. (Acyclovir vs ganciclovir)

- Acyclovir inhibits viral DNA polymerase and has been shown to decrease oropharyngeal shedding of EBV.

- Many early treatment algorithms for PTLD included antiviral therapy in an attempt to control EBV infection.

- Polyclonal disease in particular has shown responses to ganciclovir in anecdotal reports.
Chemotherapy/Immunotherapy

- Reserved for aggressive disease or disease not responding to withdrawal of immunosuppression
  - Rituximab (Most PTLDs express CD20)
  - CHOP (Cyclophosphamide, Doxorubicin, Prednisone, Vincristine)
  - CHOP-R (CHOP + Rituximab)
Multicenter Analysis of 80 Solid Organ Transplantation Recipients With Post-Transplantation Lymphoproliferative Disease: Outcomes and Prognostic Factors in the Modern Era

- Large, multicenter, retrospective analysis

AWOD—alive without disease; DOD—dead as a result of disease; AWD—alive with disease; DWOD—dead without disease

Added Benefits with Rituximab

- Progression Free Survival and Overall Survival was 70% and 73% for patient receiving rituximab, compared to 21% to 33% who did not get rituximab.

- Limitations
  - Small Study Population
  - Only studied in patient with monomorphic PTLD

PTLD: Rituximab or Chemotherapy?

University of Pennsylvania Medical Center

- Of 117 patients treated for PTLD from 1996-2005 at a single center, 35 failed immunosuppression dose reduction and survived to receive rituximab, chemotherapy, or both:

- 22 received rituximab:
  - 13 had complete response (59%), those without response received chemotherapy
  - Median survival 31 months

- 23 received chemotherapy:
  - 13 had complete response (57%)
  - Median survival 42 months
  - 26% died due to toxicities of therapy

Elstrom R et al, AJT 2006
Summary of PTLD

- Mainly EBV related lymphoma; Recipient seronegativity highest risk factor.

- Antibody-depleting induction and CNIs likely increase PTLD risk.

- Consider Campath and more rapid IS taper in EBV D+/R- recipients.

- If PTLD develops:
  - Reduction in immunosuppression is 1st line
  - Rituximab +/- chemotherapy next step
Questions