POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS AND RELATED DISEASES

Joo Y. Song, MD
Associate Clinical Professor
Department of Pathology
City of Hope

2018 Neoplastic Hematopathology Update
I have no financial disclosures
Immunodeficiencies

- Transplant
- Congenital
- Aging
- Autoimmunity
- Drugs
- EBV
- HIV
- HHV8

T-cell/immune surveillance defect
Outline

- Discuss EBV
- PTLD – updates of the classification
  - Non-destructive
  - Polymorphic
  - Monomorphomic
- Therapies
- Challenges
Epstein-Barr Virus

“Chance favors the prepared mind”
- Louis Pasteur

- Anthony Epstein (pathologist) attending Denis Burkitt’s (surgeon) talk
- First human tumor virus described
- Human Herpesvirus 4 (HHV4)
- 95% of the world’s population has this asymptomatic infection
Latency III
Express all EBNAs and LMPs

Latency II
EBNA1, LMP1, LMP2

Latency I
EBNA1

Latency 0
No protein expression

Latency III
PTLD and DLBCL

Latency II
Hodgkin

Latency I
Burkitt

Adapted Young et al, Nat Rev 2016
DETECTION OF EBV GENE EXPRESSION IN REED-STERNBERG CELLS OF HODGKIN’S DISEASE

Tzyy-Chou Wu¹, Risa B. Mann¹, Patricia Charache², S. Diane Hayward³, Steve Staal⁴, Beverly C. Lambe² and Richard F. Ambinder⁵,⁶

Departments of ¹Pathology, ²Laboratory Medicine and ³Neurology, Johns Hopkins Medical School, Baltimore, MD 21205; ⁴Department of Medicine, Kaiser Permanente, Landover, MD 20795; and ⁵Johns Hopkins Oncology Center, 418 North Bond Street, Room B319, Baltimore, MD 21231, USA.

• EBV encoded RNA
• Present at all latency of EBV
• Contributes to the activation of the innate immunity
• Best method for detecting EBV
PTLDs

**RISK FACTORS**

- Type of transplant
- Young age
- EBV seronegative
- High immunosuppression
- High EBV levels

**ADVERSE**

- Older age
- Extranodal disease (CNS)
- LDH, hypoalbuminemia
- >10 years after transplant

Up to 20% 4.5% 2.5% 1%
HSCT

- Majority of PTLDs arise after SOT
- PTLD after HSCT
  - Exclusively donor origin
  - Develops in first 6 months of transplant
  - Due to profound T-cell depleting conditioning regimen
  - Higher incidence of Hodgkin-like PTLD (late onset) (6.2% vs 3.7%)
    - Normal CD4 counts (similar to HIV)

Rowlings, JCO 1999
Grulich, Lancet 2007
EBV B-cell Spectrum

- Reactive
- Low grade B-cell
- Aggressive lymphoma
- IM-like
  - Plasmacytic hyperplasia
  - Florid follicular hyperplasia
- Variable malignant
- Polymorphic
- Marginal zone lymphoma
- DLBCL/Burkitt
Post transplant LPDs

- Non-destructive
  - Florid follicular hyperplasia (2016)
  - Plasmacytic hyperplasia
  - Infectious mononucleosis
- Polymorphic
- Monomorphic
  - DLBCL, marginal zone, Burkitt
- CHL
Reactive FH

Expanded Follicles

Non-destructive
Intact architecture
Regresses spontaneously

IM-like

Mixture of:
Immunoblasts
Plasma cells
Follicular hyperplasia

Plasma cell hyperplasia

Interfollicular plasma cells
Follicular hyperplasia
Tonsil SH workshop 2015
Follicular hyperplasia

- Flow: Polytypic B cells
- Molecular: Negative for IGH rearrangements

46,XY,add(14)(p11.2) [2]/45,XY,add(14)(q32),-19 [1]
Follicular hyperplasia

- Waldeyer’s ring most common site for FH
- Scattered EBV+ cells
- Cytogenetic abnormalities can be seen (simple, 17%)
- Polytypic flow and molecular
- Usually negative EBV titers

- Intact architecture
- Regress spontaneously most cases, rarely progress

Vakiani, Hum Path 2007
Sevilla, Hem Onc 2011
Plasmacytic hyperplasia

- Intact architecture
- Sheets of plasma cells
- Polytypic
- EBV positive
- Adenotonsillar areas involved

Said, PTLDs 2016
Plasmacytic hyperplasia

- Rare cases can progress to plasma cell neoplasm
- 57 year-old male, cardiac transplant
- 6 years later was found to have a tonsillar mass

Knowles, Blood 1995
Dunphy, Arch Lab 2002
IM-like

- Intact architecture
- Typical features of IM
- Increased number of immunoblasts (EBER+)
Post transplant LPDs

INTACT ARCHITECTURE

- Non-destructive
  - Florid follicular hyperplasia (2016)
  - Plasmacytic hyperplasia
  - Infectious mononucleosis

DESTRUCTIVE

- Polymorphic
- Monomorphic
  - DLBCL, marginal zone, Burkitt
- CHL
Polymorphic PTLD

- Full range of B-cell maturation
  - Lymphocytes, immunoblasts, plasma cells, Hodgkin-like cells
- T-cells may predominate
- Necrosis is frequent
- Many EBV-positive cells
Polymorphic PTLD

- Most common PTLD in children (20-80%)
- Frequently extranodal
- IG rearrangements are positive. TCR maybe +
- Cytogenetic abnormalities also seen (15-30%)

Vakiani, Hum Path 2007
Sevilla, Hem Onc 2011
Said, PTLDs 2016
73 yo gentleman with non-healing ulcers in the mouth for the past few months.
Diagnosis

• The patient was not on immunosuppressive therapy.
• No adenopathy was seen on radiographic scans.

• Diagnosis:
  – EBV-positive lymphoproliferative disorder
  – Age-related immunosenescence
Mucocutaneous ulcer
Mucocutaneous ulcer

- **Should not** be designated as PTLD.
- Oral mucosa, skin, GI tract
- Hodgkin-like cells
- Variable CD20 and PAX5
- CD30+, CD15-, EBER+, CD45+
- IG +/- (30%)
- Self-limited

Hart, AJSP 2014
Dojcinov, AJSP 2010
Dojcinov, Blood 2011
Monomorphic PTLD

- Fits definition for lymphoma (WHO 2017)
- Older patients
- Usually develops after a long interval following transplantation

- B-cell type (most common)
  - DLBCL, plasmacytoma/MM, Burkitt, plasmablastic
- T-cell type
Monomorphic PTLD (DLBCL)

- Features just like DLBCL
- Occasional cases can be more anaplastic.
- COO not needed.
  - Most are non-GCB
Monomorphic PTLD (DLBCL)

- **EBV+ DLBCL**
  - Differ from de novo DLBCL
  - Gains in 9p24.1 (PDCD1LG2/PDL2)
- **EBV-negative DLBCL**
  - May be a de novo DLBCL in the transplant setting

Morscio, AJ Transplant 2013
Ferreiro, AJ Transplant 2016
Monomorphic PTLD (Burkitt)

- Morphologically and molecularly the same as typical Burkitt
- Most are EBV+
- 11q abnormalities maybe more frequent (43% vs 3%)

Salaverria, Blood 2014
Ferreiro, Haematologica 2015
67 year-old woman with a history of renal and pancreatic organ transplant and breast cancer
Monomorphic PTLD (plasmacytoma)

- Rare type of PTLD
- Usually occurs in adults, 3-5 years after transplant
- Variable EBV
- Usually extranodal tumors (subcutaneous)
- May have monoclonal gammopathy
- Have normal calcium levels and mild anemia
Perry et al described 5 pediatric pts (liver/small bowel) with plasma cell neoplasms.

All EBV-negative, IGH rearranged, and presented early (median 15 months).

Achieved long complete remissions with minimal interventions (steroids).
Monomorphic PTLD (plasmablastic)

- Usually EBV-positive
- 1/3 have a MYC translocation
- CD138+, CD20-
- Maybe in other sites such as skin (compared to oral cavity in HIV)
- More frequently seen in heart transplants

Morscio, AJSP 2014
Monomorphic PTLD

• Low-grade B-cell lymphomas were not included (2008 WHO)
• Extranodal marginal zone lymphoma (*new entity*)
• Skin/orbit
• IgA+, monotypic, EBV+

Gibson, AJSP 2011
Hodgkin-type PTLD

De Jong, AJCP 2017
Hodgkin-type PTLD

- 2-3% of PTLD
- EBV-positive (latency type II)
- Most cases are mixed-cellularity type
- Ideally should be positive for CD30, CD15
- May also express CD20 or other B-cell markers
- Take caution not to confuse with other PTLDs with Hodgkin-like cells
  - Polymorphic PTLD
  - PTCL, NOS
PDL1

- PDL1-PD1 axis involved in the inhibition of T cell activation
- Located on the 9p21 locus
- 9p21 alterations were seen throughout all cases of immunodeficiency (SH workshop 2015)
- 19/19 PTLDs were positive for PDL1 by IHC
<table>
<thead>
<tr>
<th>Sparse infiltrate</th>
<th>T-cell-rich</th>
<th>Histiocyte-rich</th>
<th>Few eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centroblast/immunoblast-like</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete B-cell phenotype (CD20, CD79a, PAX5, OCT2, BOB1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hodgkin-like</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient B-cell phenotype, aberrant phenotype (CD15, granzyme B, perforin)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

De Jong, AJCP 2017 (SH Workshop 2015)
T-cell type PTLD

- 15% of PTLDs, usually “late” occurring (6 years)
- More common in Asia
- Male predominance
- Can represent any of the subtypes in WHO
  - PTCL, NOS (19%)
  - ALCL (12%)
  - Hepatosplenic TCL (12%) - Kidney transplant
- Most EBV negative (66%)
  - NK/T-cell, PTCL
- Typically have a poor prognosis

Herreman, Leukemia Lymphoma 2013
Treatment

- Reduction of immunosuppressive therapy (RIS)
- Chemotherapy/destruction of malignancy
- Suppression of viral load

- CD20+ PTLD – RIS and Rituximab
- CD20-negative PTLD - treat like immunocompetent lymphoma

Blaes, Cancer 2005
Choquet, Blood 2006
Dierickx, Blood 2015
Prognosis

- IPI still a strong predictor
- Prognosis of PTLD is poor (5-year OS 40-60%)
- 60% will die of disease, others will die of infection or toxicity
Prevention/Monitoring

- PET/CT should be used in the workup and monitoring of response in PTLD
- EBV viral load
  - There is some correlation with EBV titers and development of EBV+ PTLD
  - However it cannot replace the biopsy
  - Can be used to know when to reduce immune suppression or administer rituximab

Dierickx, Blood 2015
Questions and Challenges

• Classification
  – Are non-destructive lesions truly PTLDs?
    • May regress spontaneously, rarely progress to destructive
  – Are EBV-negative monomorphic PTLDs truly PTLDs or de novo lymphomas
    • Gene expression profiling shows no clear distinction between de novo and PTLD
Conclusions

• PTLDs have a similar morphologic spectrum as other immunodeficiency states (HIV, age)
• The disease may be a spectrum
  – Difficult to distinguish overlapping diseases such as DLBCL/T-rich B/Hodgkin PTLDs
• Reduction of immunosuppressive therapy is recommended in addition to immunotherapy/chemotherapy in unresponsive lesions
Thank you. Any questions?