Spectrum of EBV+ B-Cell Lymphoproliferative Disorders

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Outline

- Pathologic spectrum of EBV+ B-cell lymphoproliferative disorders
- Nomenclature for immunodeficiency disorders
- When to consider EBV testing and molecular clonality testing

Epstein-Barr Virus (HHV4)

- Discovered in 1964 from cultured Burkitt lymphoma cells from an Ugandan child
- EBV infected B-cells persist within the memory B-cell pool of most immunocompetent hosts
- EBV-encoded latent genes induce B-cell transformation by altering gene transcription and activating signaling pathways
- Immunosuppressed patients are at increased risk of developing EBV-associated B-cell lymphoproliferative disorders

**Immunodeficiency Disorders**

Hyperplasia  
Polyclonal  
Polyclonal  
Monoclonal  
Monoclonal  
Lymphoma

EBV  
B-cell lymphoproliferations

HHV8  
HHV8-associated lymphoproliferations

T & NK-cell lymphoproliferations

**Hyperplasias**

  - Defined as mass forming lesions with preservation of overall tissue architecture (non-destructive)

- Three types
  1. **Follicular hyperplasia** (formally recognized in WHO 2016)
  2. Infectious mononucleosis-like hyperplasia
  3. Plasmacytic hyperplasia

**EBV+ B-Cell Spectrum**

- Patterns of reactive B-cell hyperplasia
  - B-LPD of varied malignant potential
  - Polymorphic B-LPD
  - Monoclonal B-LPD
  - Marginal zone lymphoma
  - Diffuse large B-cell lymphoma

**Follicular Hyperplasia**

- Presents with isolated or multifocal lymphadenopathy
- No interfollicular expansion
- Distribution of EBER+ cells variable, often confined to 1-2 follicles
- Occasional clonal IG or simple karyotypic abnormalities
  - *Do not over-react to clones!*
- Regress spontaneously in most cases
- Rare concurrent or subsequent EBV+ B-LPD, clonally related in some

Images: Drs. Babu, Ewalt, Tennerantu
Mishellard F et al. Hum Pathol 2007
Shapiro NL et al, J Pediatr Otorhinolaryngology 2003
Williamson RA et al, Otolaryngol Head Neck Surg 2001
Sevžič ZW  et al, Hematol Oncol 2011;29:90

EBER
Hyperplasias

- Mass forming, non-destructive lesions with overlapping patterns
  - Intact architecture helpful to differentiate from polymorphic B-LPD
  - Clinical context important to separate from nonspecific causes
  - Difficult to recognize if EBV is negative
  - Small clones or abnormal karyotypes may be present
  - Majority regress spontaneously

Follicular
- Scant interfollicular proliferation

IM-like
- Numerous interfollicular immunoblasts
- Small to medium lymphoid cells
- Plasma cells - polytypic
- FH usually present

Plasmacytic
- Numerous interfollicular plasma cells
- Few scattered immunoblasts
- Plasma cells - polytypic
- FH usually present

Genetic Complexity

- Progressively increasing karyotypic abnormalities

Dasatinib-Related Hyperplasia

- Newer therapeutic agents expand spectrum of immunodeficiency-related hyperplasias

Polymorphic B-LPD

- Morphologically polymorphous lesions that efface architecture or cause destructive masses, but do not fulfill criteria for diagnosis as lymphoma
  - Exhibit full range of B-cell maturation
    - Variable number of B & T cells; T may predominate
    - Variable number of Hodgkin-like cells
      - CD45+ CD20/CD79A+ CD30+ CD15+/− PAX5+ OCT2+
      - Light chain restriction +/- or focal or biclonal
      - Clonal IG gene rearrangements in almost all cases
      - Simple karyotypic abnormalities may be present
  - Some regress with withdrawal of immunosuppression; others need more active management such as Rituximab or RCHOP

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**Polymorphic B-LPD in Iatrogenic/Autoimmune Setting**

- Iatrogenic LPDs usually arise in patients treated with immunosuppressive regimens for autoimmune disease
- **Methotrexate** commonly implicated
- Contribution of underlying autoimmune disease versus drug regimen is difficult to quantify; may depend on greater disease severity
- Longitudinal study of 10,815 RA patients on anti-TNFα meta-analyses of 14 published reports
  - Conclusion: no statistically significant difference in lymphoma rate

*Important to obtain clinical history/treatment regimens*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Drug</th>
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<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Methotrexate</td>
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<tr>
<td></td>
<td>Steroids</td>
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<tr>
<td></td>
<td>Hydroxychloroquine</td>
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<td></td>
<td>TNFα inhibitor</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>ATG</td>
</tr>
<tr>
<td></td>
<td>Methyprednisone</td>
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<tr>
<td></td>
<td>Cyclosporine</td>
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**Polymorphic B-LPD**

- 57M, HIV/AIDS
- Abnormal LFT with multiple liver lesions
- Architectural destruction, necrosis
- Polymorphic background with RS-like cells
- IHC suggestive of Hodgkin lymphoma
- Commenced HAART with resolution

**Polymorphic B-LPD in Lung**

- 41F, HIV+
- Multiple lung nodules
- HAART started after diagnosis with complete remission

**Polymorphic B-LPD: Other Features**

- RS-like cells and EBV+ cells associated with monocytoid clusters
  - Monocytoid B-cell clusters should be a trigger to test for EBER

May be associated with

- Angiodestructive growth
- Necrosis
- Hemophagocytic lymphohistiocytosis
Mucocutaneous Ulcer

- Isolated, sharply-circumscribed ulcer in oropharyngeal mucosa, skin or GI tract
- Polymorphous infiltrate with RS-like cells mimicking classical Hodgkin lymphoma
  - CD30+ EBER+ CD20+/ CD15-/ CD45+
  - Prominent rim of CD8+ T-cells at base of ulcer
- Self-limiting, indolent, IS withdrawal effective
  - Localized defect in immune surveillance?

Indolent EBV+ B-Cell Lymphomas

- Rarely reported in immunodeficiency settings
- Almost all plasmacytoid, most are MZL
  - EBV+ MZL designated as a PTLD in WHO 2016
  - Very few FL and CLL/SLL
  - Difficult to designate EBV-neg cases as immunodeficiency-related
  - IgA heavy chain predominant
  - CR with reduced IS +/- antiviral therapy, local excision, rituximab, or local radiation

EBV+ DLBCL of the Elderly

- Aggressive EBV+ monoclonal B-cell proliferation arising in patients >50y with no known immunodeficiency
- Provisional entity in WHO 2008
- Incidence increases with age
- Immune senescence leading to defective immune surveillance?
- Broader range of morphologies than usual DLBCL

“Large B-Cell Proliferations associated with Chronic Inflammation”

- Rare EBV+ clonal large B-cell proliferations arising in localized sites without mass lesions in immunocompetent patients
  - Overlap with Pyothorax-associated lymphoma
  - Associated fibrin or amorphous material adjacent to cavities
  - Clinically indolent; seldom disseminate
    - Resemble breast-implant assoc. ALCL
    - Localized alteration in host immune surveillance?
      - Using “Large B-cell lymphoma” name may cause overtreatment

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Gibson et al, Hum Pathol 2009
Hoefler et al, Hum Pathol 2010
Hochholzer et al, Mod Pathol 2011
Kato et al Cancer Sci 2014
Ok et al, Blood 2012; Clin Cancer Res 2014
Gibson et al, Leuk Lym 2015
EBV+ Large B-Cell Proliferations

- A spectrum of morphologies and immunophenotypes

**Immunophenotypic Spectrum**

<table>
<thead>
<tr>
<th>DLBCL</th>
<th>TCRBCL/Hodgkin-like</th>
<th>CHL</th>
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<tbody>
<tr>
<td>Centroblast/immunoblast-like</td>
<td>Hodgkin-like</td>
<td></td>
</tr>
<tr>
<td>Intact B-cell phenotype (CD20, CD79a, PAX5, OCT2, BOB1)</td>
<td>Deficient B-cell phenotype</td>
<td>Aberrant phenotype (CD15, granzyme B, perforin)</td>
</tr>
<tr>
<td>Sparse infiltrate</td>
<td>T-cell rich</td>
<td>Few eosinophils</td>
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**EBV+ DLBCL of the Elderly**

- Incidence 3-14%; rare in West
- DLBCL with non-GC immunophenotype
- GEP: constitutive activation of NF-kB, enriched for JAK/STAT-signaling, immune/inflammatory, cell cycle, metabolism genes

**EBV+ DLBCL in the Young**

- 46 DLBCL ≤ 45y
- Immunocompetent
- M:F = 3.6:1
- Histologic spectrum
- PDL1 expression indicative of a tolerogenic immune microenvironment
- Superior outcome of EBV+ DLBCL in the young compared to the elderly
  - CR 82%, AWD 10%, DOD 8%
  - 5 y OS of 89% vs 24.4% (p<.0001)
- Term ‘elderly’ no longer in WHO 2016
EBV+ DLBCL: Is Age relevant?

- 46 Caucasian EBV+ DLBCL
- Compared <50 vs >50
  - No difference in clinicopathologic, IHC or genetic features
  - No difference in gene expression profiles or miRNA profiles
  - No difference in clinical outcome
- Need validation in larger cohorts of patients

**Challenges...**

- Significant overlap of similar proliferations across different immunodeficiency settings
  - “Similar” lesions between immunodeficiency and immunocompetent patients and among different immunodeficiency states may not be biologically similar
  - Virus or immune status may not be causal (bystander)
- Spectrum of lymphoid proliferations, diagnostic criteria and terminology are reasonably well established for post-transplant setting, but not in other settings
  - Lack of unifying nomenclature
- Increasing use of novel immunomodulatory agents and precision in immune monitoring, increases the complexity of treatment decisions related to whether or how early to treat

**Nomenclature for Immunodeficiency Disorders**

- Current classification is organized by immunodeficiency settings

**Proposed Unifying Nomenclature for Immunodeficiency Disorders**

- 2015 SH Workshop Panel proposal
- Aims to provide a common framework for discussion and further study and is not intended as a new classification at this time

**A name with 3 components**

- **Lesion**: hyperplasia, polymorphic LPD, DLBCL, etc
- **Virus**: EBV, HHV8, other
- **Immunodeficiency setting**: PTLD, HIV, primary, iatrogenic, etc

**Example**

- Polymorphic B-lymphoproliferative disorder, EBV+, iatrogenic setting (methotrexate)
When to Test for EBV and Molecular Clonality

**EBV testing**
- Known or suspected immunodeficiency
- Clinical history and drug regimen
- When morphology is polymorphous or discordant
- Necrosis
- Hemophagocytic lymphohistiocytosis
- Monocytoid B-cell clusters
- EBV monitoring in PTLD setting

**Clonality testing**
- EBV can induce oligoclonal or clonal proliferations
- Results should be interpreted with caution and in the context of clinical and histologic findings

Role of EBV & PD1/PDL1 Pathway

- EBV LMP1 & LMP2 enhance transcriptional activity of PD1/PDL2 to create a tolerogenic microenvironment by inducing T-cell anergy and immune evasion

**PD1/PD-L1 blockade**
- Removes tumor cell resistance to cytotoxic T-cell mediated lysis
- Restores anti-tumor activity of CD4+ T-cells
- Offers a novel therapeutic option

Expressed in
- NSHL, MCHL
- PMBL
- TCR/LCL
- EBV+ DLBCL
- Plasmablastic lymphoma
- NK/T cell lymphoma
- HHV8+ PEL

**Locking in**
- DLBCL, NOS
- Burkitt
- Small B-cell lymphoma

Thank you!