LYMPHOPROLIFERATIVE DISORDERS (LPD) ASSOCIATED WITH IMMUNE DEFICIENCY

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Spectrum of Immunodeficiency Disorders

Hyperplasia
- Polyclonal
- Polymorphic
- Polytropic

EBV

B-cell lymphoproliferations

T & NK-cell lymphoproliferations

HHV8

HHV8-associated lymphoproliferations

Lymphoma
- Monoclonal
- Monotypic
- Polyclonal
**Immunodeficiency Settings**

- EBV
- Host immune status
- HHV8
- Primary/Congenital
- Transplant
- Drugs
- Aging
- HIV
- Autoimmunity
- HHV8
- EBV
To what extent does the clinical setting determine the nature of the lymphoproliferative lesion?

- Some EBV-driven lesions appear similar in different clinical settings
  - Mucocutaneous ulcer can be seen with advanced age, iatrogenic therapy (MTX), and post-transplant

- Other pathology may be more directly tied to the clinical setting
  - HIV-associated lymphomas
  - Primary immunodeficiency disorders
EBV-related Lymphoproliferative B-cell Disorders

- Infectious mononucleosis
- Post-Transplant and other iatrogenic B-cell LPD’s
- Lymphomatoid granulomatosis
- EBV+ DLBCL with chronic inflammation
  - Fibrin-associated “diffuse large B-cell lymphoma”
- Mucocutaneous ulcer
- Classical Hodgkin’s lymphoma
  - Mainly Mixed cellularity and Lymphocyte depleted
- Primary effusion lymphoma (HHV-8 & EBV)
- Germinotropics B-LPD (HHV-8 & EBV)
- Plasmablastic lymphoma
- EBV + large B-cell lymphoma, NOS
- Burkitt lymphoma (subset)
Post-Transplant LPD “Early Lesions”

**Plasmacytic hyperplasia**
- Numerous interfollicular plasma cells
- Few scattered typical immunoblasts
- FH usually present

**IM-like hyperplasia**
- Polymorphous
- Plasma cells
- FH usually present
- Often in tonsil
- Mainly in children

**Follicular hyperplasia**
- EBV often in GC

**Differentiation from polymorphic-LPD:** Intact architecture
Number of EBV-positive cells
Early Lesion or “Non-Destructive PTLD” (WHO revised 2017)
EBER+ cells, either intrafollicular or interfollicular
Polyclonal by PCR; No cytogenetic aberrations
Conservative management

Same histological picture can be seen in elderly, HIV, other iatrogenic
Plasma Cell Hyperplasia
Many plasma cells are EBER neg
Polymorphic PTLD
- Effaced architecture
- Frequent necrosis
- Spectrum of differentiation
- Plasmacytoid cells common
- Few HRS-like cells
- Often Ig negative
EBV+ Cutaneous MALT lymphoma

Gibson et al AJSP 2011

- 4 cases following solid organ transplant (PTLD)
- Children and adults
- Mainly subcutaneous disease
- Marked plasmacytic differentiation, lack necrosis, unlike PTLD
- Preferentially IgA +
- EBNA2 negative, rare LMP1+ cells
Expanding the Spectrum of EBV-positive Marginal Zone Lymphomas
A Lesion Associated with Diverse Immunodeficiency Settings
Gong et al. Am J Surg Pathol, 2018

<table>
<thead>
<tr>
<th>10 cases EBV+ MZL, Ages 18-86, 4 M, 6 Fe</th>
</tr>
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<tbody>
<tr>
<td>• Post solid organ transplant, PTLD (2)</td>
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<tr>
<td>• Iatrogenic immune suppression, rheumatoid arthritis (2)</td>
</tr>
<tr>
<td>• Prior chemotherapy (2)</td>
</tr>
<tr>
<td>• Congenital immune deficiency (1)</td>
</tr>
<tr>
<td>• Age related (3)</td>
</tr>
<tr>
<td>• Aged 69, 70, 86</td>
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EBV+ Marginal zone Lymphomas
Diverse Anatomic Sites

- Skin and subcutaneous tissue (4)
- Parotid gland, periparotid (3)
  - Rheumatoid arthritis, Sjogren’s (2)
  - Congenital immune deficiency (1)
- Lung (1)
- Breast (1)
- Lymph node (1)
70 yo male with lesion of left flank – *no iatrogenic immunosuppression*
PCR positive for IG R – Fr III, IGK
54 year old female with history of rheumatoid arthritis, Sjogren’s syndrome

Patient treated with methotrexate, etanercept, infliximab
Patient presented with parotid swelling.
PET showed hypermetabolic adenopathy in the neck, chest, pelvis, and hypermetabolic enlargement of both parotid glands
CD20

EBER

IGH & IgK Rearranged
Monomorphic B-PTLD

- Fulfills criteria for a usually aggressive B-cell lymphoma in WHO
- May be EBV+ or EBV-
- Classify with usual criteria
  - Burkitt, DLBCL, Plasma cell myeloma
  - Classical Hodgkin lymphoma
- Occurs late after transplant
EBV-positive DLBCL “of the Elderly”

Median age ~ 70; M>F
70% extranodal; 30% nodal only
Aggressive clinical course
EBV + large B-cells in an inflammatory background, with necrosis, HRS-like cells
CD30+, MUM-1+, CD20+
   ABC phenotype
   • Failure of immune surveillance

Provisional entity in WHO 2008
Adrenal Mass; CHL - like
CD30
EBER
PAX5
CD20
EBV+ Large B-cell Lymphomas are not restricted to advanced age
Nicolae et al. Blood 2015

- Identified 46 cases with no evidence of immune deficiency, patients < 45 years
- Compared with EBV+ DLBCL in elderly patients
- Tumors frequently positive for PD-L1, suggestive of a permissive immune environment
- Majority nodal in presentation, > 90%
  - Differs from presentation in elderly
Tumor cells and microenvironment promote immune tolerance

PD-L1

> 75% cases +

IDO

High expression 87%
Overall survival: Young vs. “Elderly”

- EBV+ LBCL ≤45y
  - 3/39 deaths
- EBV+ LBCL >45y
  - 15/25 deaths

p<0.0001
EBV+ diffuse large B-cell Lymphoma, NOS
Terminology revised in WHO – not restricted by age
Mucocutaneous Ulcer
(Dojcinov et al. AJSP 2010)

**Sites**: Oropharyngeal mucosa (70%); Skin (25%); GI tract (5%)

**Median Age 77 (42-101)**
- Age related only, Med 79 (64-101)
- Age + iatrogenic immunosuppression, Med 72 (42-80)

- Waxing and waning clinical course, may regress spontaneously
- Clinical options, local radiation therapy, rituximab
- No disease related deaths
Mucocutaneous ulcer
An EBV-driven lesion of limited malignant potential

85 y.o. male
EBV+ Mucocutaneous Ulcer

CD30

EBER
CD15
CD30
PAX5
CD20
Phenotype often mimics Classical Hodgkin lymphoma

Some cases probably misclassified as CHL in the past
Spontaneous resolution of MCU in a patient with RA on MTX over the course of 8 weeks following withdrawal of drug
EBV-positive Mucocutaneous Ulcer in Organ Transplant Recipients
A Localized Indolent Posttransplant Lymphoproliferative Disorder

Melissa Hart, MD,* Beenu Thakral, MD,* Sophia Yohe, MD,*† Henry H. Balfour, Jr, MD,‡ Charanjeet Singh, MD,* Michael Spears, MD,† and Robert W. McKenna, MD*

• 7 cases in series of 70 transplant recipients
  5 renal, 1 heart, 1 lung
• Involved oral mucosa in 4 and GI tract in 3
• Patients treated with reduced immunosuppression or rituximab or both
• No patient recurred or developed another PTLD
• Conservative management is sufficient
Small bowel MCU in solid organ transplant recipient
Polyclonal by PCR
Fr 2, Fr 3, IgK

Treatment & Follow up:
4x Rituximab
Reduction of Mycophenolate acid from 720mg to 360mg
No evidence of disease with 10 months follow-up
Other Iatrogenic Lymphoproliferative Diseases

- Initially described with Methotrexate, particularly low dose methotrexate for protracted period Kamel et al. NEJM 1993
  - Lymphomas resembled DLBCL, CHL
- Now associated with more diverse immunosuppressive agents
  - Anti-TNF therapy, AZT, Lenalidomide, 6-MP, Fludarabine (CLL), Alemtuzumab (CLL)
- Clinical presentation may be atypical
  - Soft tissue mass, skin, non-nodal sites
Spectrum can be seen in diverse clinical settings
Iatrogenic, also Post-Transplant, HIV, Age

- Predominantly extranodal (65%)
- Range in size & appearance of EBER + cells
- Some cases resemble polymorphic PTLD
- May regress with reduction of immunosuppression
- Must rule out secondary DLBCL associated with underlying primary disease, e.g. Rheumatoid arthritis
61 yo F Ulcerative colitis Treated with 6-MP Subcutaneous mass

Granulomatous background Range in size of EBV+ cells
71 y.o. female referred with “recent dx of classical Hodgkin lymphoma”

Fevers, night sweats, weight loss, generalized lymphadenopathy

Other history:
Rheumatoid arthritis since 1999
Rx with MTX and infliximab (anti-TNF) since 2001
CD15

CD30

EBER-range in cell size

CD20

MTX discontinued

Regression with no further therapy
81 y.o. female with RA
Rx with MTX, prednisone, Remicade
Soft tissue mass

DLBCL, EBV+
Same patient as preceding slide, Hodgkin-like picture
EBV+ DLBCL with chronic inflammation
Fibrin-associated diffuse large B-cell lymphoma
(formerly pyothorax associated lymphoma)
Aozasa 2005; Loong et al. 2010

• EBV-driven clonal proliferations of large B-cells
  – Latency III phenotype, ABC by IHC
• Arise in an sequested (insulated) environment –protected from immune surveillance e.g longstanding pyothorax, cysts, thrombi, artificial valves/ grafts
• Shows morphologic overlap with aggressive malignancies
• Clinically localized, indolent and seldom disseminates
• “DLBCL” name may cause unnecessary overtreatment
27 yo male Bilateral hernia repair
3 years earlier
Left scrotal hematoma followed by orchiectomy
Subsequent paratesticular cyst
HIV-Associated Lymphomas

- Burkitt lymphoma
- Diffuse large B-cell lymphoma
  - GCB, may be EBV-negative
  - ABC, immunoblastic, EBV-positive
- Plasmablastic lymphoma
- HHV-8-associated LPD
  - PEL, Castleman’s disease
- Classical Hodgkin’s lymphoma
- Polymorphic lymphoproliferative disorder
### Comparison of HIV-associated B-cell Lymphomas

<table>
<thead>
<tr>
<th>Histology</th>
<th>Burkitt</th>
<th>DLBCL</th>
<th>GCB</th>
<th>PBL</th>
<th>CNS</th>
<th>PEL</th>
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<tbody>
<tr>
<td>Presentation</td>
<td>LN/ BM</td>
<td>Extranodal</td>
<td>CNS</td>
<td></td>
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<tr>
<td>Prior AIDS</td>
<td>25%</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
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<tr>
<td>CD4 Count</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td></td>
<td></td>
<td>Decreased</td>
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<tr>
<td>EBV</td>
<td>30-50%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHV-8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>C-MYC</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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Plasmablastic Lymphoma

- Plasmablastic lymphoma
  - Most often presents at mucosal sites
    - Oral cavity, GI tract
    - May be primary in skin
- Associated with immunodeficiency
  - Immunodeficiency disorders, often HIV
  - Elderly
  - Congenital and Acquired, Post – Transplant
- Clinically aggressive
- \textit{Latency I}, MYC translocations reported in 50\%
Plasmablastic Lymphoma
Colomo 2004; Valera et al, 2010

Gingival lesion, HIV+ male
CD20 negative, often CD138+

EBER+/ LMP1-
Latency I
MYC translocations in Plasmablastic Lymphoma
Valera et al 2010; Taddesse-Heath et al 2010

- 50% incidence in PBL
  - More frequent in EBV pos (74%) than EBV neg (43%)
- MYC/IG most common
- No concurrent rearrangements of BCL2, BCL6, MALT1 or PAX5
- Deletions 13q, 17p
- Frequent “myeloma” type aberrations
  - gains of odd numbered chromosomes
- MYC rearrangement also a late event in myeloma (Kuehl et al)
Plasmablastic transformation of myeloma
“Plasmablastic Lymphomas”

Several different entities can have plasmablastic morphology and phenotype

- Loss of B-cell antigens, plasmacytic differentiation

- Plasmablastic lymphoma “of the oral cavity”
  - Mucosal associated sites, Often HIV+
  - Monomorphonic, no inflammatory background

- Plasmablastic myeloma

- ALK+ Large B-cell lymphoma

- Primary effusion lymphoma, HHV8+
Multicentric Castleman’s Disease, HHV-8/KSHV

- HIV-associated, elderly patients from endemic areas
  - Mediterranean, North Africa
- Rare cases with similar clinical features may be unrelated to HHV8 (TAFRO syndrome)
  - Requires stringent clinical and laboratory criteria
  - Should not be a wastebasket for diverse immune syndromes
- Distinguish from HHV8-associated lymphomas
  - PEL, extracavitary PEL, Germinotropic LPD
• “Microlymphomas” in MCD
  Part of the spectrum of MCD, does not represent histological progression
• IgMλ expressed in plasmablasts/immunoblasts but polyclonal by PCR
• Viral IL-6 expressed

• Lymphoid cells positive for HHV8 can be found in PB, PF
• Not necessarily evidence for progression to lymphoma

_Du et al. Blood 2001_
HHV-8 Associated Primary Effusion Lymphoma - PEL
Germinotropic LPD
HIV-negative
Often elderly
Good prognosis

Germinal center B-cells
Co-infected with EBV/HHV8
## HHV-8 Associated Lymphoproliferations

<table>
<thead>
<tr>
<th></th>
<th>MCD</th>
<th>PEL &amp; extracavitary PEL</th>
<th>Germinotropic LPD</th>
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</thead>
<tbody>
<tr>
<td>HIV-associated</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>EBV</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PCR Clonality</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IG Class</td>
<td>IgM lambda</td>
<td>Neg</td>
<td>IgG</td>
</tr>
<tr>
<td>Viral IL-6</td>
<td>+</td>
<td>+</td>
<td>+</td>
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EBV+ B-Cell Spectrum

Patterns of reactive B-cell hyperplasia
- Follicular hyperplasia
- IM-like hyperplasia
- Plasmacytic hyperplasia

B-LPD of varied malignant potential
- Polymorphic B-LPD
- Mucocutaneous ulcer
- Large B-cell proliferation

Indolent B-cell lymphoma
- Marginal zone lymphoma

Aggressive B-cell lymphoma
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Classical Hodgkin lymphoma

Hyperplasia
- Polymorphic
- Polyclonal
- Polytypic

Lymphoma
- Monomorphic
- Monoclonal
- Monotypic
T-cell lymphomas associated with immunodeficiency

- Post-Transplant T-cell lymphomas
  - Can be EBV pos or EBV neg
  - Occur many years after transplant
    - Classified as Monomorphic PTLD
      - Distinguish from aberrant CD3 in a EBV+ or HHV-8+ large B-cell lymphoma
- Most EBV+ T-cell lymphomas are not directly linked to immune deficiency, but genetics may play a role
EBV+ Immunodeficiency Associated T-cell Lymphomas

- Usually have a cytotoxic phenotype
- May be associated with hemophagocytic syndrome
- Occur rarely with HIV, advanced age
- Clinically aggressive
  - Systemic EBV+ T-cell lymphoma
  - PTCL, NOS, EBV+
Immunodeficiency Settings

- Host immune status
- Primary/Congenital
- Aging
- Drugs
- Transplant
- HIV
- Autoimmunity
- HHV8
- EBV