POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

Definition: A spectrum of reactive to malignant lymphoid proliferations caused by immune suppression in solid organ or stem cell transplant recipients and is strongly associated with EBV

Risk of PTLD: <1% renal transplant, 1-2% allogeneic stem cell transplant, 1-5% hepatic or cardiac transplant, >5% lung, heart-lung, or intestine transplant

B-cell phenotype in 85-90%, T/NK-cell phenotype in 10-15%

Association with EBV: B-cell type: 2/3 EBV+, 1/3 EBV-; T/NK-cell type: 1/3 EBV+, 2/3 EBV-

Most PTLD arise within 1 year of transplant, smaller numbers arise later (4-5, even >10 years)

Clinical features highly variable, ranging from asymptomatic, to vague symptoms, to overt constitutional symptoms and organ-specific symptoms

Serum EBV viral load is useful in disease monitoring

Prognosis varies depending on subtypes and clinical features (better to worse: ND-PTLD > P-PTLD > M-PTLD). Higher mortality in stem cell recipients than solid organ recipients

NON-DESTRUCTIVE PTLD (ND-PTLD)

A mass lesion with expansion of reactive cells but with preserved normal architecture

Evidence of EBV in the lesions

Three subtypes: plasmacytic hyperplasia, infectious mononucleosis-like, florid follicular hyperplasia

Morphology: Considerable morphologic overlap between subtypes

Plasmacytic hyperplasia: Plasma cell proliferation is the dominant feature

Infectious mononucleosis-like: Mixed paracortical proliferation of T-lymphocytes, plasma cells, immunoblasts

Florid follicular hyperplasia: Follicular hyperplasia is the dominant feature

Phenotype: Normal lymphoid phenotype. EBV+ by EBER in situ hybridization

Genetics: Small monoclonal or oligoclonal IGH rearrangements may be present. Large dominant clone of IGH absent

Prognosis: Excellent. Regresses spontaneously with reduction of immune suppression. Surgical resection in persistent cases

POLYMORPHIC PTLD (P-PTLD)

Mass or destructive lesion with effacement of normal tissue by a mixed lymphoid and inflammatory infiltrate and is associated with EBV in nearly all cases

Morphology: Effacement of underlying tissue with a mixed inflammatory infiltrate: small to medium-sized lymphocytes, plasma cells, immunoblasts (in single forms), HRS-like cells may be present

Large areas of geographic necrosis common

Phenotype: Lymphocytes are mixed B and T cells (often T-cell predominant), Immunoblasts and HRS-like cells are CD30+, CD20+, CD15- (differ from true HRS cells). EBV+ by EBER in situ hybridization (vast majority)

Genetics: Monoclonal IGH gene rearrangement in up to 50%. Oligoclonal IGH rearrangements are common
**Prognosis:** Considered as benign lesion. Spontaneous regression after reduction in immunosuppression in some cases. Other cases require immunotherapy or chemotherapy in addition of reduction/cessation of immune suppression.

**Monomorphic PTLD (M-PTLD)**
60-80% all PTLD
B and T/NK lymphomas similar to the lymphomas in immunocompetent population
 Nearly all are aggressive lymphomas (except for MALT)
Specific entities:
- **B-cell M-PTLD** (85-90%): Diffuse large B-cell lymphoma, Burkitt lymphoma, Plasmacytoma, MALT lymphoma of skin and subcutaneous tissue
- **T/NK-cell M-PTLD** (10-15%): Peripheral T-cell lymphoma NOS, hepatosplenic T-cell lymphoma, T-cell large granular lymphocytic leukemia, extranodal NK/T cell lymphoma nasal type, mycosis fungoides, anaplastic large cell lymphoma

**Morphology:** Morphology identical to lymphomas in immunocompetent population, geographic necrosis common

**Phenotype:** Phenotype identical to lymphomas in immunocompetent population

**EBV status:** B-cell PTLD: 70% EBV+, 30% EBV-
T/NK cell PTLD: 1/3 EBV+, 2/3 EBV-

**Genetics:**
- **B-cell types:** Clonal IGH gene rearrangement, coexisting TCR clones common
- **T-cell types:** Clonal TCR rearrangement in T-cell types

**Prognosis:** Worse than P-PTLD (except for MALT lymphoma which has a better prognosis). Usually requires reduction/cessation of immune suppression plus combination chemotherapy

**Classical Hodgkin Lymphoma PTLD (cHL-PTLD)**
Classical Hodgkin lymphoma arising after transplant and is associated with EBV
Least common type of M-PTLD
**Morphology:** Most cases are mixed cellularity type

**Phenotype:** Classical Hodgkin lymphoma phenotype, more frequent CD20+. EBV+ in HRS cells

**Genetics:** Small monoclonal or oligoclonal IGH rearrangement or TCR rearrangement may be present

**Prognosis:** Usually requires reduction/cessation of immune suppression plus combination chemotherapy

**Immunoglobulin and T-cell receptor rearrangements in PTLD**

<table>
<thead>
<tr>
<th>PTLD type</th>
<th>Immunoglobulin gene rearrangement</th>
<th>T-cell receptor gene rearrangement</th>
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</thead>
<tbody>
<tr>
<td>ND</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>P</td>
<td>50% Positive, 50% Negative</td>
<td>May be positive</td>
</tr>
<tr>
<td>M B-cell</td>
<td>Positive</td>
<td>May be positive</td>
</tr>
<tr>
<td>M T/NK-cell</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>cHL</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**HIV-Associated Lymphoproliferative Disorders**
Reactive and neoplastic lymphoid disorders arising after HIV infection
Malignant lymphomas are considered as AIDS-defining conditions
Incidence of non-Hodgkin lymphoma compared to general population: 60-200 times with cART therapy, 120-400 times before cART therapy.
Incidence of Hodgkin lymphoma compared to general population: 5-20 times regardless cART treatment
 Improvement of CD4 count reduces the risk of lymphoma
 40% are associated with EBV
 HHV8+ in primary effusion lymphoma (in addition to EBV+)
 Extranodal involvement more common (GI, CNS, liver, bone marrow, oral cavity, lung, skin, testes, heart, breast)

**HIV-related benign lymphadenopathy (HIV-BL)**
 Most common HIV-related lymphoid disorder
 Persistent generalized lymphadenopathy
 Systemic symptoms common: fever, fatigue, night sweat, weight loss
 Represents stages of progression with 4 morphologic patterns: florid follicular hyperplasia, mixed follicular hyperplasia and involution, follicular involution, lymphocyte depletion
  **Morphology:** Massively hyperplastic follicles with various geographic shapes (“dumbbell” and other bizarre shapes), clusters of monocytoid B cells
 Involuting follicles are reduced in size, with regressed, often hyalinized germinal centers
 Lymphocyte depleted lymph nodes are reduced in size and replaced by connective tissue stromal cells, scant lymphoid elements and absent germinal centers
  **Prognosis:** Benign

**Benign lymphoepithelial cyst (BLEB)**
 Affects salivary glands
 Caused by epithelial metaplasia and duct obstruction that result in cyst formation and lymphoid hyperplasia
  **Morphology:** Columnar, cuboidal, or squamous lined benign cysts, containing pink or clear fluid, surrounded by hyperplastic lymphoid tissue
  **Prognosis:** Benign

**HIV-related multicentric Castleman disease (HIV-MCD)**
 Most cases are plasma cell variant or mixed variant
 Often coexists with Kaposi sarcoma
 HHV8 positive
 Increased risk of developing lymphoma (15 times more)
  **Morphology:** Similar to plasma cell and mixed type MCD in immunocompetent population
 Follicular hyperplasia and hyalinization and interfollicular plasma cells may be more prominent
  **Plasmablastic variant:** Lambda restricted immunoblasts in mantle zone
  **Prognosis:** Protracted course

**HIV-associated non-Hodgkin and Hodgkin lymphomas**
 Lymphoma types include (in decreasing frequency): diffuse large B-cell lymphoma, primary central nervous system lymphoma, Burkitt lymphoma, classical Hodgkin lymphoma, plasmablastic lymphoma, primary effusion lymphoma
  **Morphology:** Similar to their counterparts in immunocompetent population
 Association with EBV: DLBCL 40%, CNS lymphoma 80-100%, Burkitt lymphoma 50%, classical Hodgkin lymphoma ~100%, plasmablastic lymphoma 60-70%, primary effusion lymphoma ~100%
  **Prognosis:** Variable response to chemotherapy, generally poor outcome
Primary Immune Deficiency-Associated Lymphoproliferative Disorders

Primary immunodeficiency with increased susceptibility to LPDs:

**Common variable immune deficiency (CVID):** A group of diseases with reduced serum IgG, IgM, and/or IgA. Sporadic and inherited with variable inheritance. 2-7% develop lymphoma

**Severe combined immunodeficiency (SCID):** A group of diseases with severe deficiency of T-lymphoid immunity and some with additional B-cell immunity deficiency. Nearly 100% develop EBV+ lymphoma

**Hyper IgM syndrome (HlgM):** A group of diseases with deficiency of either CD40 or CD40 ligand. Variable inheritance.

**Ataxia-Telangiectasia (AT):** Immune deficiency, cerebella degeneration. 20% develop lymphoma or leukemia

**Wiskott-Aldrich syndrome (WAS):** X-linked inheritance affecting only male. Immune deficiency, thrombocytopenia and microthrombosis, eczema. 10-20% develop hematologic malignancy

**X-linked lymphoproliferative disorder (XLP):** X-linked inheritance affecting only male. Immune deficiency, Nearly 100% develop EBV-associated lesions or lymphoma

**Autoimmune lymphoproliferative syndrome (ALPS):** Caused by mutation of FAS gene or other related genes. Asymptomatic lymphadenopathy and/or splenomegaly, cytopenia, autoimmune disorder. Benign lymphoid hyperplasia in lymph node with increased CD4-/CD8- T cells. 3-10% develop lymphoma (EBV+ or EBV-)

### Primary immune deficiency and associated LPDs

<table>
<thead>
<tr>
<th>Immune Deficiency Type</th>
<th>Associated Disorders (EBV+)</th>
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<tbody>
<tr>
<td>CVID</td>
<td>DLBCL, cHL, MALT, SLL, LPL, PTCL</td>
</tr>
<tr>
<td>SCID</td>
<td>Fatal IM, aggressive lymphomas</td>
</tr>
<tr>
<td>AT</td>
<td>T-cell lymphoma, DLBCL, BL, cHL</td>
</tr>
<tr>
<td>WAS</td>
<td>LYG, DLBCL, cHL</td>
</tr>
<tr>
<td>HlgM</td>
<td>DLBCL, cHL, LGL</td>
</tr>
<tr>
<td>XLP</td>
<td>Fatal IM, DLBCL, BL</td>
</tr>
<tr>
<td>ALPS</td>
<td>NLPDH, cHL, DLBCL, BL (some EBV-)</td>
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Other iatrogenic (Medication and Age-Related) Immunodeficiency-Associated Lymphoproliferative Disorders

Reactive and neoplastic lymphoid proliferations arising in individuals receiving immune suppressants or immune modulatory medication other than transplant settings and in individuals with age-related immune senescence

The reactive lesions are self-limited with withdrawal of medication. The lymphomas require treatment with single agent or combination chemotherapy
**Lymphoproliferative disorders associated with iatrogenic medication**

Two loosely-divided categories:

**Therapy for autoimmune/chronic inflammatory disorders:** Therapies for rheumatoid arthritis, inflammatory bowel disease, psoriasis & psoriatic arthritis, systemic lupus erythematosus, ankylosing spondylitis

- Commonly used drugs include methotrexate, azathioprine, 6-mercaptopurine, infliximab, adalimumab, etanercept, anakinra, tocilizumab, abatacept, tocilizumab

**Therapy for hematologic malignancies:** Immune modulators for chronic lymphocytic leukemia, plasma cell myeloma

- Commonly used drugs include fludarabine, cyclophosphamide, methotrexate, alemtuzumab, chlorambucil, cyclosporine, bendamustine, bortezomib, doxorubicin, melphalan, dasatinib

**Types of lymphoproliferative disorders associated with iatrogenic medication:**

- **Polymorphic lymphoid proliferation (PID):** A spectrum of benign morphologic changes including follicular hyperplasia, paracortical hyperplasia, atypical lymphohistiocytic proliferation, lymphoid proliferation with Hodgkin-like cells

- **Dasatinib-associated reactive follicular hyperplasia:** Hyperplastic lymph node with follicular hyperplasia and progressive transformation of germinal centers

- **Methotrexate-associated diffuse large B-cell lymphoma:** Typical morphology of DLBCL, EBV+ in >3/4 cases. CD30 frequently positive

- **Classical Hodgkin lymphoma and Hodgkin-like lesions:** Majority of cHL express EBV. Hodgkin-like lesions have similar morphology to cHL but with activated B-cell phenotype (CD20+, CD45+, CD30+, CD15-) in large cells. Some Hodgkin-like lesions arise from CLL treated with fludarabine

**Lymphoproliferative disorder associated with age-related immune senescence**

- **EBV positive mucocutaneous ulcer:** A very rare disease presented with EBV+ ulcerative lesions in gingiva or less commonly in other mucocutaneous locations

  - Seen in individuals receiving immunosuppressive therapy (50%), elderly age (40%), primary immune deficiency (10%)

  - Polymorphic infiltrate with scattered atypical large Hodgkin-like B cells with abundant T cells in the background. The large cells are positive for CD30 and EBV