Overview of Lymphoproliferative Disorders Associated With Primary Immunodeficiency Disorders

TERMINOLOGY
Definitions
- Primary immunodeficiency disorders (PID) are a heterogeneous group of inherited diseases
- Focus here on lymphomas and lymphoma-like lesions that arise in setting of PID designated as
  - Primary immunodeficiency-associated lymphoproliferative disorders (LDPs)

EPIDEMIOLOGY
1st Report of PID
- Described by Ogden Bruton in 1952
  - Now known as X-linked agammaglobulinemia

Spectrum of PIDs
- ~ 200 known types of PID
- Primary immunodeficiencies are grouped into 9 general categories by Expert Committee of International Union of Immunological Societies, 2015
  - Combined immunodeficiencies
  - Combined immunodeficiencies with associated or syndromic features
  - Predominantly antibody deficiencies
  - Immune dysregulation diseases
  - Congenital defects of phagocyte number &/or function
  - Defects in innate immunity
  - Autoinflammatory disorders
  - Complement deficiencies
  - Phenocopies
    - Somatic mutations that mimic inherited mutation and PID

Incidence
- Variable incidence of clinically evident PID in USA
  - Cumulative incidence: 1 in 10,000
    - ~ 400 new cases/year in USA
- PIDs are more common in children
  - Exception: Common variable immunodeficiency disease (CVID) occurs in adults

Risk of LPDs
- Patients with PID are at increased risk of developing neoplasms
  - Risk increased 10-200x depending on type of PID
    - Cumulative risk of LPD ranges from 0.7-15.0% according to specific PID
  - ~ 60% of all neoplasms are LDPs; non-Hodgkin lymphoma (HL) most common

Age Range
- Median age of onset of LPD: ~ 7 years

Gender
- PIDs are more common in males

ETIOLOGY/PATHOGENESIS
Etiology
- Gene mutations account for many PIDs
  - Ataxia-telangiectasia (AT): ATM
  - Nijmegen breakage syndrome (NBS): NBN (NBS, NBS1)
  - X-linked hyper-IgM syndrome: CD40 or CD40 ligand (CD40LG)
  - Wiskott-Aldrich syndrome: WAS
  - Cartilage hair hypoplasia syndrome: RMRP
  - X-linked lymphoproliferative syndrome (XLP): SH2D1A or BIRC3/XIAP
  - Autoimmune lymphoproliferative syndrome (ALPS): FAS (TNFRSF6)
- Etiology of many PIDs poorly understood and defined by their phenotype

Pathogenesis
- Gene mutations cause functional defects that compromise immune system
- Basis for increased risk of hematologic neoplasms is likely multifactorial
  - Impaired host immunosurveillance
  - Chronic antigen stimulation
  - Epstein-Barr virus (EBV) infection drives subset of LDPs
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- Defective DNA mismatch repair involved in AT and NBS
- Possible unknown oncogenic viruses may be involved

**CLINICAL IMPLICATIONS**

**Clinical Presentation**
- Patients with PID often present with recurrent infections
  - Fever, fatigue, infectious mononucleosis-like syndrome
  - Often diagnosed in 1st year of life
  - LPDs are often extranodal
- CVID
  - Incidence: 1 in 10,000; more common in whites
  - Onset of infections at 20-30 years of age
  - Autoimmune manifestations; low serum immunoglobulin levels
- IgA deficiency
  - Incidence: 1 in 700
  - Onset in adults; often resembles CVID clinically
- AT
  - Incidence: 1 in 80,000
  - Progressive neuronal degeneration, radiosensitivity, combined immunodeficiency
- NBS
  - Incidence: 1 in 100,000
  - Short stature, microcephaly, dysmorphic facial features
  - Intellectual impairment, recurrent infections
  - Severe combined immunodeficiency (SCID)
  - Failure to thrive in 1st few months, infections
- Wiskott-Aldrich syndrome
  - Incidence: 1 in 250,000
  - Classic triad: Eczema, microthrombocytopenia, recurrent infections
  - Combined defects in T cells, B cells, and phagocytes
- Hyper-IgM syndrome
  - Recurrent bacterial infections
  - Defects in cell-mediated immunity
- X-linked agammaglobulinemia
  - Incidence: 1 in 100,000
  - Recurrent bacterial infections
- XLP
  - Patients often present with lymphadenopathy &/or hepatosplenomegaly
  - Fulminant infectious mononucleosis can occur; can be fatal
- ALPS
  - Autoimmune phenomena
  - Lymphadenopathy &/or hepatosplenomegaly
  - Related syndrome that overlaps with ALPS
    - RAS-associated leukoproliferative disease
      - NRAS mutation: Increased risk of juvenile myelomonocytic leukemia
  - Cartilage hair hypoplasia syndrome
    - Sparse hair, metaphyseal chondro dysplasia, anemia
    - Symptoms attributable to combined immunodeficiency
  - Interleukin-2-inducible T-cell kinase deficiency
    - Lymphadenopathy and lung infiltrates
    - Clinical overlap with XLP
    - Mutations of ITK at 5q31-32

**Treatment**
- Reduced risk of LPD after allogeneic stem cell transplant in PID patients
- Limited data due to rarity of PIDs and lack of randomized trials
- Recommendation is to treat with lymphoma type-specific protocol

**Prognosis**
- Related to both underlying PID and type of LPD
  - Most LPDs in PID patients are clinically aggressive
  - Clinically indolent, CVID
- Antimicrobial agents facilitate more aggressive treatments and have improved prognosis

**MICROSCOPIC**

**Morphologic Spectrum of PID-Associated LPDs**
- These lesions resemble LPDs that occur in other immunodeficiency settings
  - Posttransplant, iatrogenic, HIV infection

**Nonneoplastic Lesions in Lymph Nodes**
- Common findings
  - Lymphoid depletion
  - Atrophic follicles with progressive depletion of germinal centers
  - Depletion of small lymphocytes in paracortical region
  - Similar findings observed in spleen and tonsils
- Secondary changes
  - Chronic granulomatous inflammation secondary to infections
  - Florid reactive hyperplasia; atypical hyperplasia
- Fatal infectious mononucleosis resulting from EBV infection (XLP, SCID)
  - Systemic uncontrolled proliferation of abnormal B cells
  - Polymorphous lymphoid cells with plasmacytoid and immunoblastic differentiation
  - Frequent hemophagocytic syndrome
- Waxing and waning lymphoproliferations (CVID)
  - Variable morphology; follicular hyperplasia and paracortical expansion
  - Characteristic nodular lymphoid hyperplasia in gastrointestinal tract
- X-linked hyper-IgM syndrome
  - Extensive accumulation of IgM-producing plasma cells in extranodal sites
  - Peripheral blood B cells express only IgM and IgD
- ALPS
  - Expansion of CD4(-), CD8(-) T cells (so-called double-negative cells)
  - Prominent follicular hyperplasia

**Precursor Lesions**
- Broad morphologic spectrum
- Increasingly dominant clonal population, from polyclonal to oligoclonal to monoclonal
- Monoclonal expansions may or may not progress to major persistent lesions
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Neoplastic Lesions

- Increased risk of developing lymphomas and leukemias (lymphoma > leukemia)
- Also increased risk for nonhematopoietic tumors
- Polymorphous cytologic features are common
- Non-HL
  - B-cell lymphomas more common than T-cell lymphomas
  - Diffuse large B-cell lymphoma (DLBCL) is most common
    - Immunophenotype similar to DLBCLs in immunocompetent patients
    - Frequently EBV(+)
  - Burkitt lymphoma is more common in XLP than in other PIDs
- HL
  - 2nd most common LPD
  - ~ 10% of all lymphomas in PID patients
  - Classic HL most common in PID patients
    - Lymphocyte depleted and mixed cellularity types common
      - Attributable to feeble immune response
    - Reed-Sternberg + Hodgkin cells: CD15(+/-), CD30(+), pax-5 (dim +), CD45/LCA(-)
  - Nodular lymphocyte-predominant HL uncommon except in patients with ALPS

Differential Diagnosis for Nonneoplastic Lesions

Neoplastic Hematologic Lesions in PID

- Critical to determine whether LPD is benign or malignant
  - Benign lesions can histologically mimic lymphoma
  - Immunophenotyping and molecular studies are useful for this purpose
Benign Lymphoid Tissue in Neonates

- Morphology in normal newborns may be difficult to distinguish from PID-related changes
  - Lymph nodes at birth composed of small primary follicles and poorly developed paracortex
  - Other lymphoid tissue sites show similar changes (e.g., spleen)

Lymphoid Depletion in Longstanding Infections

- Lymphoid depletion in non-PID babies with longstanding infections can mimic PID

Angioimmunoblastic T-Cell Lymphoma

- Can show overlapping features with PID
  - Lymphoid depletion, paracortical expansion, polymorphous cell population
  - Distinguishing features
    - Occurs in adults and usually elderly
    - T cells in PID do not express CD10, Bcl-6, or CXCL13

Castleman Disease, Hyaline Vascular Type

- Overlapping features with PID
  - Atrophic follicles with lymphocyte depletion and hypervascularity
  - Distinguishing features
    - Lymph nodes are not enlarged in PID and lack features of Castleman disease

Differential Diagnosis for Neoplastic Lesions

Primary Immunodeficiency-Associated LPDs

- Overt LPDs in PID are histologically and immunophenotypically similar to lesions arising in immunocompetent hosts
- Clinical history is critical for establishing diagnosis

Selected References

### Overview of Lymphoproliferative Disorders Associated With Primary Immunodeficiency Disorders

### Primary Immunodeficiency Disorders With Increased Risk of Malignancy*

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
<th>Inheritance</th>
<th>Population Frequency</th>
<th>Frequency of PID (%)</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>T- and B-cell immunodeficiencies</td>
<td>SCID</td>
<td>AR, X</td>
<td>1 in 100,000 live births</td>
<td>1-5</td>
<td>Severe recurrent infections</td>
</tr>
<tr>
<td></td>
<td>XHIGM</td>
<td>X</td>
<td>1 in 20 million live male births</td>
<td>1-2</td>
<td>Pancytopenia, hepatobiliary tract disease, <em>Pneumocystis jiroveci</em> infections</td>
</tr>
<tr>
<td>Antibody deficiencies</td>
<td>CVID</td>
<td>AD, S</td>
<td>1 in 10-50,000 live births</td>
<td>21-31</td>
<td>Recurrent bacterial infections, low serum immunoglobulin levels</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>AD, S</td>
<td></td>
<td>1 in 700 individuals of European origin</td>
<td>&gt; 50 (most common)</td>
<td>Prone to bacterial infections, low IgA serum levels</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>X</td>
<td></td>
<td>1 in 100,000</td>
<td>&lt; 1</td>
<td>Recurrent bacterial infections; low serum immunoglobulin levels</td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td>XLP</td>
<td>X</td>
<td>~ 500 documented cases</td>
<td>&lt; 1</td>
<td>EBV infections trigger clinical and immunologic abnormalities</td>
</tr>
<tr>
<td></td>
<td>ALPS</td>
<td>AD, AR</td>
<td>Unknown</td>
<td>&lt; 1</td>
<td>Lymphadenopathy, splenomegaly autoimmune phenomena</td>
</tr>
<tr>
<td></td>
<td>WAS</td>
<td>X</td>
<td>1 in 250,000 live male births</td>
<td>1-3</td>
<td>Thrombocytopenia with small platelets, eczema</td>
</tr>
<tr>
<td>DNA repair defects</td>
<td>AT</td>
<td>AR</td>
<td>1 in 40-100,000 live births</td>
<td>2-8</td>
<td>Cerebellar degeneration, oculocutaneous telangiectasia, hypersensitivity to ionizing radiation</td>
</tr>
<tr>
<td></td>
<td>NBS</td>
<td>AR</td>
<td>1 in 100,000 live births</td>
<td>1-2</td>
<td>Microcephaly, short stature, dysmorphic facial features, impaired intellect</td>
</tr>
</tbody>
</table>

* Only common or well-known PIDs are included in this table.

### Malignancies in Primary Immunodeficiency Disorders*

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
<th>Malignancy Rate (%)</th>
<th>Median Age (y)</th>
<th>Gender (M:F)</th>
<th>Hematologic</th>
<th>Nonhematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>T- and B-cell immunodeficiencies</td>
<td>SCID</td>
<td>1.5</td>
<td>1.6</td>
<td>3.3:1.0</td>
<td>DLBCL, CHL, leukemias</td>
<td>Renal and pulmonary leiomyomata</td>
</tr>
<tr>
<td></td>
<td>XHIGM</td>
<td>7.8</td>
<td>7.2</td>
<td></td>
<td>DLBCL, CHL, LGL leukemia</td>
<td>n/a</td>
</tr>
<tr>
<td>Antibody deficiencies</td>
<td>CVID</td>
<td>2.5 (onset &lt; 16 years), 8.5 (onset &gt; 16 years)</td>
<td>23</td>
<td>1.3:1.0</td>
<td>DLBCL, CHL, SLL, MALT lymphoma, LPL, PTCL</td>
<td>Epithelial tumors (39%; stomach, breast, bladder, cervix, vulva)</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>Rare</td>
<td>n/a</td>
<td>n/a</td>
<td>CHL, DLBCL, leukemia</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>Rare</td>
<td>&lt; 10</td>
<td>M</td>
<td>DLBCL</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td>XLP</td>
<td>30</td>
<td>n/a</td>
<td>n/a</td>
<td>EBV(+) fatal infectious mononucleosis, DLBCL, Burkitt</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>ALPS</td>
<td>10-20</td>
<td>&lt; 1</td>
<td>n/a</td>
<td>DLBCL, NLPHL, CHL, DLBCL, Burkitt, PTCL</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>WAS</td>
<td>13</td>
<td>6.2</td>
<td>M only</td>
<td>DLBCL, CHL</td>
<td>Cerebellar astrocytoma, Kaposi sarcoma, muscle tumors</td>
</tr>
<tr>
<td>DNA repair defects</td>
<td>AT</td>
<td>33</td>
<td>8.5</td>
<td>1.7:1.0</td>
<td>DLBCL, Burkitt, T-PLL (young adults), T-ALL/LBL (age: 1-5 years), CHL</td>
<td>Epithelial tumors</td>
</tr>
<tr>
<td></td>
<td>NBS</td>
<td>Rare</td>
<td>n/a</td>
<td>n/a</td>
<td>DLBCL, PTCL, T-ALL/LBL, CHL</td>
<td>Brain tumors</td>
</tr>
</tbody>
</table>

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*(Left)* This lymph node biopsy specimen from a patient with CVID shows atypical lymphoid hyperplasia. The overall architecture is distorted but not effaced. The paracortical region is expanded and shows vascular proliferation, and sinuses are patent. *(Right)* This lymph node from a CVID patient shows atypical lymphoid hyperplasia. In this field, a large follicle without a mantle zone is shown in the center.

*(Left)* Lymph node involved by polymorphic B-cell lymphoproliferative disorder (LPD) in a patient with ataxia-telangiectasia (AT) is shown. Note the effacement of the interfollicular region. Monoclonal immunoglobulin heavy chain gene rearrangement was detected by PCR. *(Right)* Lymph node involved by polymorphic B-cell LPD in a patient with AT is shown. A residual follicle is surrounded by the lymphoma in this field.

*(Left)* Lymph node involved by polymorphic B-cell LPD in an AT patient is shown. The interfollicular region shows a polymorphic lymphoid infiltrate of predominantly medium-sized lymphocytes admixed with large transformed cells. *(Right)* Lymph node involved by polymorphic B-cell LPD in a patient with AT is shown. Most lymphocytes are CD20(+) and show a primarily interfollicular distribution. By flow cytometry, B cells were CD19(+), CD20(+), and dim monoclonic kappa (+).
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**Polymorphic B-Cell LPD in AT: CD3**

Lymph node involved by polymorphic B-cell LPD in a patient with AT is shown. The atypical cells are CD3(-). There is a marked increase of CD3(+) T lymphocytes in a dystrophic follicle. (Right) Lymph node involved by DLBCL in a WAS patient is shown. The neoplastic cells are intermediate to large with irregular nuclear contours, prominent nucleoli, and abundant cytoplasm. There are scattered interspersed eosinophils and a mitotic figure.

**DLBCL in WAS**

(Last) Touch imprint of a lymph node involved by DLBCL in a patient with WAS is shown. Note the many large cells. A mixed inflammatory cell infiltrate is also present in the background. (Right) Lymph node involved by DLBCL in a WAS patient is shown. Anti-CD20 antibody highlights large atypical B cells.

**DLBCL in WAS: Touch Imprint**

**DLBCL in WAS: CD20**

**DLBCL in WAS: Kappa (+)**

**DLBCL in WAS: Lambda (-)**

(Last) Lymph node involved by DLBCL in a WAS patient is shown. The large neoplastic cells are kappa (+), shown by immunohistochemistry. (Last) Lymph node involved by DLBCL in a patient with WAS is shown. The large neoplastic cells are lambda (-) shown by immunohistochemistry.