REACTIVE LYMPH NODE DISEASES

Viral Lymphadenitis
Enlarged lymph nodes with expansion of lymphoid follicles and paracortex in variable degrees
Granulomas are usually absent
Clinical presentation variable but usually associated with fever, tender lymphadenopathy

Lymph node morphology:
- **Infectious mononucleosis (IM)**
  Interfollicular proliferation of mixed lymphoid population consisting of small lymphocytes, plasma cells, histiocytes, and immunoblasts. Immunoblasts may form sheets (mimic large cell lymphoma). Variable degree of follicular hyperplasia. The immunoblasts have a mixed B-cell (CD20) and T-cell (CD3) phenotype, and express EBER and CD30 (variable). Necrosis or granuloma absent

- **Human immunodeficiency virus (HIV)-associated lymphadenopathy**
  Early stage: Marked follicular hyperplasia with expanded germinal centers. Expanded follicles often have bizarre shape such as “dumb bell” shape and “naked” germinal centers. Follicle lysis with “bleeding” into the follicles. Clusters of monocytoid B cells usually present. Necrosis and granuloma absent
  Late stage: Lymphocyte-depleted morphology with "burned out" follicles

- **Herpes lymphadenitis (HSV)**
  Prominent paracortical hyperplasia with necrosis without associated granulomas. The necrotic areas contain neutrophils and karyorrhectic or amorphous eosinophilic debris. Viral inclusions may be present

- **Cytomegalovirus lymphadenitis (CMV)**
  Morphology identical to infectious mononucleosis. Absent EBV positive cells. Cells with viral inclusions may be present but are infrequent. CMV immunostain rarely positive

Diagnosis (Blood Work):
- **IM**: Serum monospot (heterophile antibodies) test, EBV IgG and IgM serology test
- **HIV**: HIV serology test, HIV quantitative viral RNA test
- **HSV I/II**: HSV serology test
- **CMV**: CMV serology antibody test

Treatment and Prognosis: IM, CMV are self-limited. Antiviral therapy for Herpes. Anti-retroviral therapy (ART) for HIV

Bacterial Lymphadenitis
Enlarged lymph nodes with expansion of lymphoid follicles and paracortex in variable degrees
Granulomas are nearly always present in interfollicular areas and are mostly necrotizing
Clinical presentation variable but usually associated with fever, tender lymphadenopathy, pharyngitis (strep and staph), lung disease (TB), HIV (MAI), exposure to cat (cat scratch disease)

Lymph node morphology:
- **Cat scratch disease**
  Early stage: Follicular and monocytoid B-cell hyperplasia. Small foci of abscess (neutrophils and debris) usually starting in monocytoid B-cell aggregates
**Later stage:** Epithelioid granulomas with stellate necrotization containing neutrophils and debris. Palisading histiocytes in granulomas

**Tuberculous lymphadenitis**
Epithelioid granulomas with central caseating necrosis in paracortical areas. Langhans type giant cells frequent. Follicular hyperplasia often present

**Atypical mycobacterial lymphadenitis**
Most immunocompetent patients are young children. Presented with unilateral non-tender lymphadenopathy. Necrotizing or non-necrotizing granulomas

Immunocompromised (HIV) patients present with disseminated lymphadenopathy. Granulomas may be well-forms or loosely-formed. Rare patients develop so-called “mycobacterial pseudotumor” resembling soft tissue tumor

**Diagnosis:**
- **Cat scratch:** Caused by spirochetes *Bartonella henselae*. Warthin-starry stain may be positive, but very insensitive. Serology tests confirm disease
- **TB:** Caused by *M. tuberculosis*. Acid-fast stain often negative. In positive cases, bacteria are usually rare. Culture (slow growing) and DNA test confirm disease
- **Atypical mycobacteria:** Caused by *M. avium-intracellulare* (most common), *M. scrofulaceum, M. malmoense, M. kansasii*. Acid-fast stain frequently positive, often numerous in immune compromised patients (HIV). Culture (slow growing) and DNA test useful to confirm disease

**Treatment and Prognosis:** Antibiotics

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**Protozoal Lymphadenitis**

**Toxoplasmosis**
Clinical presentation most frequent with cervical lymphadenopathy. Other forms of disease include encephalitis, chorioretinitis, disseminate infection, congenital infection

Children and young adults most commonly affected

Caused by *Toxoplasma gondii*

**Lymph node morphology:** Very unique triad morphology: Follicular hyperplasia, monocytoïd B-cell hyperplasia, microgranulomas (non-necrotizing)

**Diagnosis:** No special stains available on tissue section. Disease confirmed by serology

**Treatment and Prognosis:** Lymph node disease usually self-limited

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**Lymphadenitis associated with Autoimmune Diseases**

**Lupus lymphadenitis**
60% systemic lupus erythematosus patients develop lymphadenopathy

Most common site is cervical, other sites can be involved

**Lymph node morphology:**
- Paracortex involvement by foci of necrosis with central zone of amorphous material.
- Follicular hyperplasia may or may not present
- **Hematoxylin body:** Clusters of purple, amorphous material representing degenerated nuclei reacted to antinuclear antibody (Pathognomonic)
- **Azzopardi phenomenon:** Dark blue colored degenerated nuclear material deposit in blood vessel wall (Pathognomonic)

**Diagnosis:**
- Characteristic morphology of lymph node is diagnostic, however since SLE is a systemic syndrome, clinical features and serologic tests are required to diagnose SLE
Treatment and Prognosis: Immune suppressants, anti-inflammatory

**Rheumatoid arthritis-associated lymphadenitis**
75% rheumatoid arthritis patients develop lymphadenopathy
Most common site is axillary, other sites can be involved

**Lymph node morphology:**
- Prominent follicular hyperplasia, expanded sinuses with histiocytes, polyclonal plasma cells in interfollicular region, which may contain Russel bodies. Some cases show extensive hyaline material in lymph node

**Diagnosis:** Clinical presentation and serologic test

**Treatment and Prognosis:** Immune suppressants, anti-inflammatory

**IgG4-related lymphadenopathy**
A group of chronic inflammatory diseases caused by increased IgG4 plasma cells, most commonly involving pancreas (autoimmune pancreatitis), salivary glands (chronic sialadenitis), retroperitoneum (retroperitoneal fibrosis), orbit (sclerosing dacryoadenitis), and lymph node (IgG4-lymphadenitis)
Clinical presentation related to specific organ affected. Usually no systemic symptoms
Lymphadenopathy can be regional or generalized, most commonly mediastinal, abdominal, and axillary, and other organ diseases are often present
IgG4 is secreted by plasma cells, functions in allergic reaction and in IgE mediated reaction
Etiology of IgG4-related disease is unknown

**Lymph node morphology:**
- Lymph nodes are usually <2cm. Increased polytypic plasma cells present in either follicles or interfollicular region, or both
- Multiple histologic patterns are described, all with increased IgG4 plasma cells. The lymph node may show involuted follicles (pattern 1), hyperplastic follicles (pattern 2), and interfollicular expansion (pattern 3). Other rare patterns include PTGC-like (pattern 4), inflammatory pseudotumor-like (pattern 5)
- Diagnosis must fulfill 2 criteria: >50 IgG4 plasma cells in high power field, >40% IgG4/IgG ratio
- Diagnostic clues: vasculitis (phlebitis) and fine background collagen fibrosis

**Diagnosis:** Confirmative diagnosis by immunostains for IgG4 and IgG. Kappa/lambda stains to rule out clonal plasma cell disorder
- Other features include elevated serum IgG4 titer, elevated serum IgE, elevated ESR and C-reactive protein

**Differential diagnosis:** Other entities may have increased IgG4 plasma cells: follicular hyperplasia, multicentric Castleman disease, MALT lymphoma

**Treatment and Prognosis:** Corticosteroids

**Lymphadenitis with Unknown Etiology**

**Kikuchi disease**
Aka histiocytic necrotizing lymphadenitis
More frequent in Asian, young female predominant
Present with unilateral, frequent painful cervical lymphadenopathy, may affect other locations.
May precede with flu-like symptoms
Etiology unknown

**Lymph node morphology:**
**Early stage (proliferative stage):** Expansion of paracortex with T cells, mixed CD4 and CD8 T cells with increased CD8+, cytotoxic T cells. Apoptosis may be present, but no necrosis.

**Later stage: (necrotizing stage):** In addition to the features of early stage, large areas of geographic necrosis present. The necrosis contains histiocytes and apoptotic debris, but no neutrophils. Characteristic “crescent histiocytes” are hallmarks. Histiocytes may express MPO. Clusters of plasmacytoid monocytes are present (CD68+).

**Xanthomatous type:** mostly foamy histiocytes, with or without necrosis.

**Diagnosis:**
- No blood tests are available. Diagnosis based on clinical features and lymph node morphology.

**Treatment and Prognosis:** Self-limited.

**Kimura disease**
- A chronic inflammatory disease presented with subcutaneous nodules and lymphadenopathy, primarily affecting head and neck region.
- More common in Asian (a similar disease known as **angiolympid hyperplasia with eosinophilia** in Western countries).
- Affect young adults with male predominance.
- Associated with peripheral eosinophilia and increased IgE.
- Etiology unknown, may be immune mediated.

**Lymph node morphology:**
- Dense infiltrate of lymphocytes, plasma cells, mast cells, and invariably eosinophils in soft tissue and in lymph node (in both paracortex and hyperplastic lymphoid follicles).
- Eosinophilic microabssesses and polykaryocytes frequent.
- IgE positive dendritic networks in germinal centers.

**Diagnosis:**
- Histologic morphology, clinical presentation, CBC and serum IgE.

**Treatment and Prognosis:** Surgical excision if indicated.

**Sarcoidosis**
- Systemic granulomatous disorders involving most common lung and lymph nodes, but may involve other organs.
- Most common complication is progressive pulmonary fibrosis.
- Unknown etiology.

**Lymph node morphology:**
- Involved lymph node is usually entirely replaced by confluent epithelioid granulomas with frequent hyalinization. Minimal or no associated lymphoid aggregates. Multinucleated giant cells (Langhans cells) common. Asteroid bodies characteristic. Minimal necrosis in the granulomas.

**Diagnosis:**
- Diagnosis of exclusion.

**Treatment and Prognosis:** Steroids.

**Castleman Disease (CD)**
- A group of benign diseases with localized (unicentric) or generalized (multicentric) lymphadenopathy, with either hyaline-vascular or plasma cells or mixed histologic morphology.
- HHV8 may play a role in HIV+ multicentric CD and in a subset (half) of HIV- cases.
- The etiology of unicentric CD and HHV8- multicentric CD is unknown.
**Unicentric Castleman disease**

Painless enlargement of single or single group of lymph nodes, often large in size, Most commonly involving mediastinum, followed by abdomen and neck

Symptoms are associated with local mass effect. No constitutional symptoms

**Lymph node morphology:**
- Vast majority (>80%) are hyaline vascular type
- Lymph node is partially effaced by many regressed lymphoid follicles and expanded interfollicular region. Hyalinization present in both follicles and interfollicular region. The lymphoid follicles show “onion skin” and “lollipop” morphology. The interfollicular area shows increased hyaline small vessels and mixture of mature lymphocytes, variable plasma cells, immunoblasts. Clusters of plasmacytoid monocytes are present. Sinuses are usually obliterated

**Diagnosis:**
- Histologic diagnosis

**Differential Diagnosis:**
- Each of the histologic features are not specific, can be seen in reactive lymph node

**Treatment and Prognosis:**
- Surgical excision

**Multicentric Castleman disease**

A systemic disease with lymphadenopathy in 2 or more separate anatomic regions, peripheral or central

Always associated with constitutional symptoms (night sweat, fever, fatigue, weight loss)

Anemia, hypergammaglobulinemia, and elevated inflammatory markers such as ESR, C-reactive protein are often present

IL-6 may play a role; its level appears to associate with degree of inflammatory manifestation

All CD arising in HIV patients are multicentric type

HHV8 is positive in all HIV-associated CD and approximately 50% of non-HIV-associated CD

**Lymph node morphology:**
- Nearly all multicentric CD are plasma cell type or mixed type
- Lymph node with plasma cell type is partially effaced by expanded interfollicular region containing sheets of mature plasma cells. The plasma cells are usually polytypic but may be lambda-restricted. Hyperplastic follicles are often present. Hyalinization is not prominent
- Lymph node with mixed type shows features of both hyaline-vascular and plasma cell

**Diagnosis:**
- Clinical features and histologic diagnosis

**Differential Diagnosis:**
- Rheumatoid arthritis-associated lymphadenitis
- HIV-lymphadenitis
- Plasma cell neoplasm in lymph node

**Complications:**
- *Kaposi sarcoma*: Kaposi sarcoma may develop in multicentric CD. Usually HHV8+
- *Primary effusion lymphoma*: Rare, HIV+ and HHV8+
- *POEMS syndrome* (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin change)

**Treatment and Prognosis:**
- Prognosis variable, treated with chemotherapy, corticosteroids, IL-6 inhibitor

**Plasmablastic Castleman disease**

Present in a small number of multicentric CD exclusively in HIV+ patients

**Lymph node morphology:**
Large sized immunoblasts or plasmablasts in mantle zones and in germinal centers, may be isolated or in clusters, IgM monotypic lambda, HHV8+

*Microlymphoma:* Monotypic clusters of plasmablasts in germinal centers. Not considered as malignant. May progress to overt large cell lymphoma

**Diagnosis:** Based on clinical features and histologic morphology

**Treatment and Prognosis:** Treated with chemotherapy, corticosteroids, IL-6 inhibitor