Mediastinal (thymic) Large B-cell Lymphoma
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- Subtype of DLBCL of putative thymic B-cell origin which arises in the mediastinum with distinctive clinical, immunophenotypic and genotypic features
Synonyms

- Large-cell lymphoma of the mediastinum
- Primary mediastinal clear-cell lymphoma of B-cell type
- Mediastinal diffuse large-cell lymphoma with sclerosis
- REAL: Primary mediastinal (thymic) large B-cell lymphoma
Epidemiology

- Most patients in their third to fifth decade
- Female predominance
Clinical features

- Patients present with localized disease
- Signs and symptoms relating to anterior mediastinal masses
- Superior vena cava syndrome
- Disseminated disease in other extranodal sites such as kidney, adrenal, liver, skin and brain
Etiology

- No epidemiologic clustering or evidence of specific risk factors have been identified
- EBV is not present
Morphology

- Diffuse proliferation with variably dense compartmentalising fibrosis
- Identification of thymic remnants may be facilitated by IHC
- These remnants may organize in clusters mimicking carcinoma
- Neoplastic cells vary in size and nuclear shape
Morphology

- In most cases the cells have abundant cytoplasm
- Small numbers of interspersed benign lymphocytes and eosinophils may raise the suspicion of HL
- An association with nodular sclerosis HL (so-called “composite lymphoma”) has been reported in rare cases
- Mediastinal tissue biopsies may be obscured by fibrosis and cellular crush artifact
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Immunophenotype

- B-cell immunophenotype: expression of CD19 and CD20
- Both immunoglobulin and HLA class I and II molecules are incompletely expressed or absent
- CD10 and CD5 are also absent
- CD30 expression is weak
- Tumor cells express CD45 (LCA)
- Cytokeratin shows thymic remnants
Genetics

- Immunoglobulin gene rearrangements are demonstrable
- Gains in chromosome 9p and amplification of the REL gene
- Overexpression of MAL has been identified
- The cells lack BCL2, BCL6 and MYC rearrangements
Postulated cell of origin

Thymic B-cell
Prognosis and Predictive Factors

- Response to chemotherapy with or without radiotherapy is usually good.
- Patients with disease extending into adjacent thoracic viscera have poorer prognosis than patients with disease confined to the mediastinum.
- Variations in microscopic appearance do not predict differences in survival.
Intravascular Large B-Cell Lymphoma
Intravascular large B-cell Lymphoma

- Definition: rare subtype of extranodal DLBCL characterised by the presence of lymphoma cells only in the lumina of small vessels, particularly capillaries
Intravascular large B-cell Lymphoma

Synonyms:

- Malignant angioendotheliomatosis
- Intravascular lymphomatosis
- Kiel: angio-endotheliotrophic (intravascular) lymphoma
- Lukes-Collins: angiotropic large cell lymphoma
- REAL: diffuse large B-cell lymphoma
Intravascular large B-cell Lymphoma

- Epidemiology:
  - Seen in adults
  - Based on the small number of cases reported in the literature, no distinctive epidemiological features can be identified
Sites of involvement

- This lymphoma is usually widely disseminated in extranodal sites at presentation (CNS, skin, lung, kidneys, adrenals)
- Intravascular involvement may also be seen in the marrow
Clinical features

- Symptoms are highly variable since most result from occlusion of small vessels by tumour cells in a variety of organs.
- It most commonly presents with skin lesions (skin plaques and nodules) or neurological symptoms (dementia, focal symptoms).
Clinical features

- About 9% of patients present with “B symptoms”
- Multiple organs may be involved and a variety of clinical presentations have been described. This include nephrotic syndrome, pyrexia and hypertension, breathlessness and hematological abnormalities (autoimmune hemolytic anemia, leukopenia, pancytopenia and disseminated intravascular coagulation)
The intravascular growth pattern has been hypothesised to be secondary to a defect in homing receptors of the neoplastic cells.

Some evidence in favor of this comes from a study showing a lack of CD29 (beta-1 integrin) and CD54 (ICAM-1) adhesion molecules in 6 cases of intravascular large B-cell lymphoma.
Macroscopy

- The gross features often only appreciated at post mortem are mostly those of hemorrhage, thrombosis and necrosis in a wide range of tissues
- Actual deposits of tumour may not be visible to the naked eye
Morphology

- The neoplastic lymphoid cells are mainly lodged in the lumina of small vessels in many organs.
- Fibrin thrombi may be seen in some cases.
- The tumour cells are large vesicular nuclei, prominent nucleoli and frequent mitotic figures.
Morphology

- Rare cases have cells with anaplastic features
- In organs such as the lung and bone marrow, the involvement may be very subtle. The recognition of single neoplastic cells may be enhanced by immunostains for CD45 and CD20
- Malignant cells are rarely seen in cerebrospinal fluid and blood
Intravascular large B cell lymphoma, brain biopsy
Bone marrow
Intravascular Lymphoma
Tumor cells are usually positive for B-cell associated antigens (e.g. CD19, CD20, CD22, CD79a). CD5 coexpression is seen in some cases.

Rare cases of intravascular lymphoma of T-cell phenotype have been reported.

Factor VIII may be detected, but is considered to represent absorption of factor VIII, rather than expression by the neoplastic cells.
Genetics

- The majority of cases studied have immunoglobulin gene rearrangements
- Rare reports of intravascular lymphoma with T-cell receptor rearrangements
- Karyotypic abnormalities have been described, but too few cases have been studied for any consistent patterns to emerge
Postulated cell of origin

- Transformed peripheral B-cell
Prognosis and predictive factors

- In general this is an extremely aggressive lymphoma which responds poorly to chemotherapy
- Death occurs in most cases within a short time of presentation
- The poor prognosis in these patients reflects in part frequent delays in diagnosis due to their great diversity in presentation
Prognosis and predictive factors

- There is some evidence for a variant confined to skin which may have a relatively better prognosis but the number of patients studied is small.
Primary Effusion Lymphoma
Primary Effusion Lymphoma

- Primary effusion lymphoma (PEL) is a neoplasm of large B-cells usually presenting as serous effusions without detectable tumor masses
- It is universally associated with human herpes virus 8 (HHV-8)/Kaposi sarcoma herpes virus (KSHV), most often occurring in the setting of immunodeficiency
Synonym

- Body cavity-based lymphoma
Epidemiology

- The majority of cases arise in the setting of HIV infection.
- Most patients are young to middle aged homosexual males.
- This neoplasm is rare even in the setting of HIV infection. At least one case has been reported in an HIV negative allograft recipient.
Epidemiology

- The disease also occurs in the absence of immunodeficiency especially in elderly males most often from areas with high prevalence for HHV-8/KSHV infection such as the Mediterranean.
Sites of involvement

- The most common sites of involvement are the pleural, pericardial and peritoneal cavities.
- Typically only one body cavity is involved.
- Other sites of involvement include the gastrointestinal tract, soft tissue and other extranodal sites.
Clinical features

- Patients typically present with effusions in the absence of lymphadenopathy or organomegaly
- Some patients have preexistent Kaposi sarcoma
- Rare cases may be associated with multicentric Castleman disease
Etiology

- The neoplastic cells are positive for HHV-8/KSHV in all cases
- Most cases are coinfected with EBV
- High levels of cytokines, in particular IL-6 and IL-10 may be found in the effusions
Morphology

• With Wright or Giemsa staining performed on cytocentrifuge preparations, the cells exhibit a range of appearances, from large immunoblastic or plasmablastic cells to cells with more anaplastic morphology
• Nuclei are large, round to more irregular in shape, with prominent nucleoli
Morphology

- The cytoplasm can be very abundant and is deeply basophilic with the presence of vacuoles in occasional cells.
- A perinuclear hof consistent with plasmacytoid differentiation may be seen.
- Some cells can resemble Reed-Sternberg cells.
Morphology

- The cells often appear more uniform in histological sections than in cytospin preparations.
- However, the cells are generally large, with some pleomorphism, ranging from large cells with round or ovoid nuclei to very large cells having irregular nuclei and abundant cytoplasm.
Primary Effusion Lymphoma
Primary Effusion Lymphoma
Primary Effusion Lymphoma
Morphology

- Pleural biopsies show tumor cells adherent to the pleural surface often embedded in fibrin and occasionally invading the pleura.
- This disease should be distinguished from pyothorax-associated DLBCL which usually presents with a pleural mass lesion.
- The cells of that tumor (DLBCL) are EBV positive and HHV8/KSHV negative.
Primary effusion lymphoma, Pleural Biopsy
Immunophenotype

- Lymphoma cells usually express leukocyte common antigen (CD45) but are usually negative for pan-B-cell markers such as CD19, CD20 and CD79a
- Surface and cytoplasmic expression of immunoglobulin is likewise often absent
- Activation and plasma cell-related markers such as CD30, CD38, and CD138 are usually demonstrable
Immunophenotype

- Aberrant cytoplasmic CD3 expression has been reported.
- Because of the markedly aberrant phenotype, it is often difficult to assign a lineage with immunophenotyping.
Immunophenotype

- The nuclei of the neoplastic cells are positive by immunohistochemistry for the HHV-8/KSHV-associated latent protein. This is very useful in establishing the diagnosis.

- Despite the usual presence of EBV, staining for LMP-1 is negative.
Genetics

- Immunoglobulin genes are rearranged and are mutated
- Some cases also have aberrant rearrangement of T-cell receptor genes
- No characteristic chromosomal abnormalities have been identified
Genetics

- Comparative genomic analysis has revealed gain in sequence of chromosomes 12 and X, in common with other HIV-associated lymphomas.
- HHV-8/KSHV viral genomes are present in all cases.
- EBV is found in most cases and is most reliably detected by EBER in situ hybridization.
- EBV tends to be absent in elderly HIV-negative patients.
Postulated cell of origin

- Post-germinal center B-cell.
Prognosis and predictive factors

- The clinical outlook is extremely unfavourable, with or without therapy.
- Median survival is less than six months