Mediastinal (thymic) Large B-cell Lymphoma

Mediastinal (thymic) large B-cell lymphoma

- 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 symptons relating to anterior mediastinal masses
- Superior vena cava syndrome
- Disseminated disease in other extranodal sites such as kidney, adrenal, liver, skin and brain

Etiology

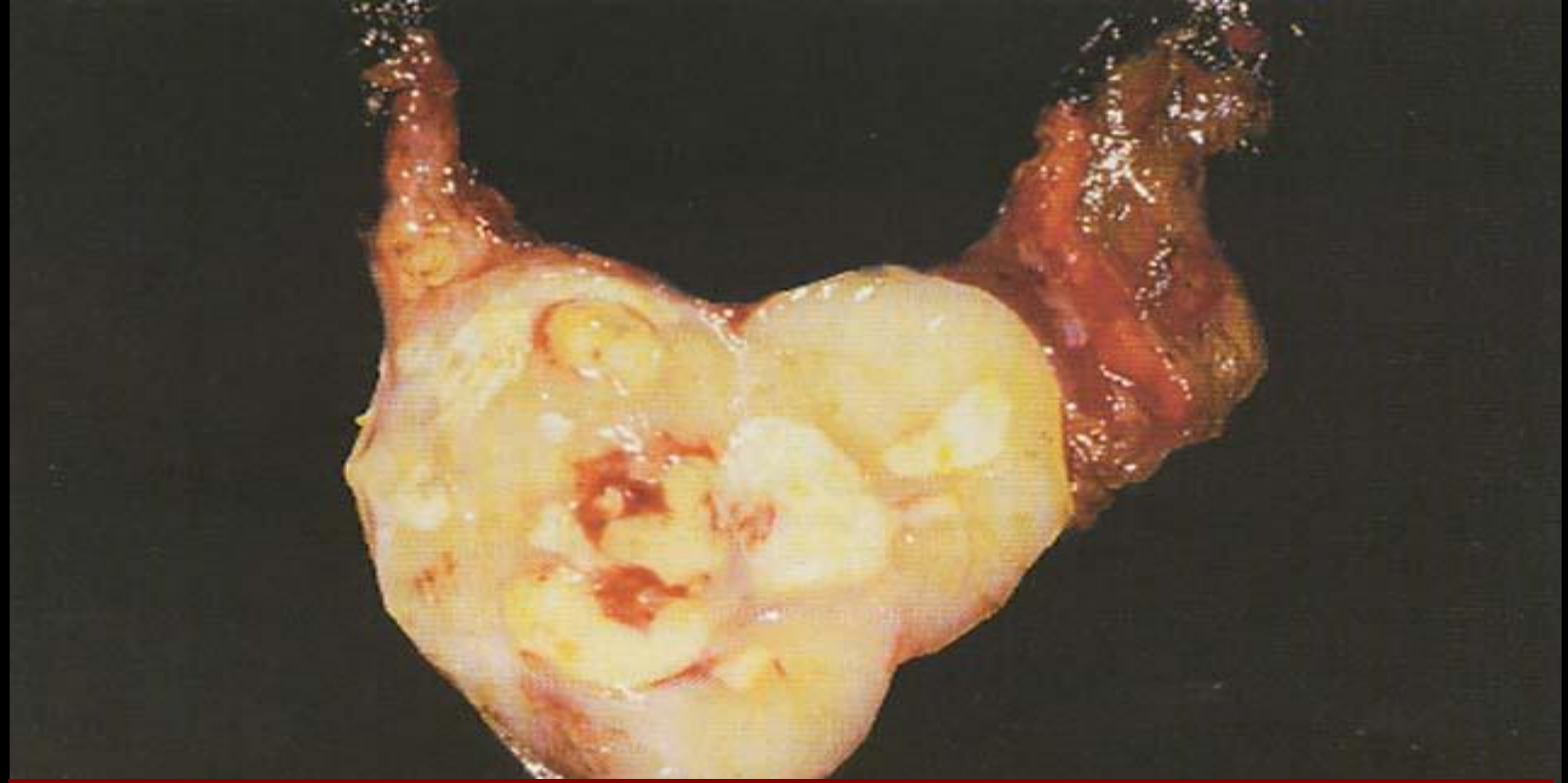
- No epidemiologic clustering or evidence of specific risk factors have been identified
- EBV is not present

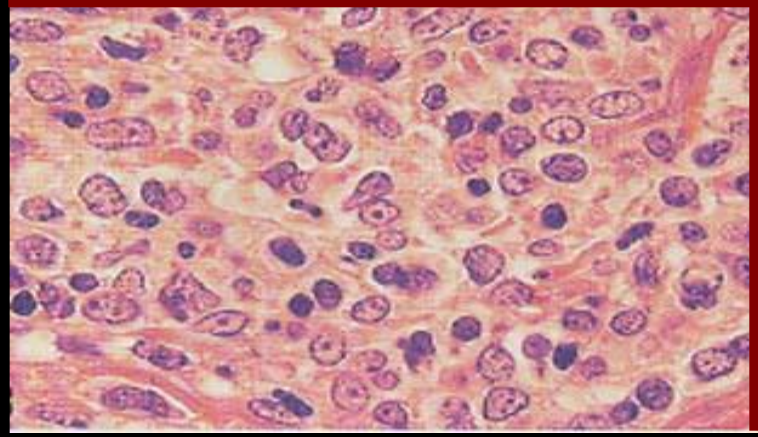
Morphology

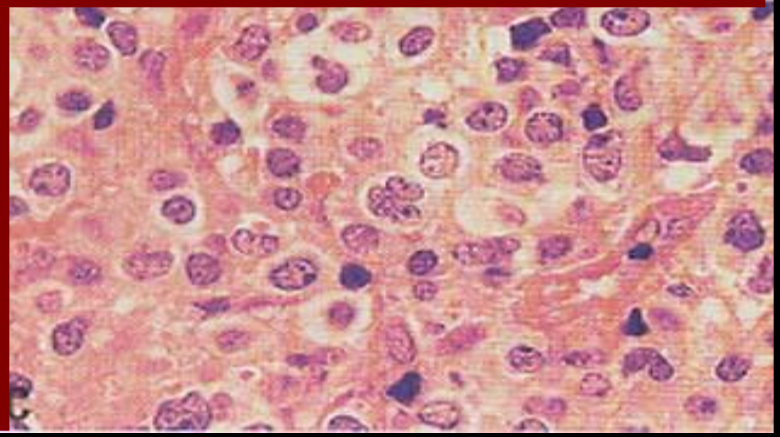
- Diffuse proliferation with variably dense compartmentalising fibrosis
- Identification of thymic remnants may be facilitated by IHC
- These remnants may organize in clusters mimicking carcinoma
- Neoplastic cells vary in size and nuclear shape

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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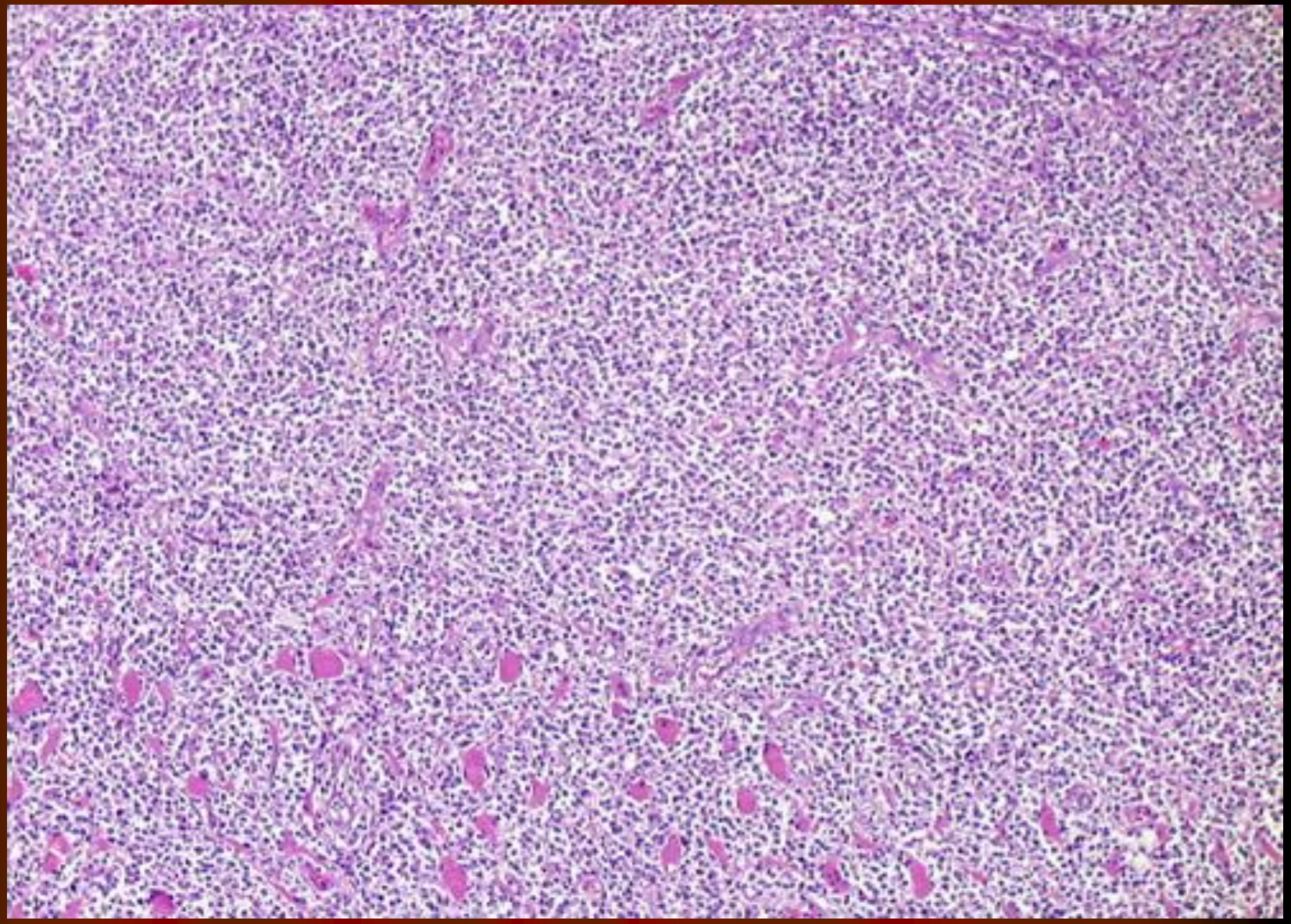

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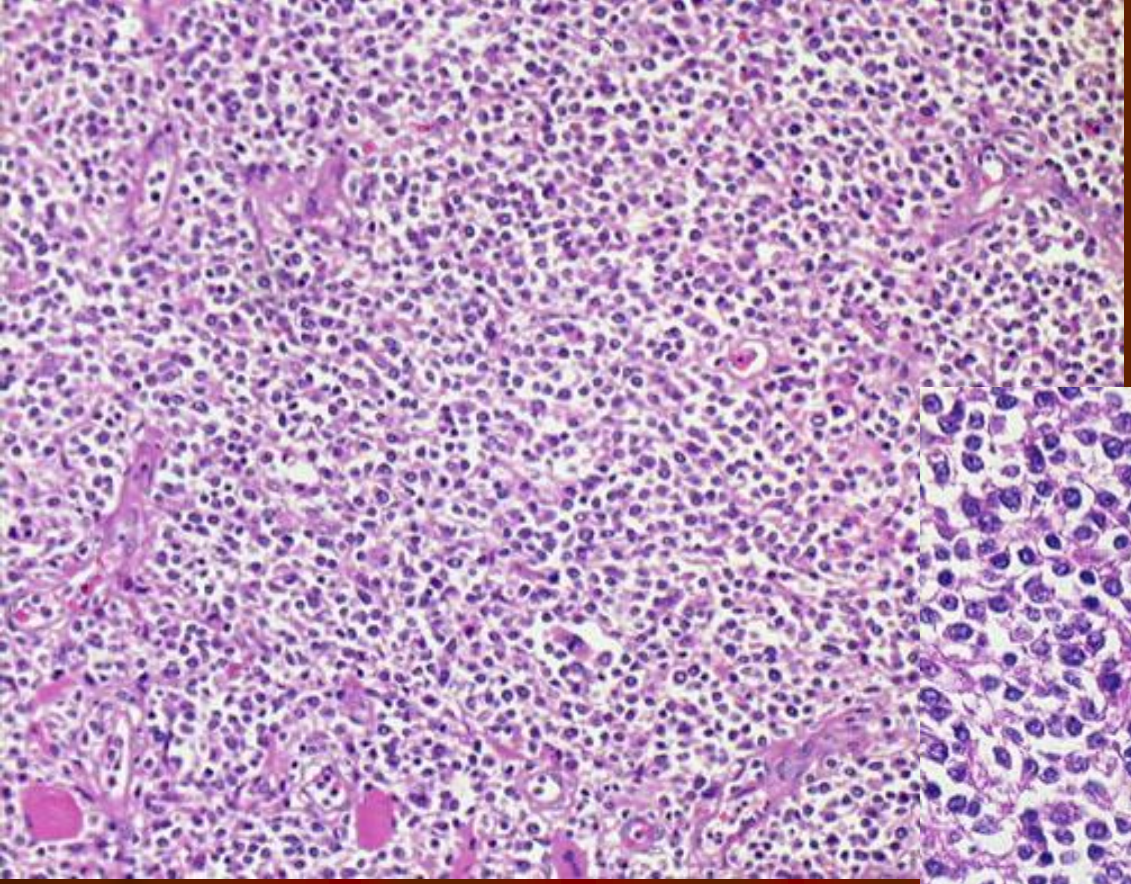
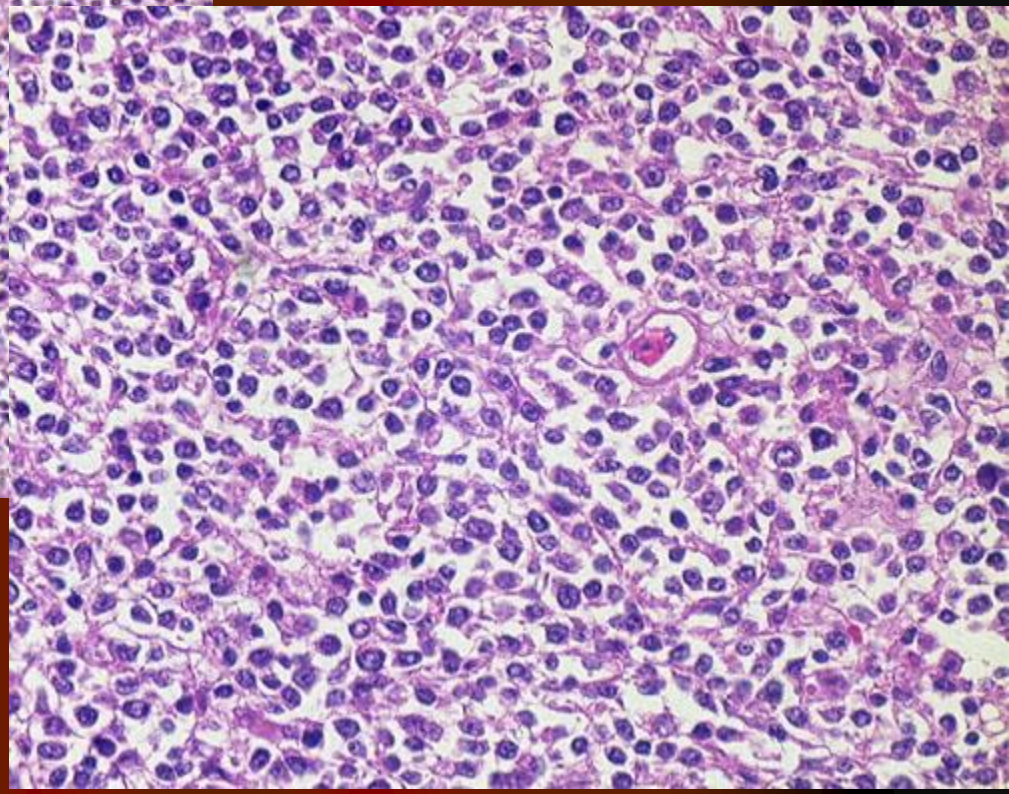
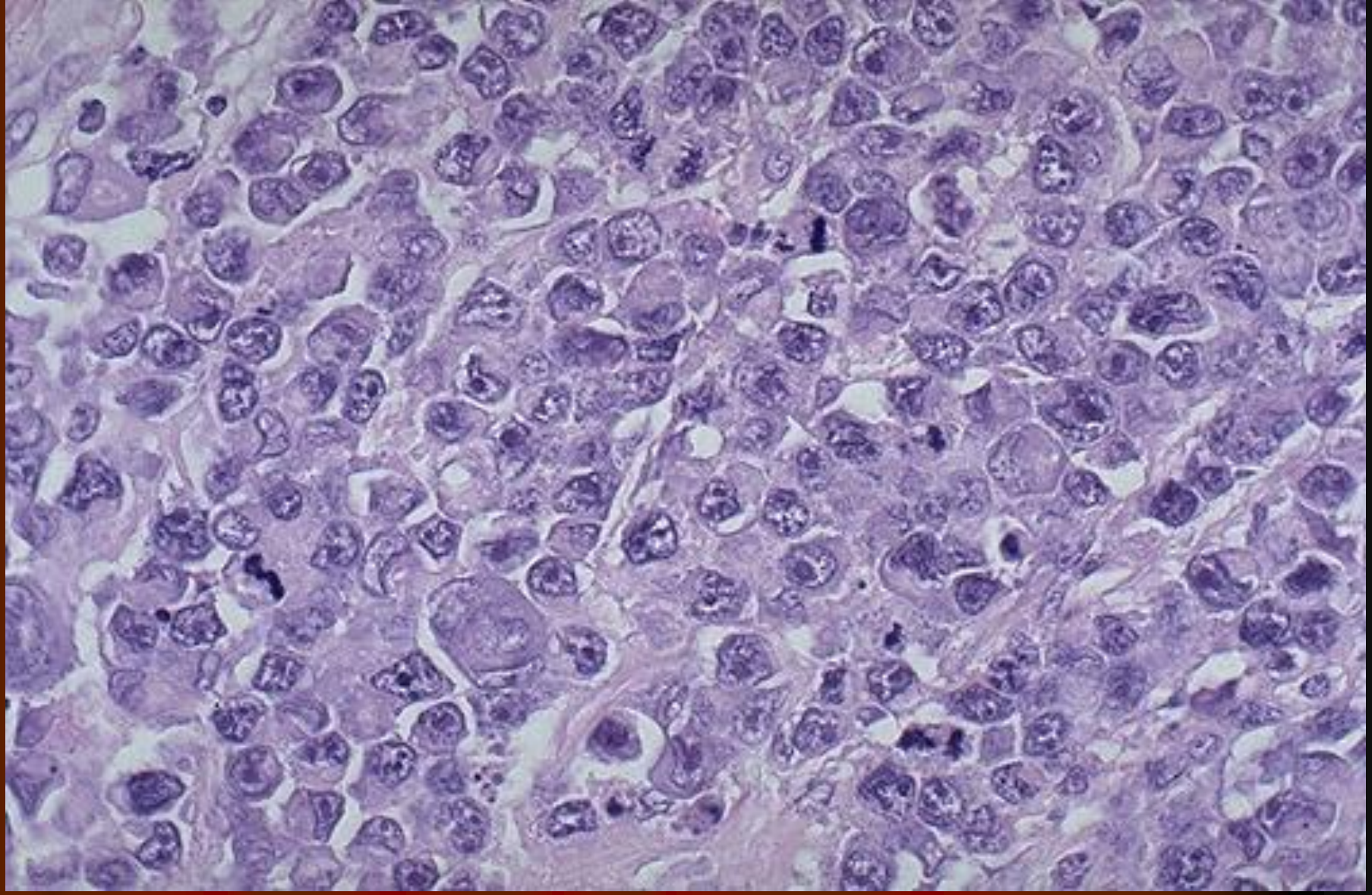


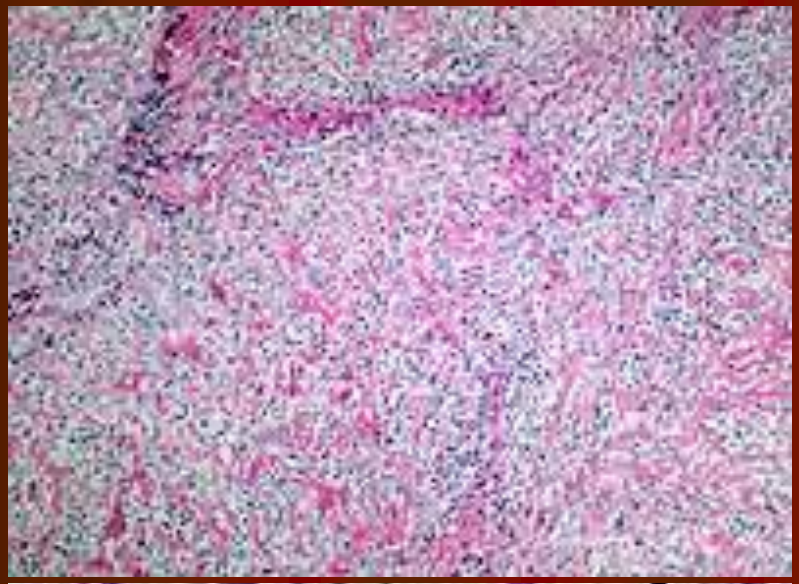


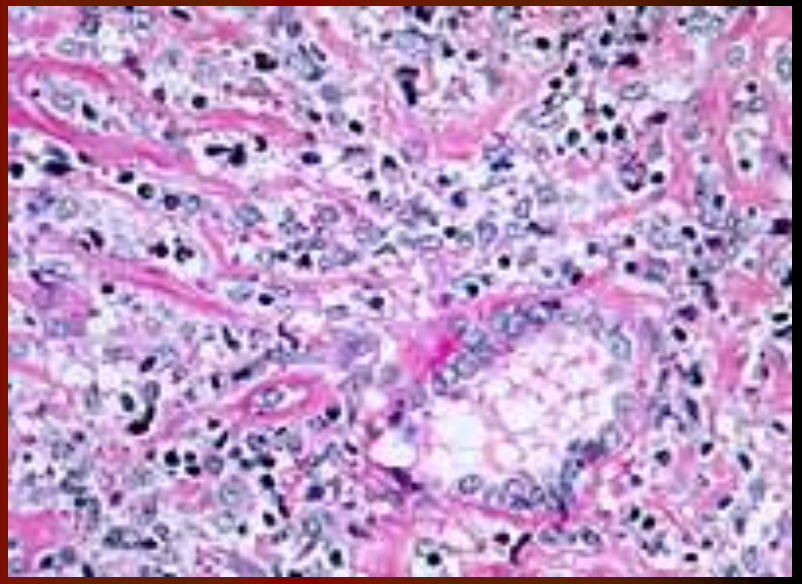
Mediastinal (thymic) large B-cell lymphoma

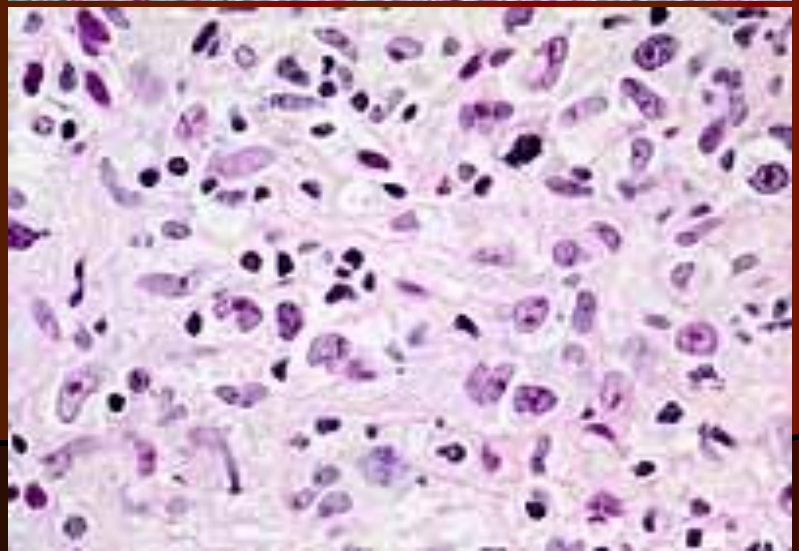


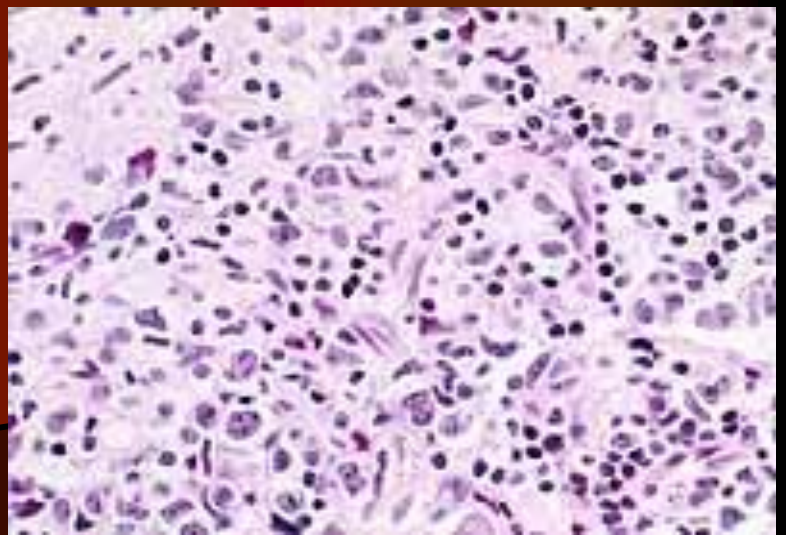
Mediastinal (thymic) large B-cell lymphoma

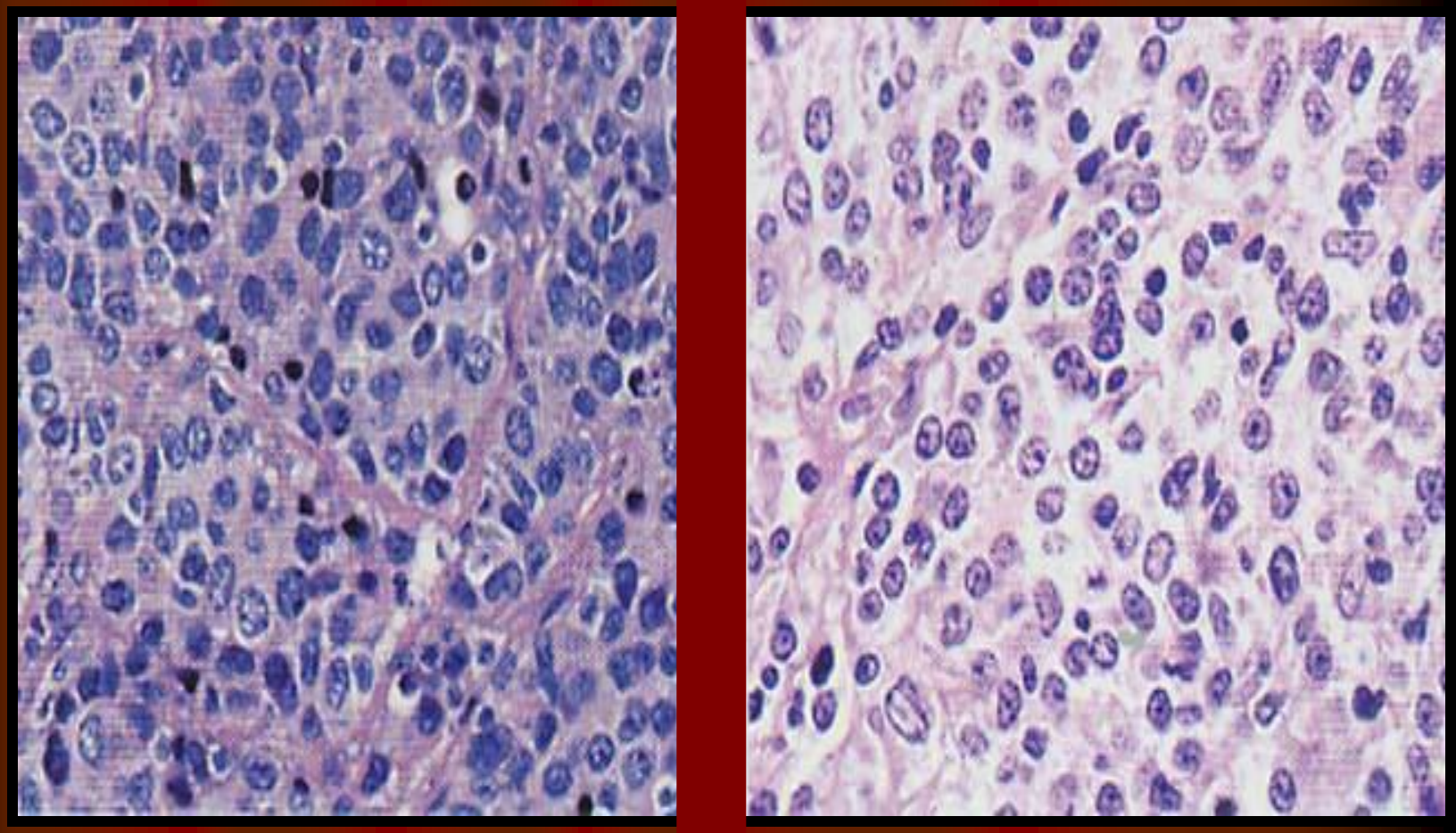
Mediastinal (Thymic) Large B-Cell Lymphoma



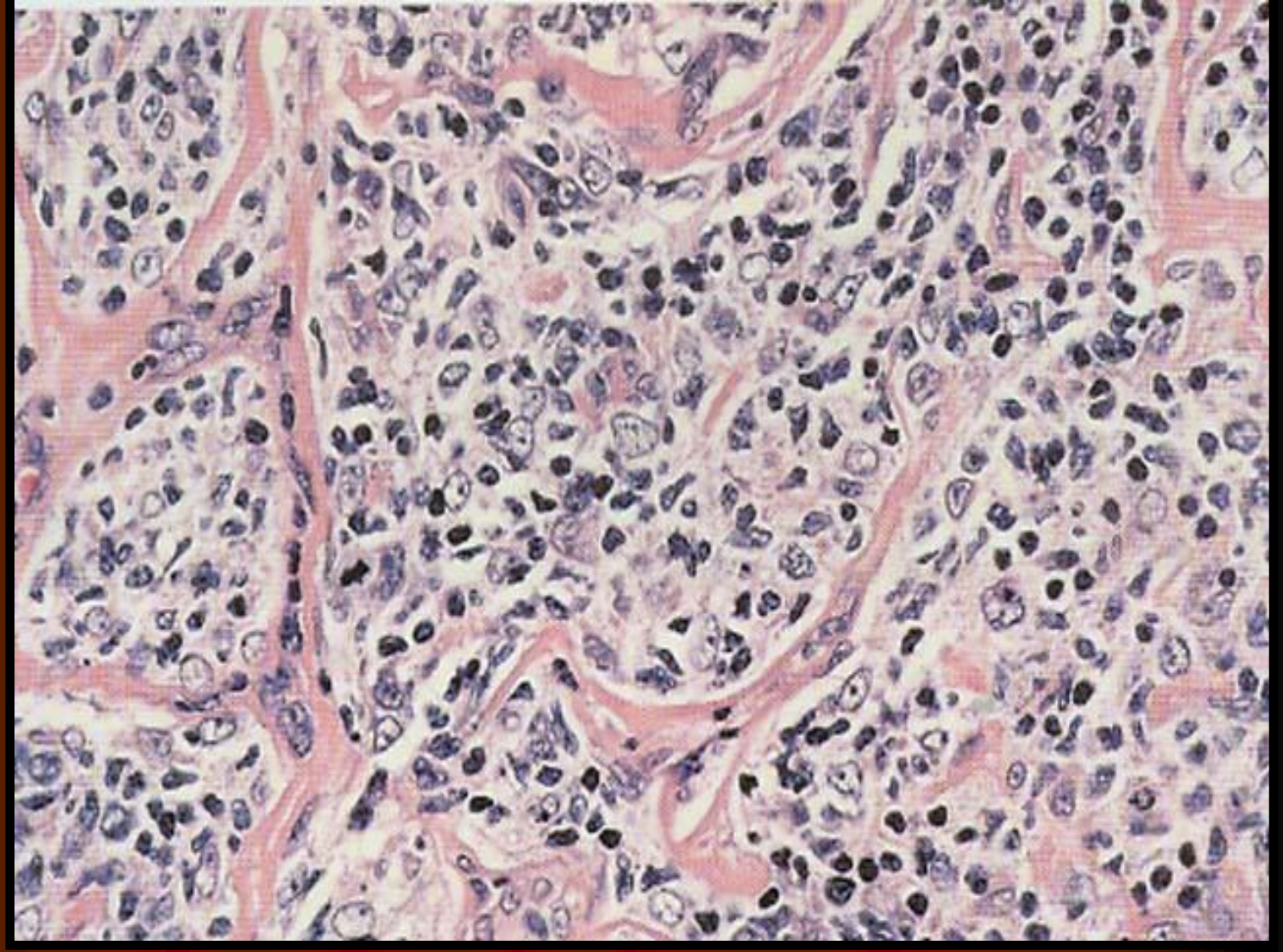








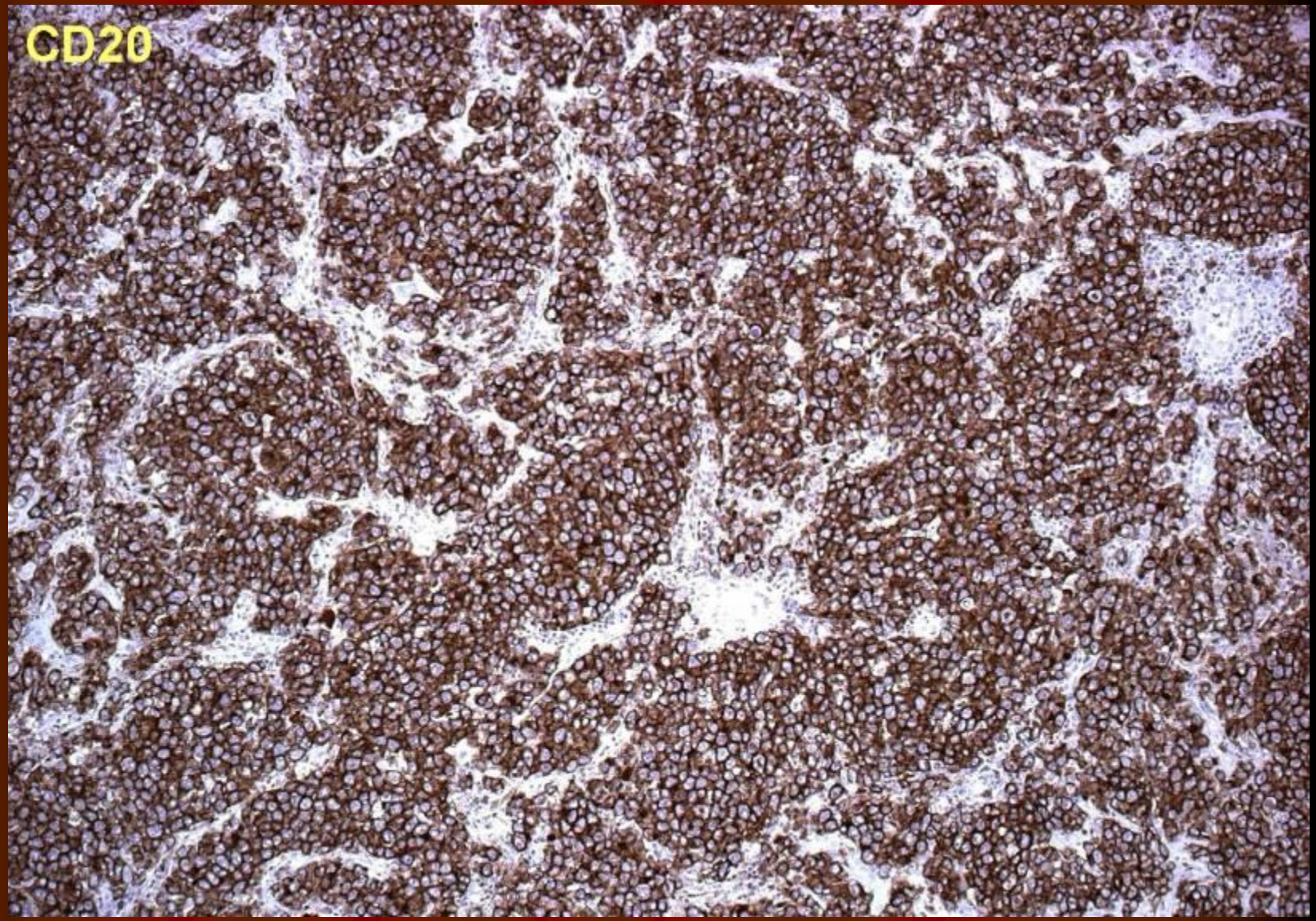
Mediastinal (thymic) large B-cell lymphoma



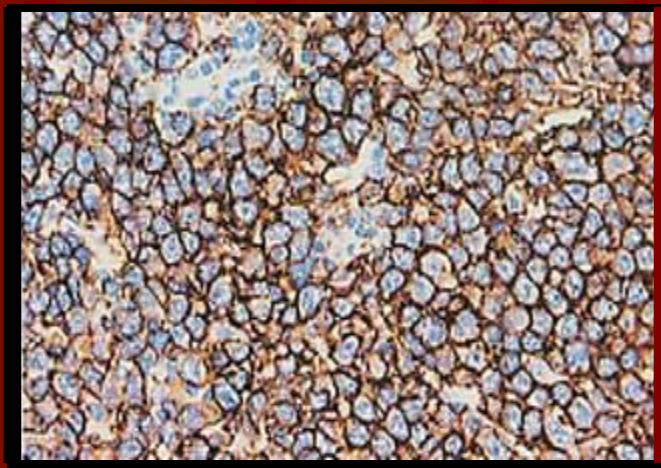
Mediastinal (thymic) large B-cell lymphoma

Immunophenotype

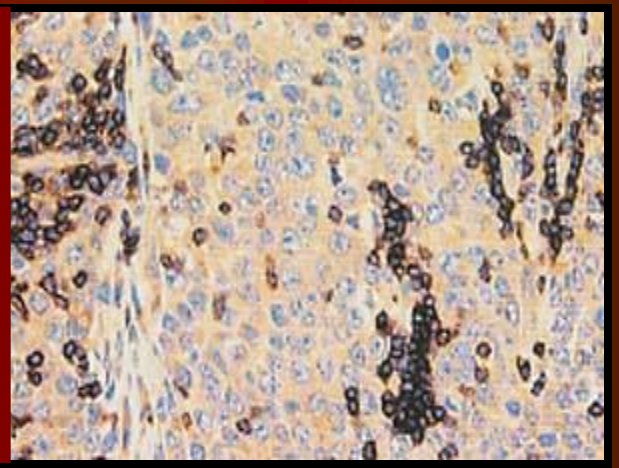
- B-cell immunophenotype: expression of CD19 and CD20
- Both immunoglobulin and HLA class I and II molecules are incompletely expressed or absent
- CD10 and CD5 are also absent
- CD30 expression is weak
- Tumor cells express CD45 (LCA)
- Cytokeratin shows thymic remnants


CD20

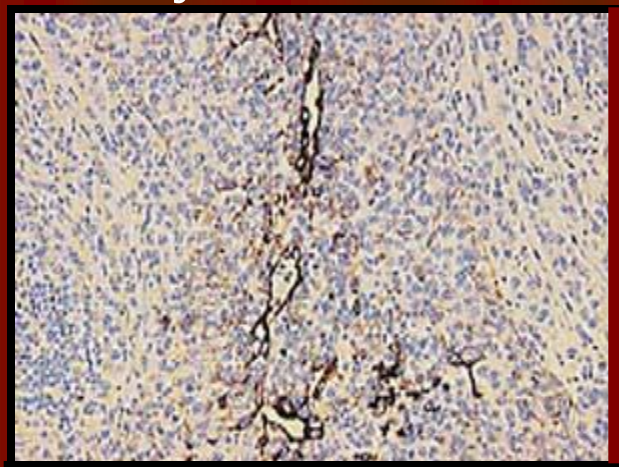
CD20



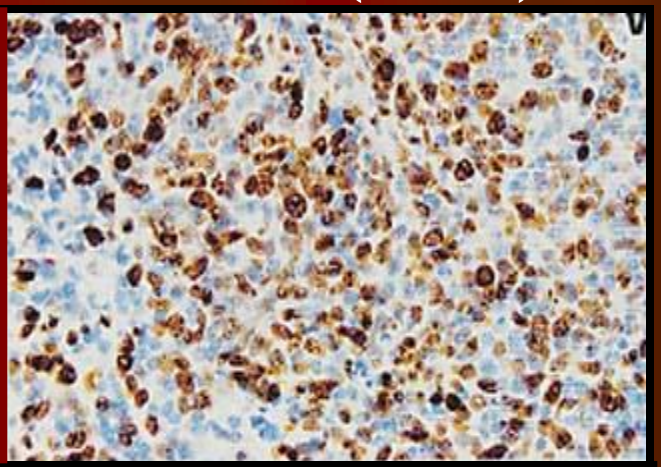
CD3



Cytokeratin



Ki-67 (>60%)



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-endotheliotropic (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)

Pathophysiology

- 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

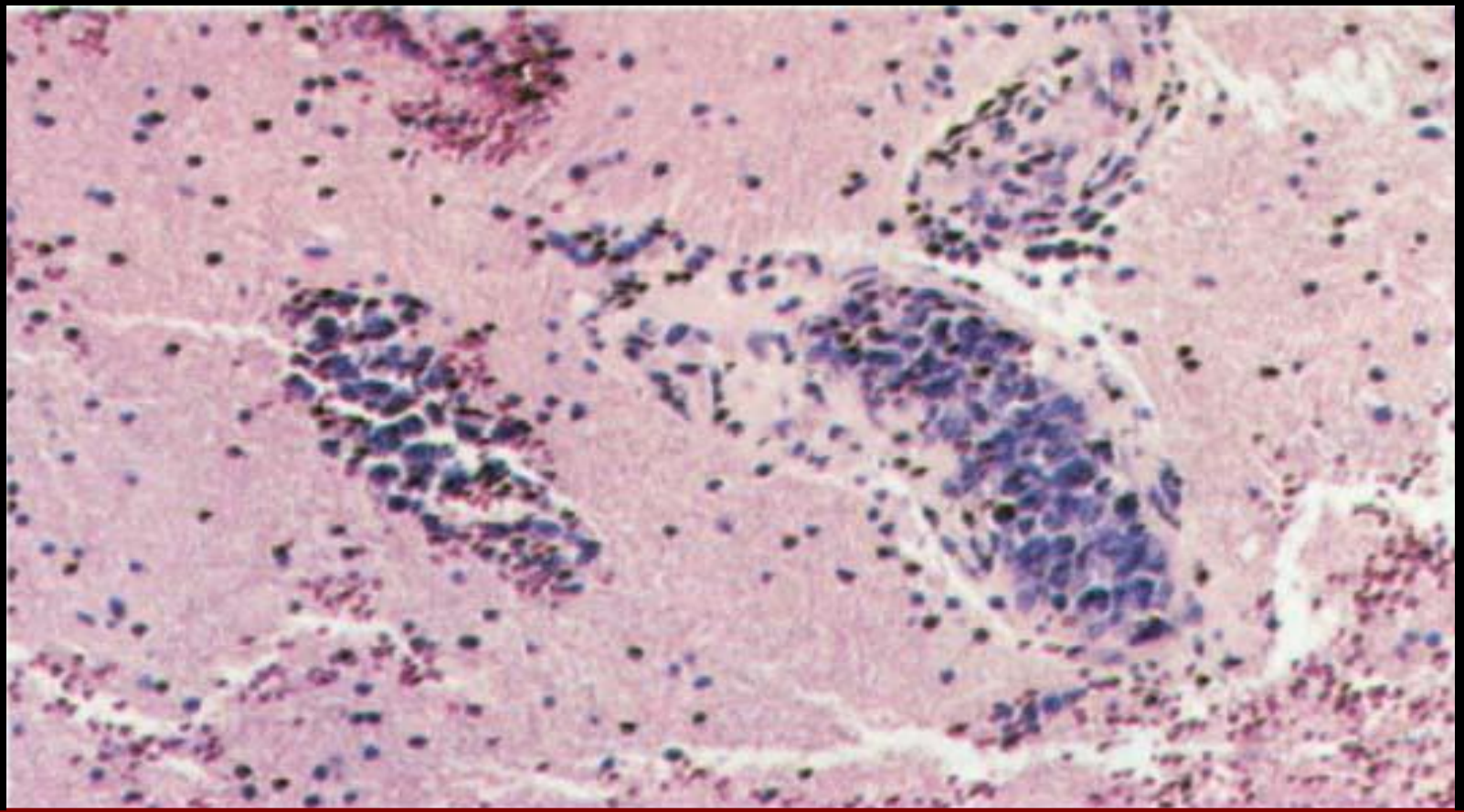
- The gross features often only appreciated at post mortem are mostly those of hemorrage, thrombosis and necrosis in a wide range of tissues
- Actual deposits of tumour may not be visible to the naked eye

Morphology

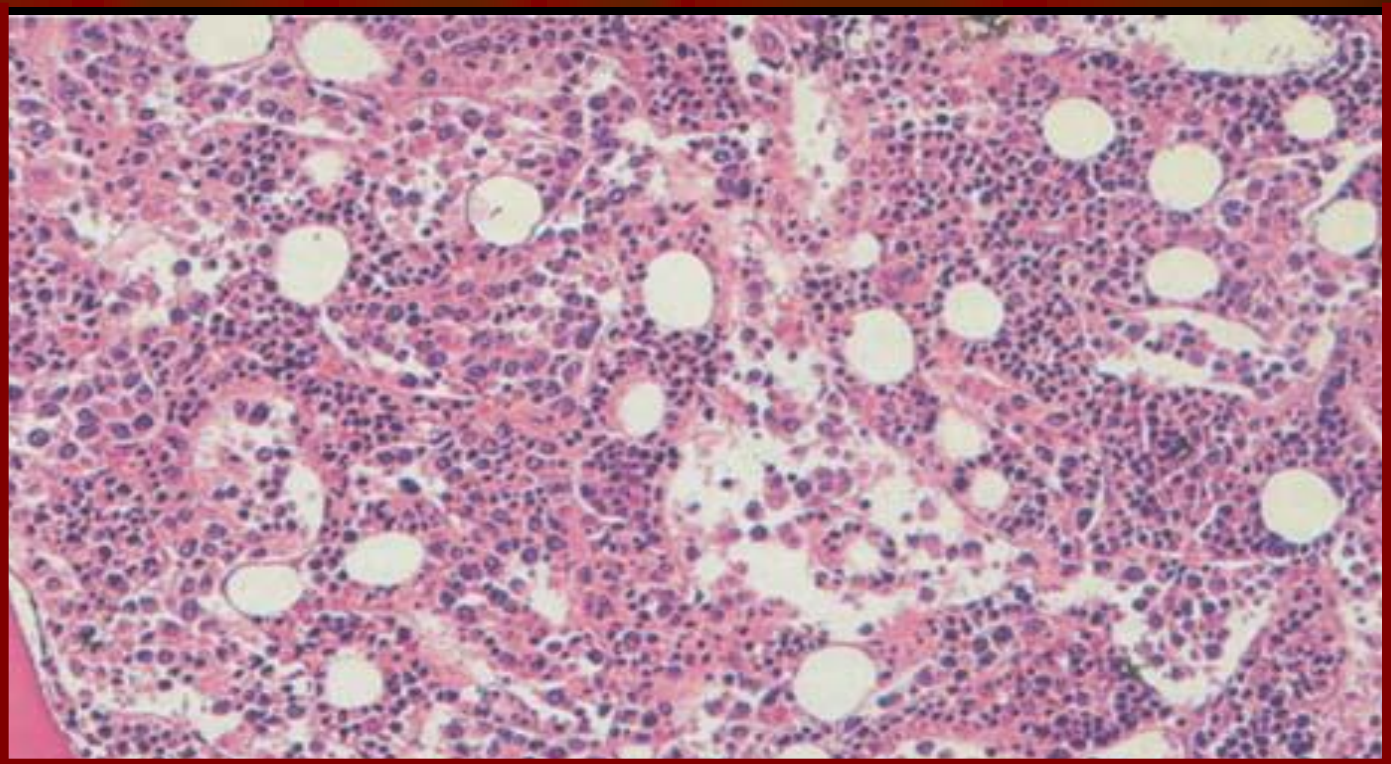
- The neoplastic lymphoid cells are mainly lodged in the lumina of small vessels in many organs
- Fibrin thrombi may be seen in some cases.
- The tumour cells are large vesicular nuclei, prominent nucleoli and frequent mitotic figures

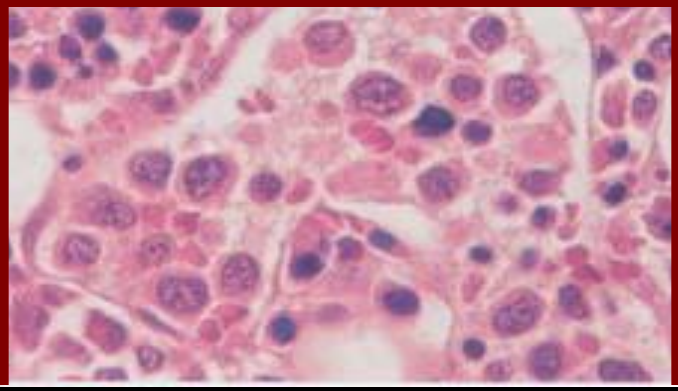
Morphology

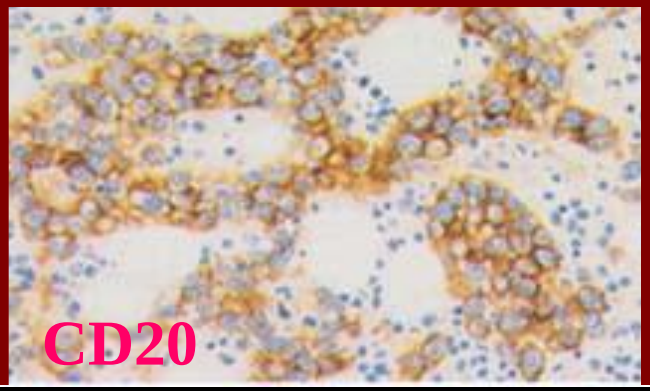
- Rare cases have cells with anaplastic features
- In organs such as the lung and bone marrow, the involvement may be very subtle. The recognition of single neoplastic cells may be enhanced by immunostains for CD45 and CD20
- Malignant cells are rarely seen in cerebrospinal fluid and blood



Intravacular large B cell lymphoma, brain biopsy

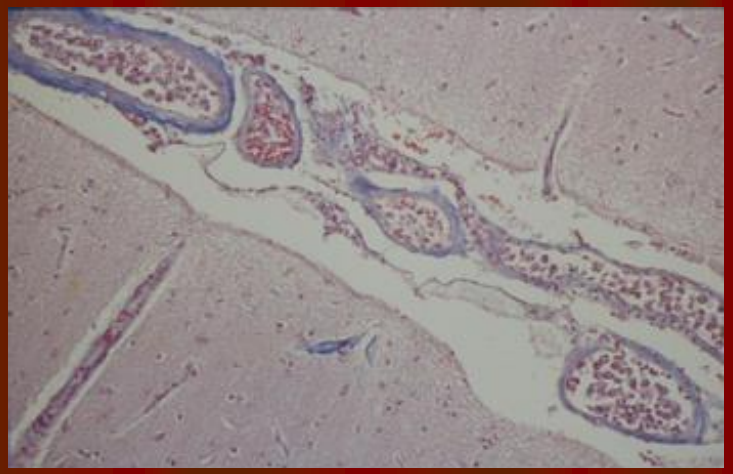


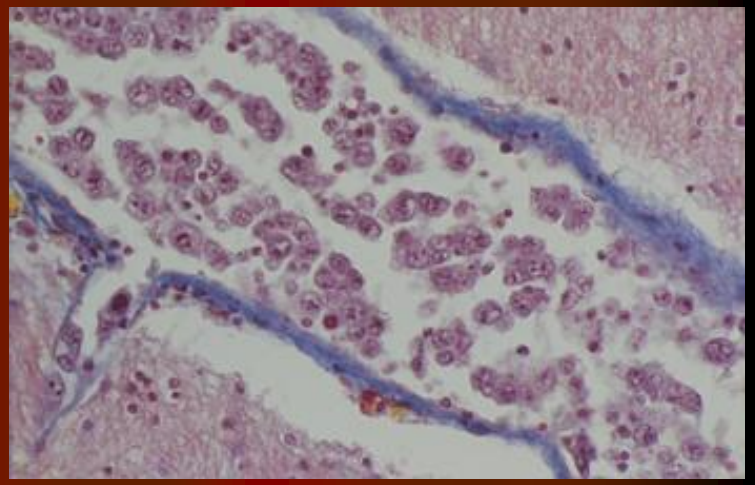


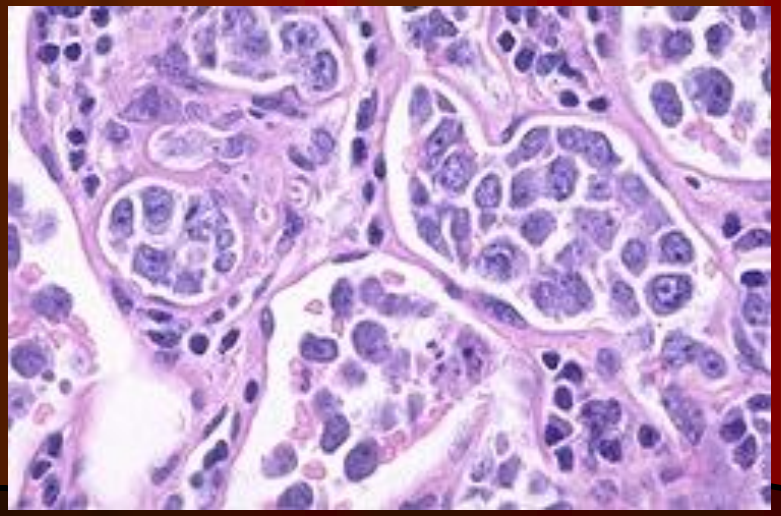


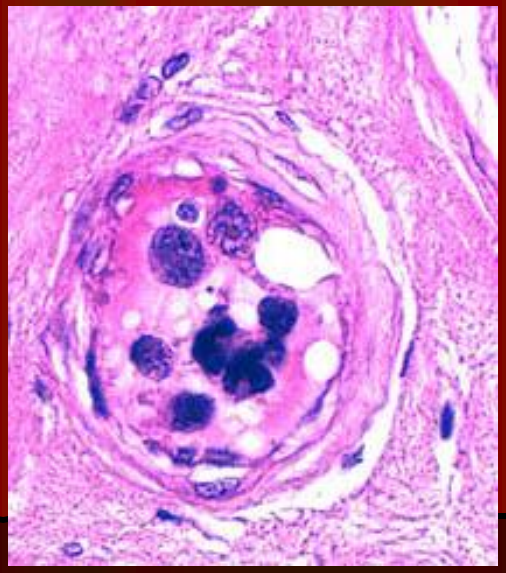
Bone marrow

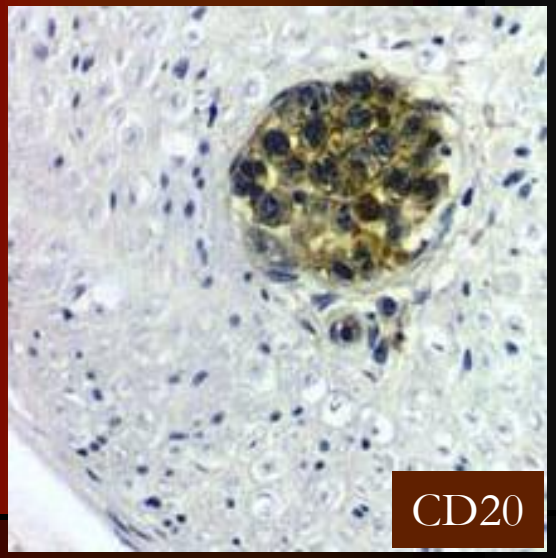
Intravascular Lymphoma

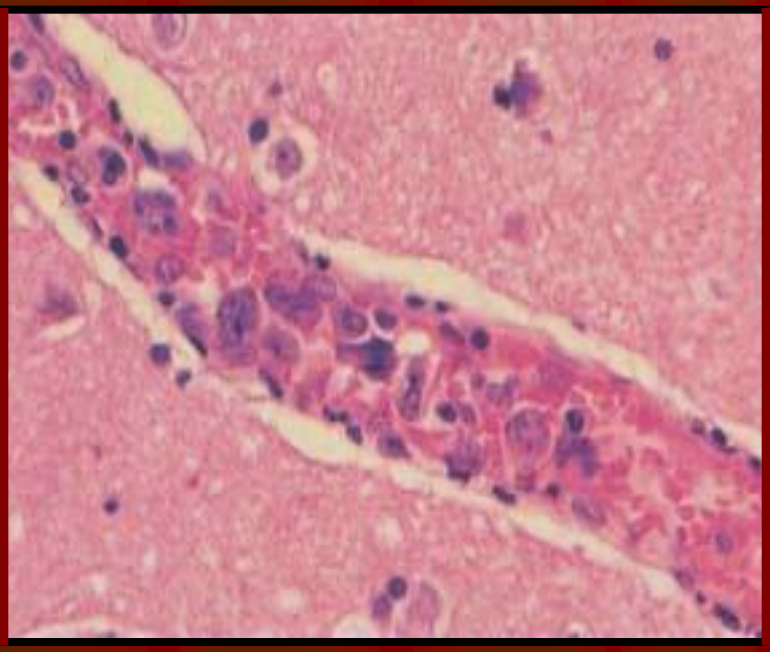


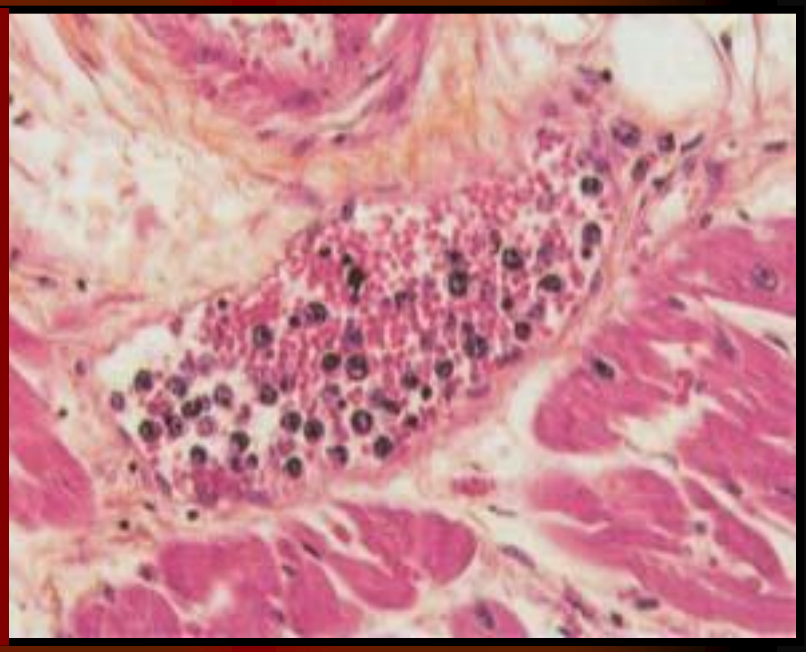












Immunophenotype

- 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

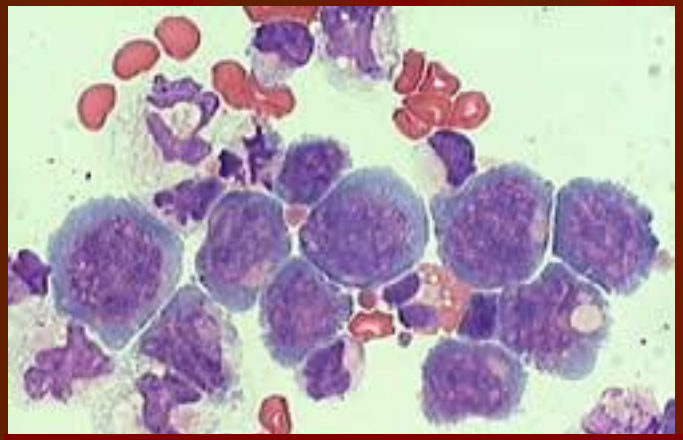
Morphology

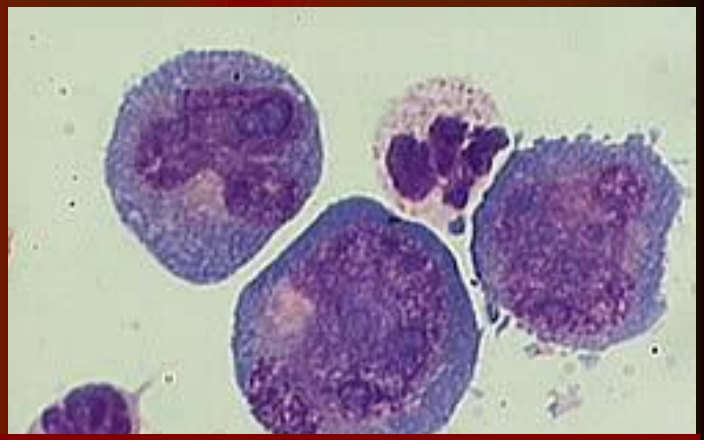
- The cytoplasm can be very abundant and is deeply basophilic with the presence of vacuoles in occasional cells
- A perinuclear hof consistent with plasmacytoid differentiation may be seen
- Some cells can resemble Reed-Sternberg cells

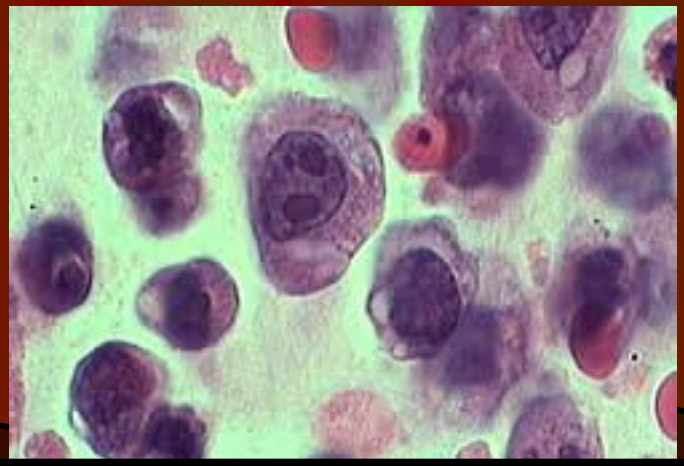
Morphology

- 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







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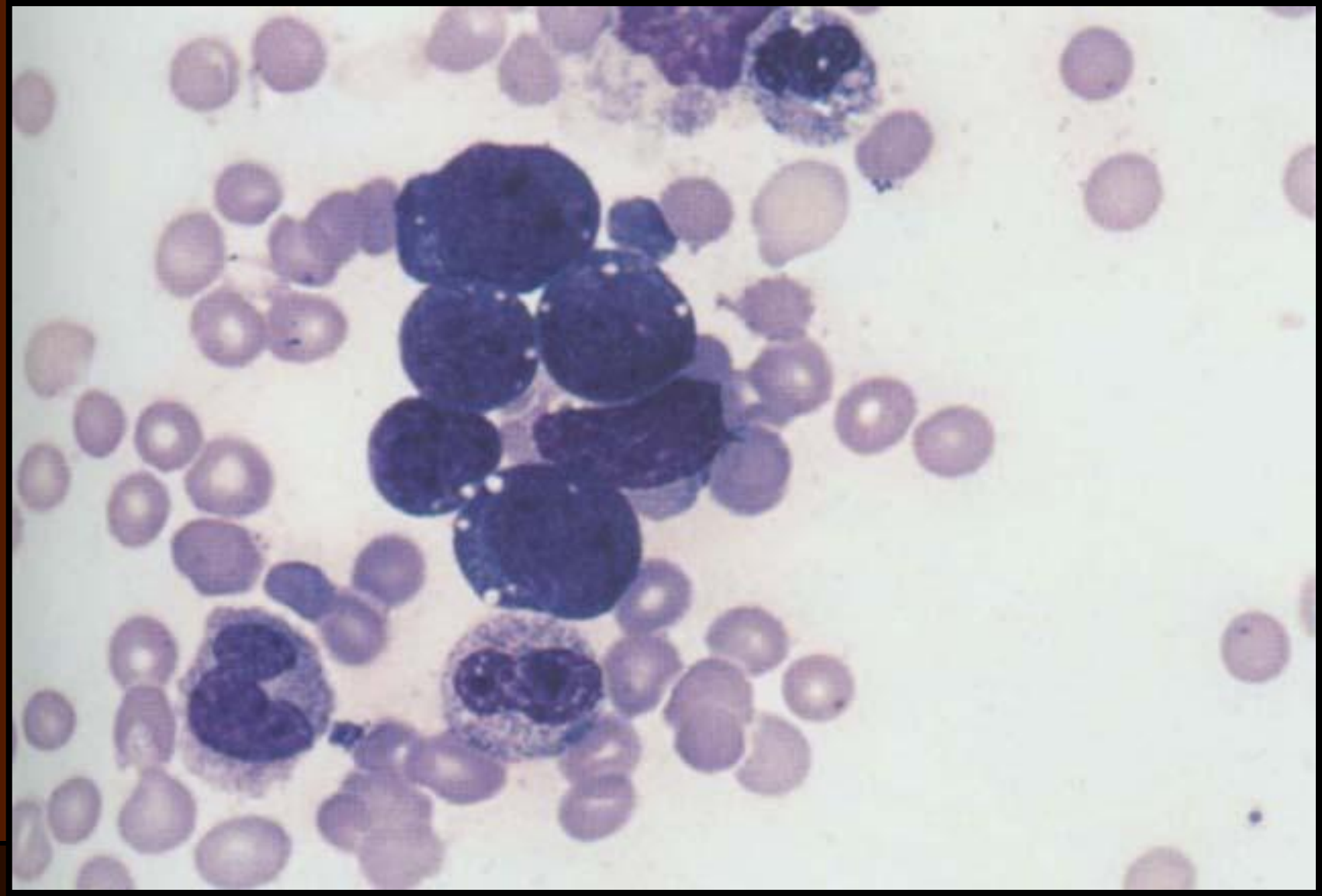
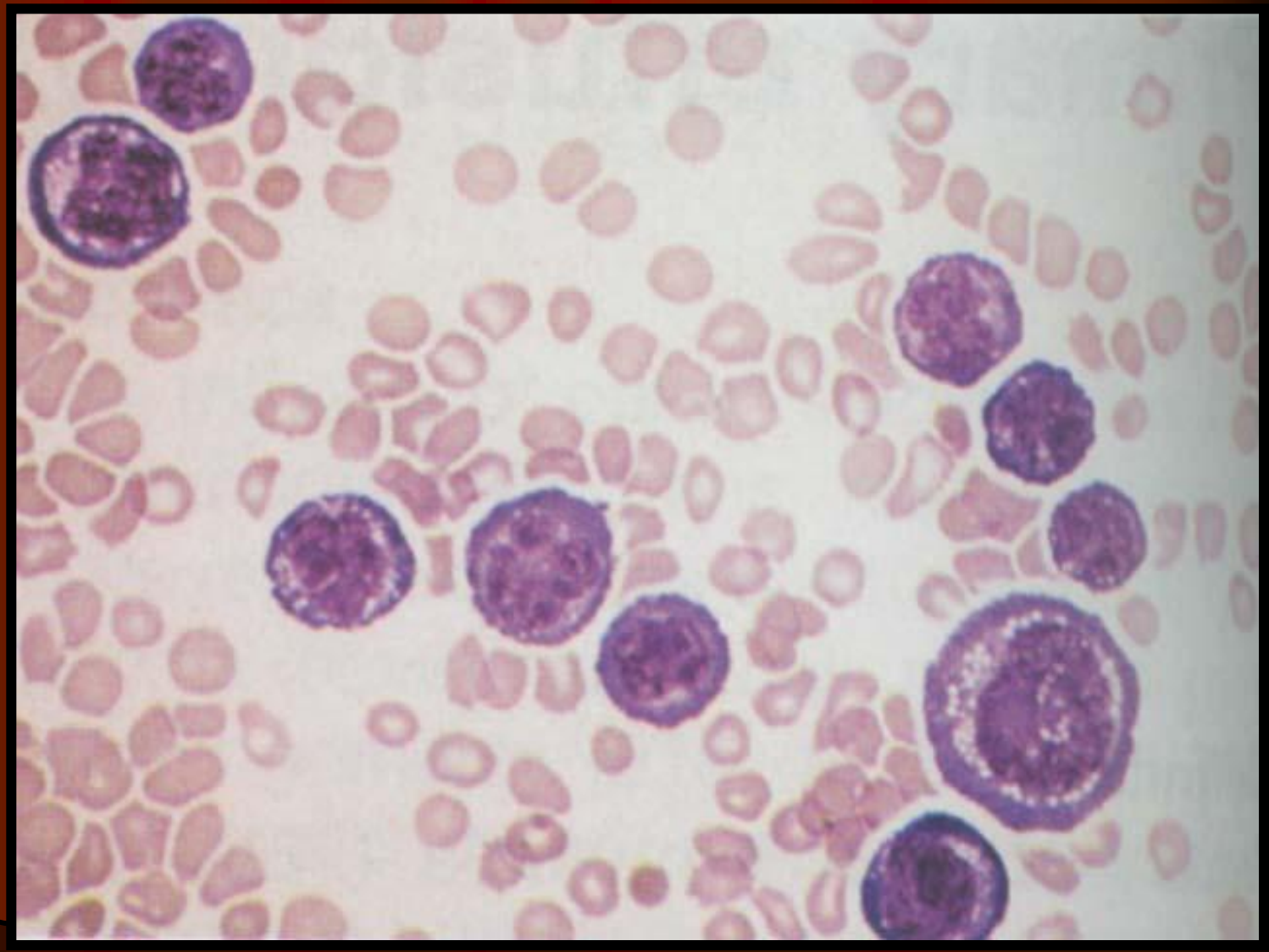
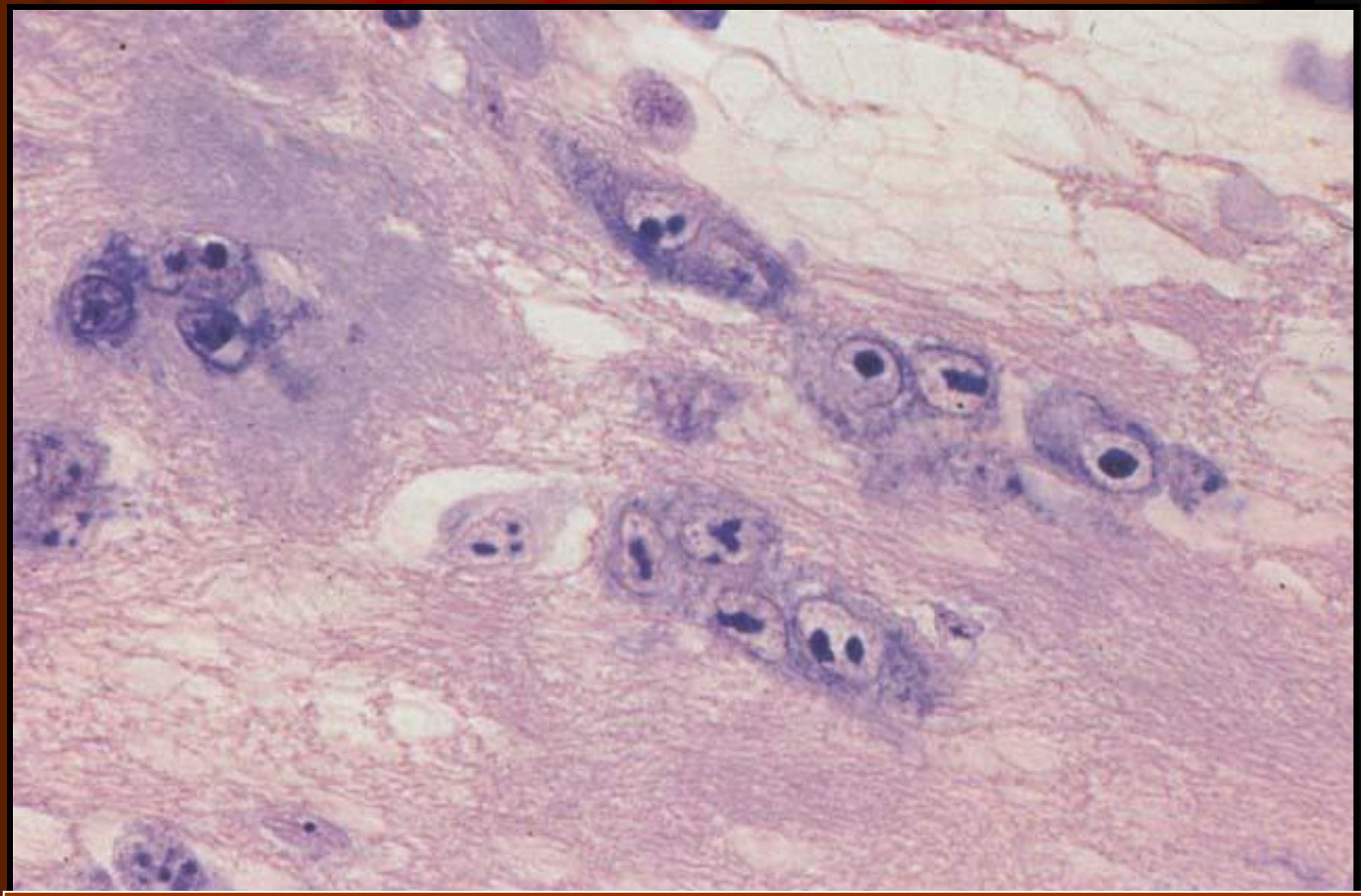


Primary Effusion Lymphoma



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