Osteosclerotic Myeloma (**POEMS** Syndrome)

Osteosclerotic Myeloma (**POEMS** Syndrome)

Synonyms

- Crow-Fukase syndrome
- Multicentric Castleman disease
- Takatsuki syndrome
- Acronym coined by Bardwick

POEMS

- Scheinker, first report in an autopsy case (1938)
- Crow described two cases (1956)

POEMS: Definition

- Plasma cell dyscrasias often associated with peripheral neuropathies
- 30-50% of patients with osteosclerotic myeloma have peripheral neuropathy
- Only 1-8% patients with classical myeloma have neuropathy

(**POEMS** Syndrome)

Osteosclerotic myeloma often associated with

- **P**olyneuropathy: sensorimotor demyelination
- **O**rganomegaly: liver, spleen
- **E**ndocrinopathy: diabetes mellitus, gynecomastia, testicular atrophy, impotence
- **M**onoclonal gammopathy
- **S**kin changes: hyperpigmentation, hypertrichosis

POEMS

Not included in acronym:

- Sclerotic bone lesions (multiple)
- Castleman disease
- Papilledema
- Pleural effusion, edema, ascites
- Thrombocytosis

Osteosclerotic Myeloma (**POEMS** Syndrome)

- Plasma cell proliferative disorder
- Plasma cell infiltrate in bone marrow
- Thickened trabeculae
- Lymph nodes with angiofollicular hyperplasia (Castleman disease)
- Relationship to typical plasma cell myeloma not known

Osteosclerotic Myeloma (**POEMS** Syndrome)

- 1-2% of plasma cell dyscrasias
- Adults (median age 50 years)
- Male-to-female ratio 1.4:1
- Some association with Kaposi sarcoma and Herpes Virus 8 (HHV 8)

POEMS Syndrome Clinical Presentation

- Only about 13% of cases with all features of POEMS
- Polyneuropathy
- Endocrine dysfunctions
- Lymphadenopathy
- Erythrocytosis (anemia rare)
- Thrombocytosis

POEMS Syndrome
Clinical Presentation

- Unlike multiple myeloma, rare findings of hypercalcemia, renal insufficiency, and pathologic fractures
- Paraprotein (IgG or IgA lambda type) is usually low

POEMS: Diagnostic Criteria

Dispenzieri *et al*, Blood. 2003; 101:2496-2506

Major Criteria

- Polyneuropathy
- Monoclonal plasmaproliferative disorder

POEMS

Minor Criteria

- Sclerotic bone lesions
- Castleman disease
- Organomegaly and lymphadenopathy
- Edema (effusions)
- Endocrinopathies (multiple)
- Skin changes
- Papilledema

POEMS (Diagnosis)

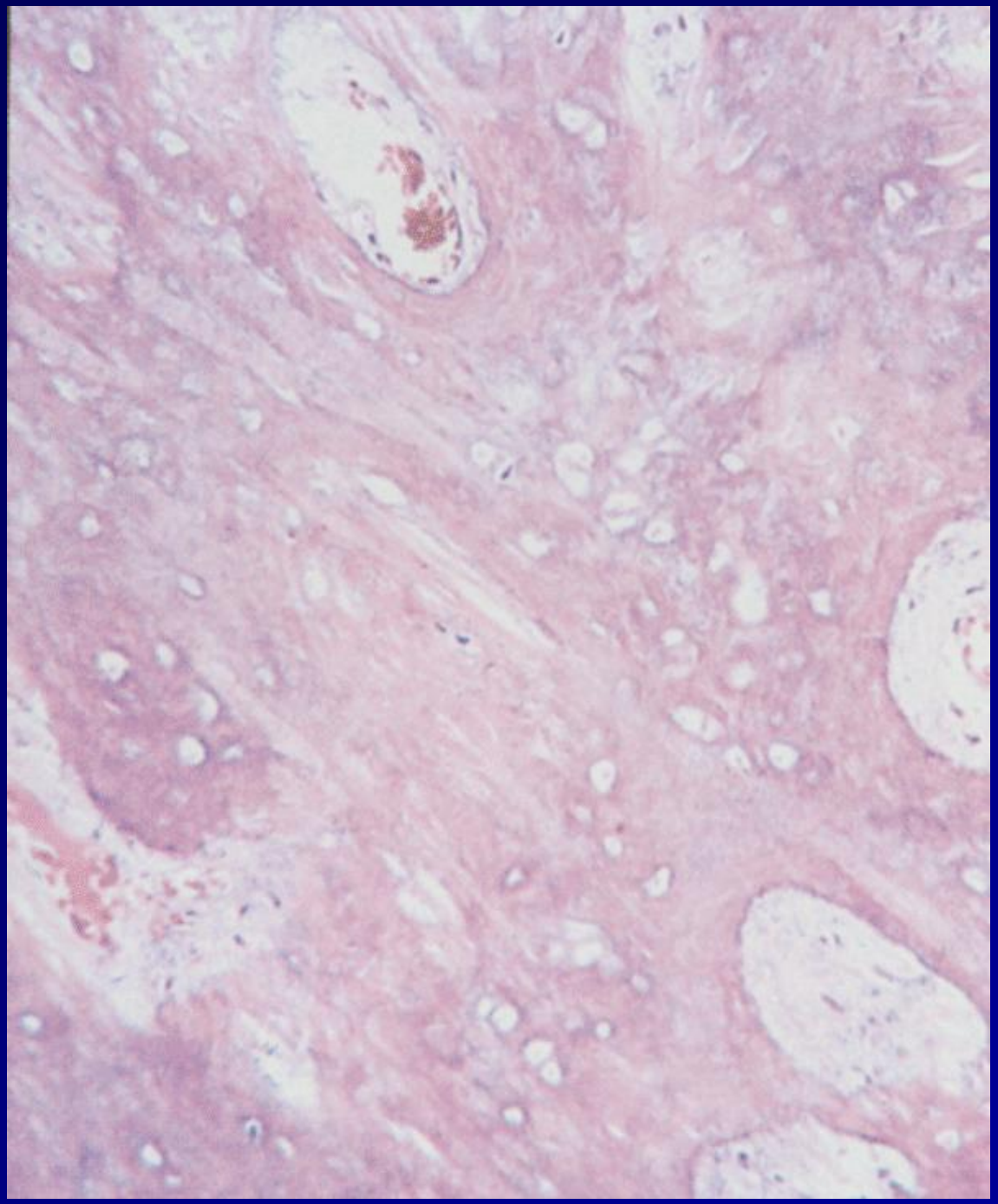
- Two major criteria
- And at least one minor criterion

Osteosclerotic Myeloma Morphology

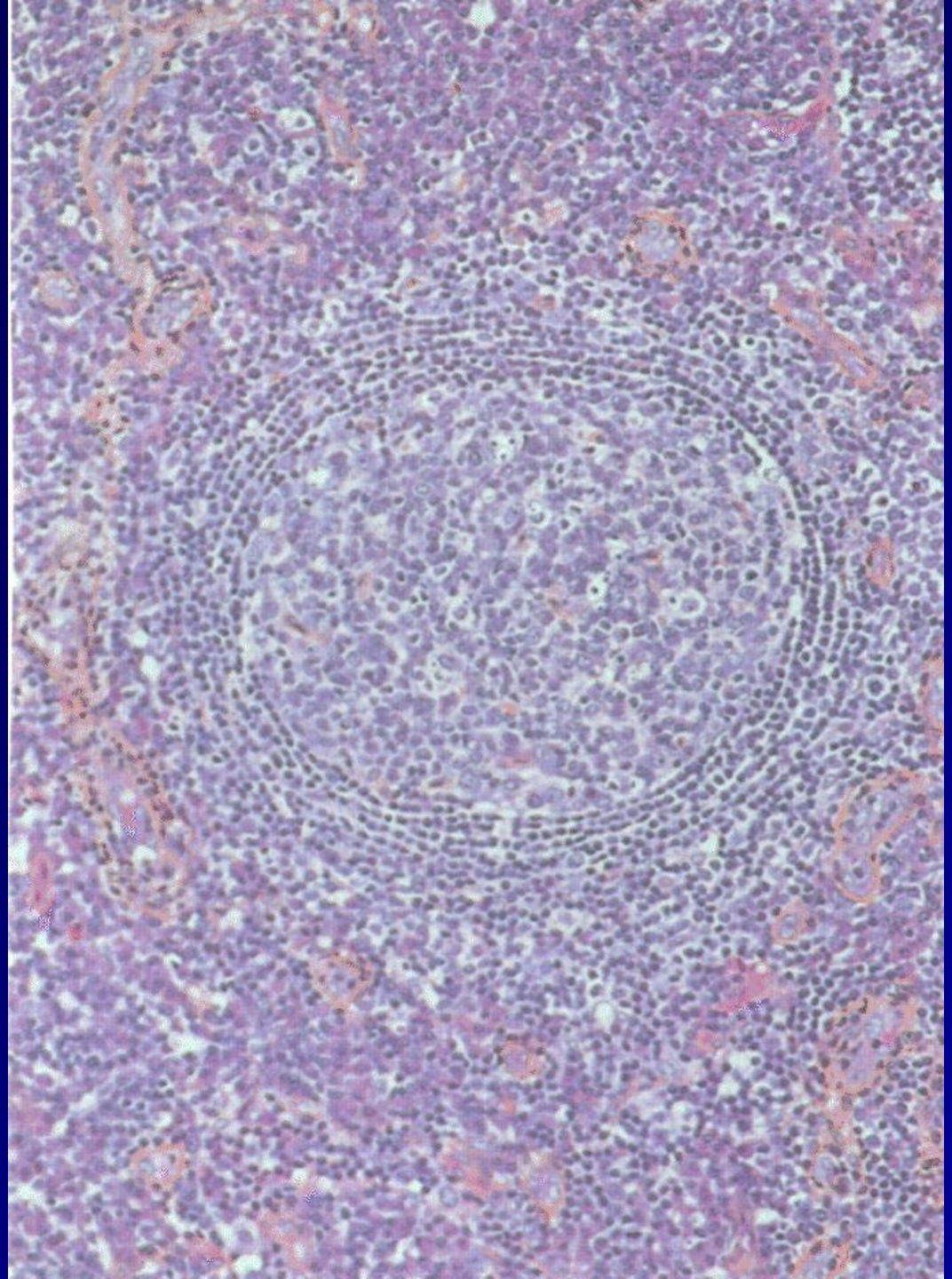
- Thickened trabeculae
- Peritrabecular fibrosis
- Entrapped plasma cells
- Bone marrow away from lesion has less than 5% mature plasma cells

Osteosclerotic Myeloma Morphology

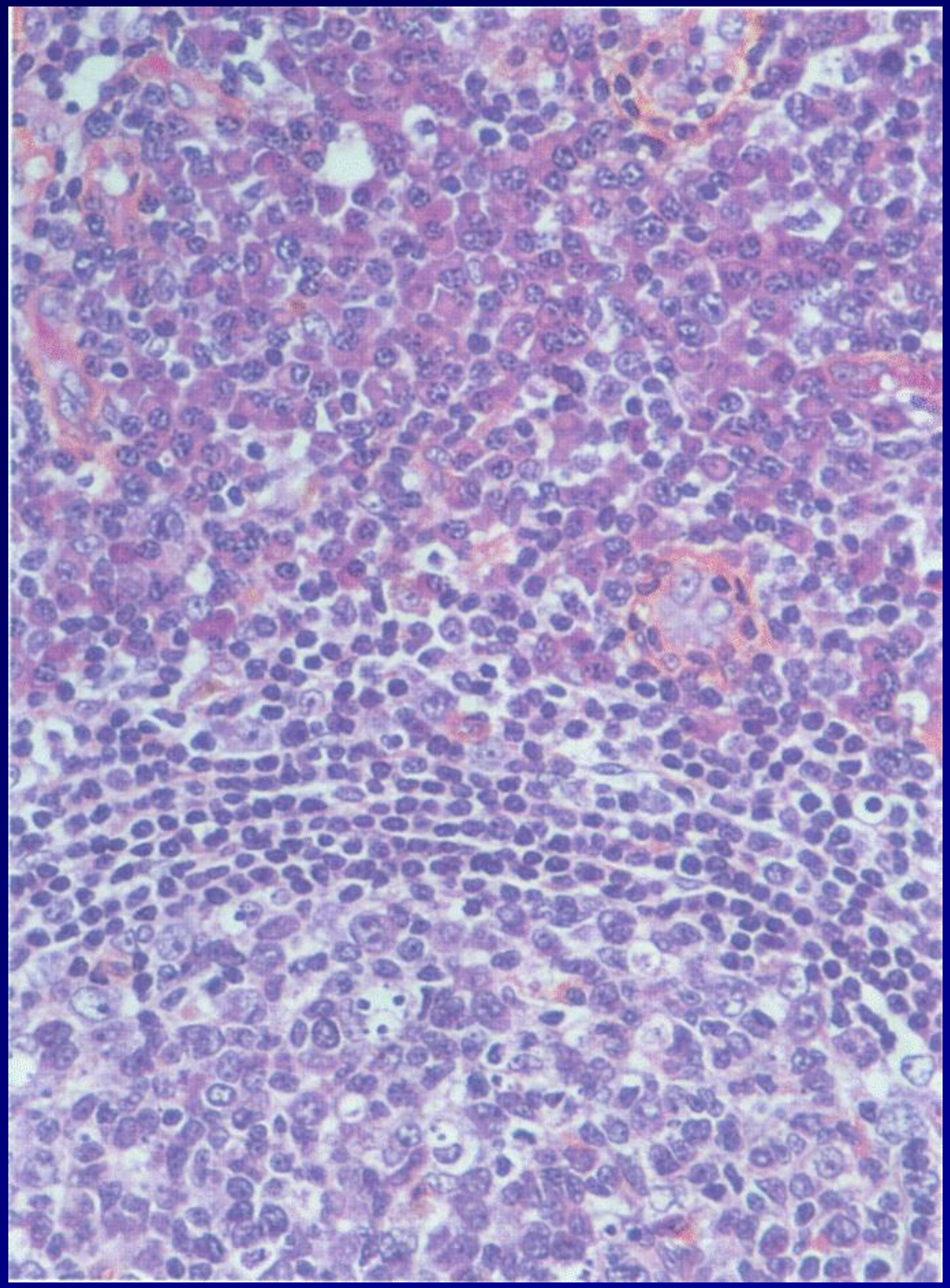
- Lymph nodes with plasma cell variant of Castleman disease
- Follicular proliferation with regressed (hyaline vascular) and reactive follicles
- Interfollicular plasma cells



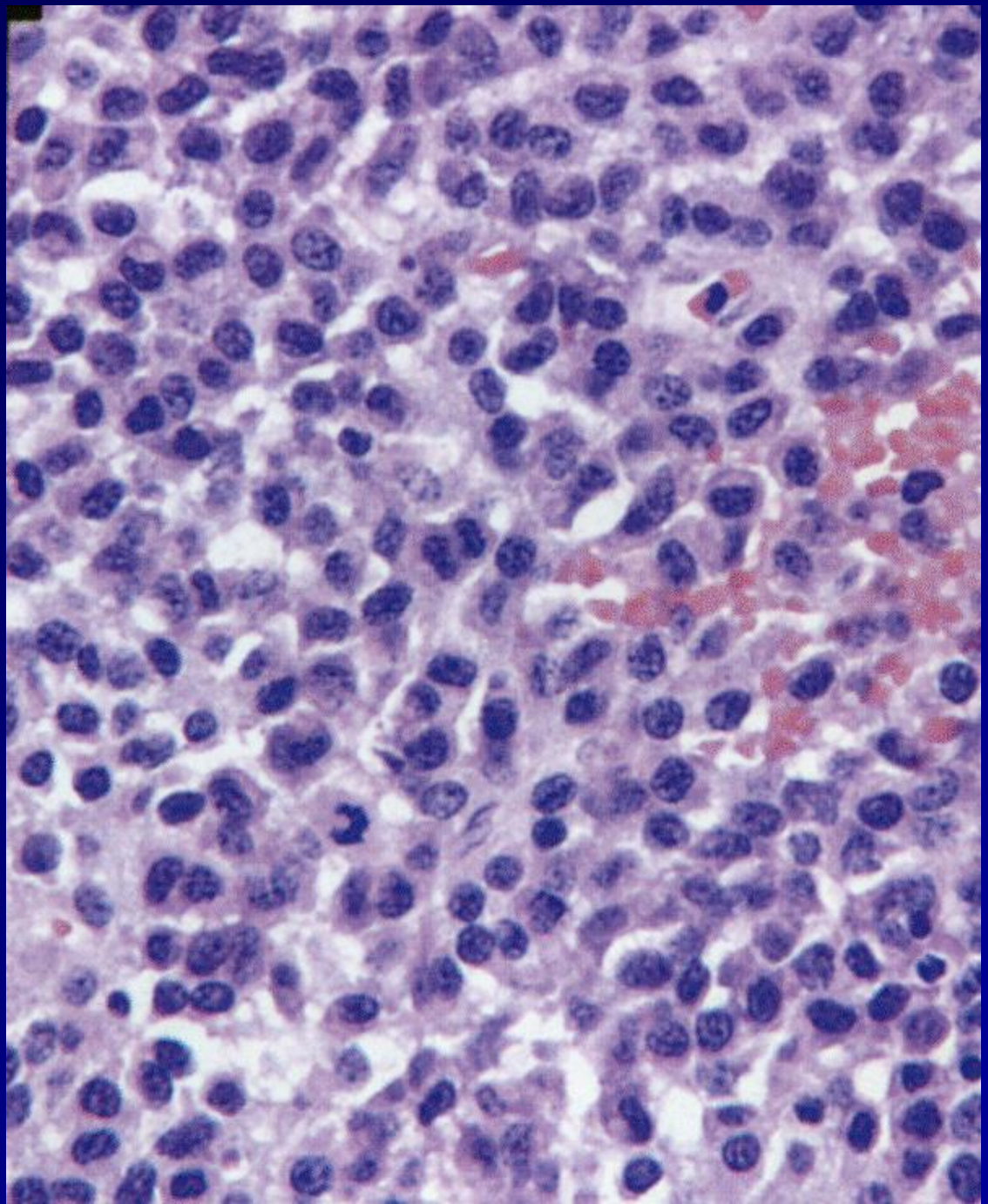
Osteosclerotic bone marrow



Lymph node with plasma cell variant of Castleman disease



Lymph node with plasma cell variant of Castleman disease



Plasma cell infiltrates

Osteosclerotic Myeloma (**POEMS** Syndrome)

Immunophenotype

- Monoclonal cIg (IgG or IgA heavy chain type)
- Light chain lambda in >90%

Osteosclerotic Myeloma (**POEMS** Syndrome)

Prognosis

- Survival 60% at 5 years (better than that for typical multiple myeloma)

Heavy Chain Diseases (HCD)

Heavy Chain Diseases

- Definition
  - Rare B-cell neoplasms that produce exclusively monoclonal heavy chains and no associated light chains
  - Not considered true plasma cell neoplasms
  - Representations of unusual variants of lymphomas

Heavy Chain Diseases (HCD)

- Morphologically, clinically heterogeneous
- Abnormal serum monoclonal component
  - Not always apparent
  - SPEP may appear normal
- Subtypes
  - IgA, IgG, or IgM

HCD and Immunoglobulins

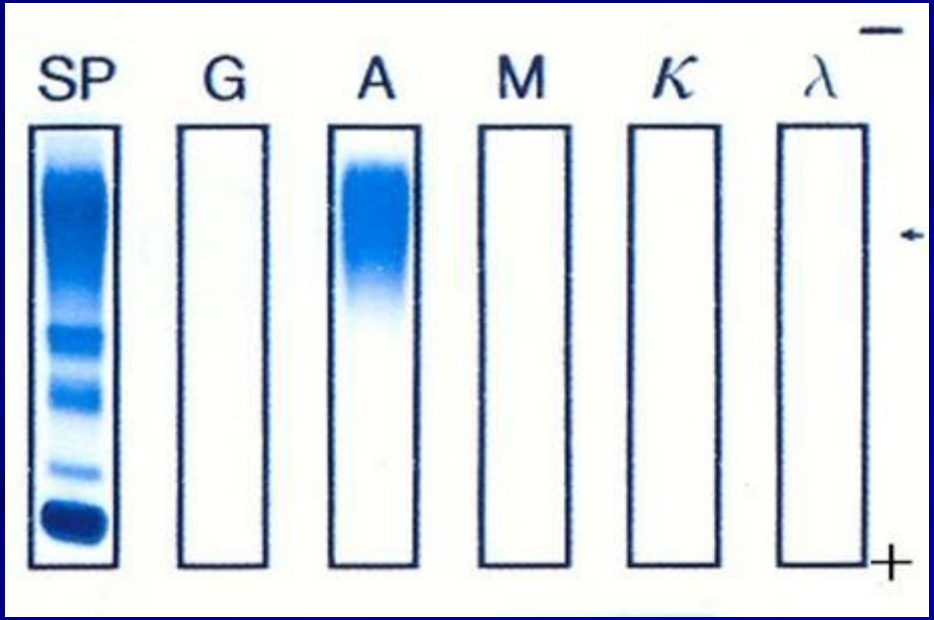
- Incomplete (truncated) immunoglobulins
- Due to mutations, large deletions in variable and constant regions
- Almost all have CH1 domain deletion
  - Can account for secretion of abnormal Ig
- Light chain alteration in alpha-HCD and gamma-HCD
- Normal light chains in mu-HCD, rarely in alpha-HCD and gamma-HCD

Laboratory Diagnosis

- Diagnostic
  - Detectable immunoglobulin heavy chains and absence of light chains in serum
- Negative SPEP
  - 50 % of alpha-HCD
  - 67% of mu-HCD
  - 33% of gamma-HCD

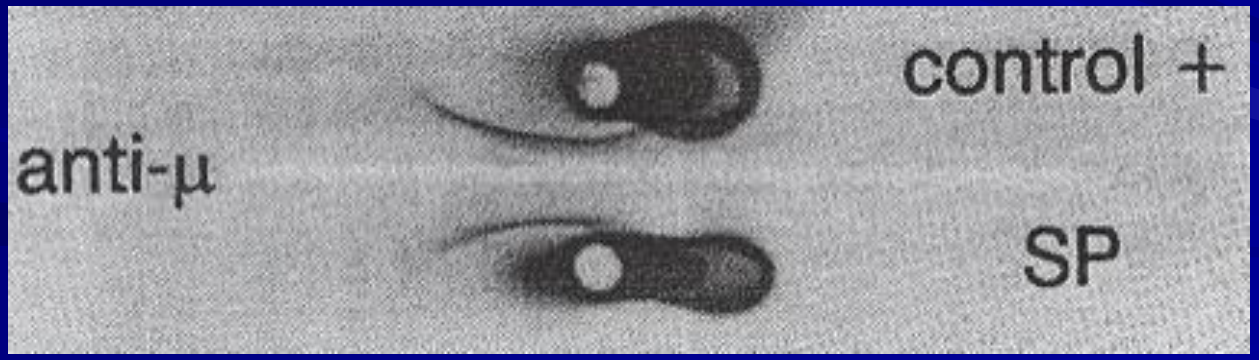
Laboratory Diagnosis SPEP

- Broad band in alpha-2 to beta-region
  - Polymerization, smearing of alpha-2
  - Variability, defectiveness of protein



Laboratory Diagnosis

- Immunoselection
  - Light chain antibodies mixed in gel
  - Molecules without light chains migrate
  - Quantify by distance of migration



Alpha Heavy Chain Disease

- Also known as Seligmann's disease
- Most frequent of HCDs
- Variant of extranodal marginal B-cell lymphoma
- Secretion of defective alpha heavy chains
- Young age group, 15-35 y/o
- Rare in Western world

Clinical Features

- Uniform clinical presentation
- Malabsorption, diarrhea, abdominal pain, wasting
- Low socioeconomic class, poor hygiene
- Recurrent infectious diarrhea, chronic parasitic infections
- Improvement following broad spectrum antibiotics

Clinical Features

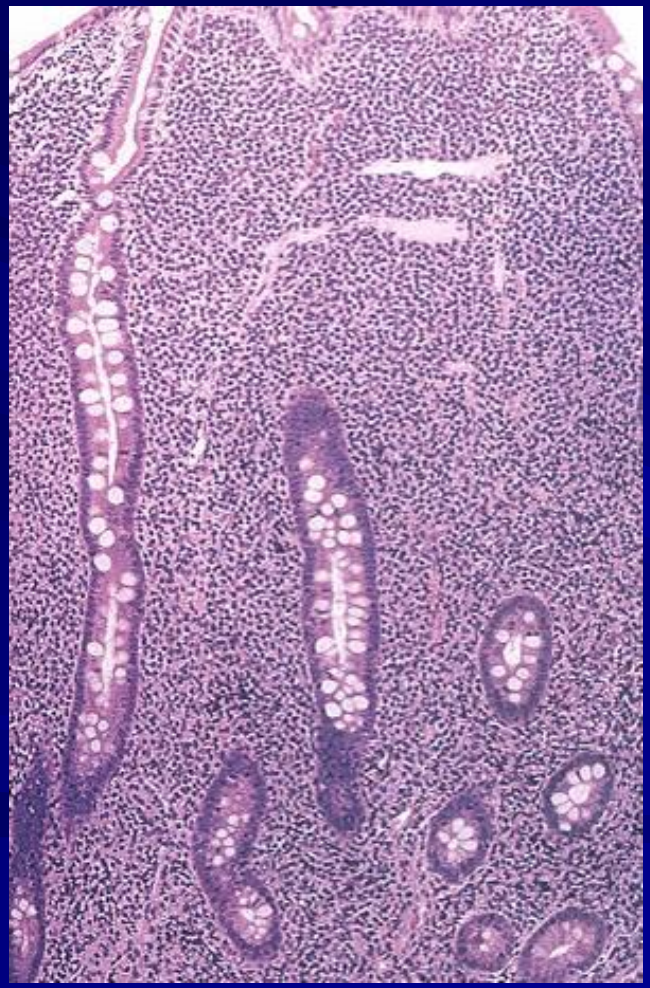
- Involvement of GI tract, lymph nodes
- Extensive mesenteric, para-aortic adenopathy
- Prognosis
  - Correlates with stage, generally poor

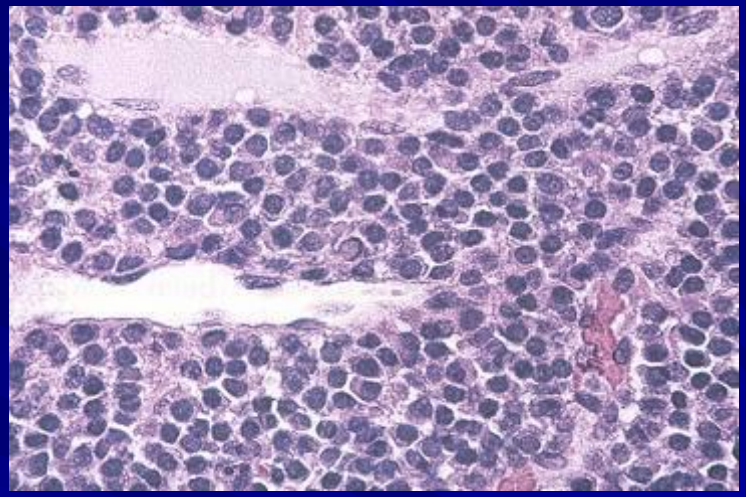
Histology

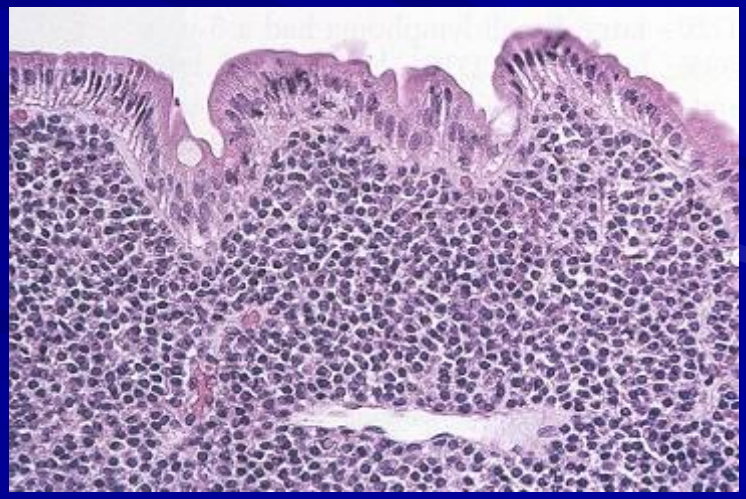
- Three stages of increasing malignancy
  - A: Mature plasmacytic/lymphoplasmacytic infiltrate in lamina propria, villous atrophy
  - B: Intermediate, dystrophic plasma cells, atypical immunoblast-like cells,

    Invasion at least to mucosa
  - C: Immunoblastic lymphoma, discrete & ulcerated tumors or extensive infiltration of long segments of intestinal wall

Stage A, alpha-HCD







Histology

- Heterogeneous presentation
- Different stages present at the same time in different organs
- Different stages present at different sites within same organ system

Possible Pathogenesis

- Background bacterial stimulation
- Alpha-HCD cell arises in germinal center
- Other genetic alterations occur to selected cell
- Clone expansion through local lymphokines
- Other genetic alterations cause malignant proliferation
- No causative organism yet identified

Gamma HCD

- Also known as Franklin's disease
- Lymphoplasmacytic neoplasm
- Heterogeneous condition
- May not represent a single disease process
- Age: adults with wide range, median 60 y/o
- No geographic area of origin

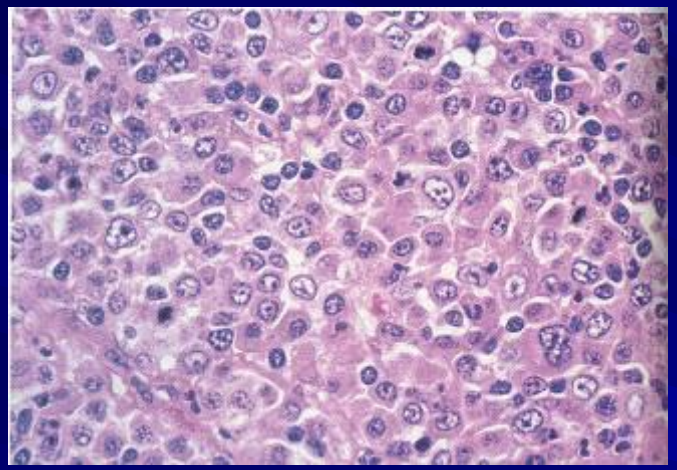
Clinical Presentation

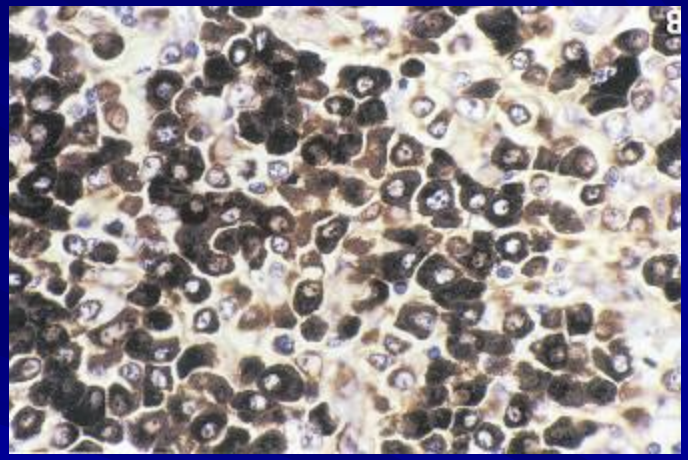
- Presents as lymphoproliferative disorder
- Generalized lymphadenopathy, splenomegaly, constitutional symptoms
- Palatal edema, uvular swelling (Waldeyer's ring involvement) in only 15%
- Mediastinal lymphadenopathies, bone marrow less common
- Eosinophilia, thrombocytopenia

Gamma HCD: Histology

- No specific pattern
- Most common, polymorphous lymphoplasmacytic proliferation
- Involves bone marrow, lymph nodes
- Associated unusual features
  - Admixed eosinophils, large immunoblasts, giant cells

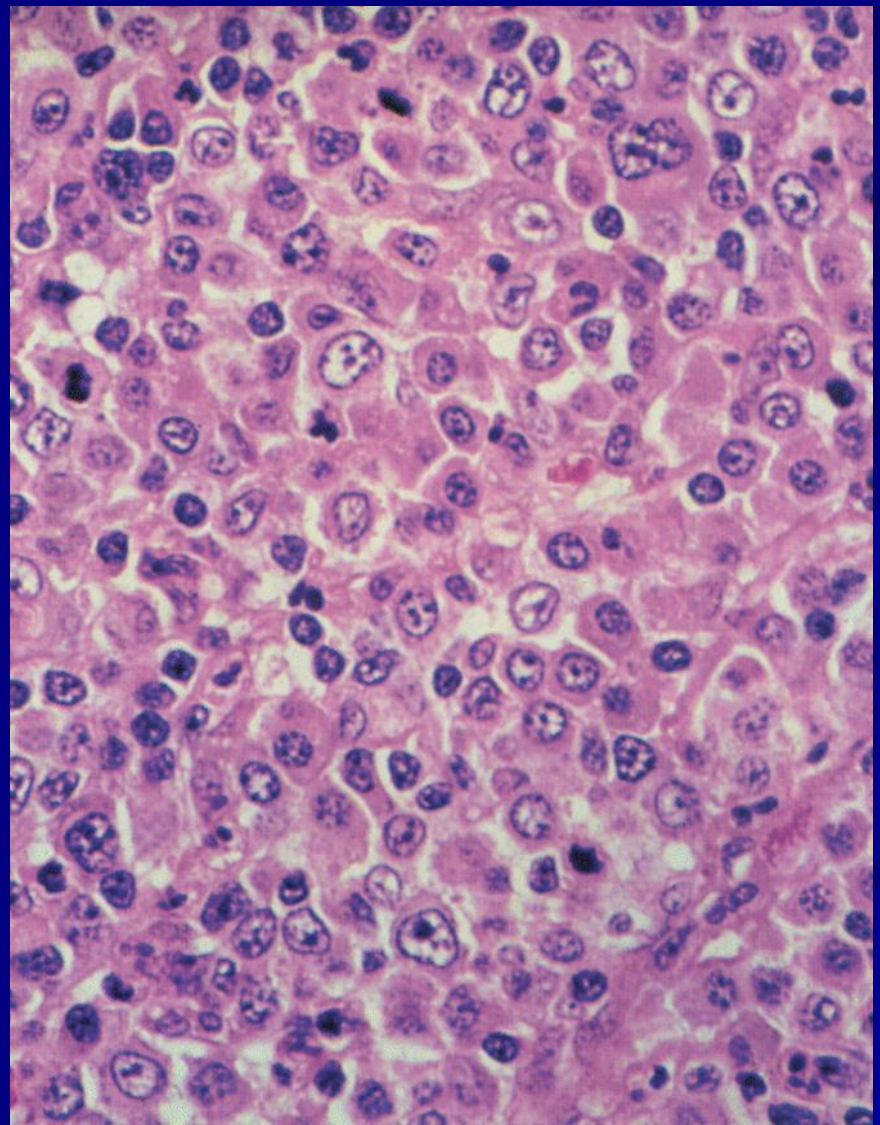
Gamma HCD: Histology



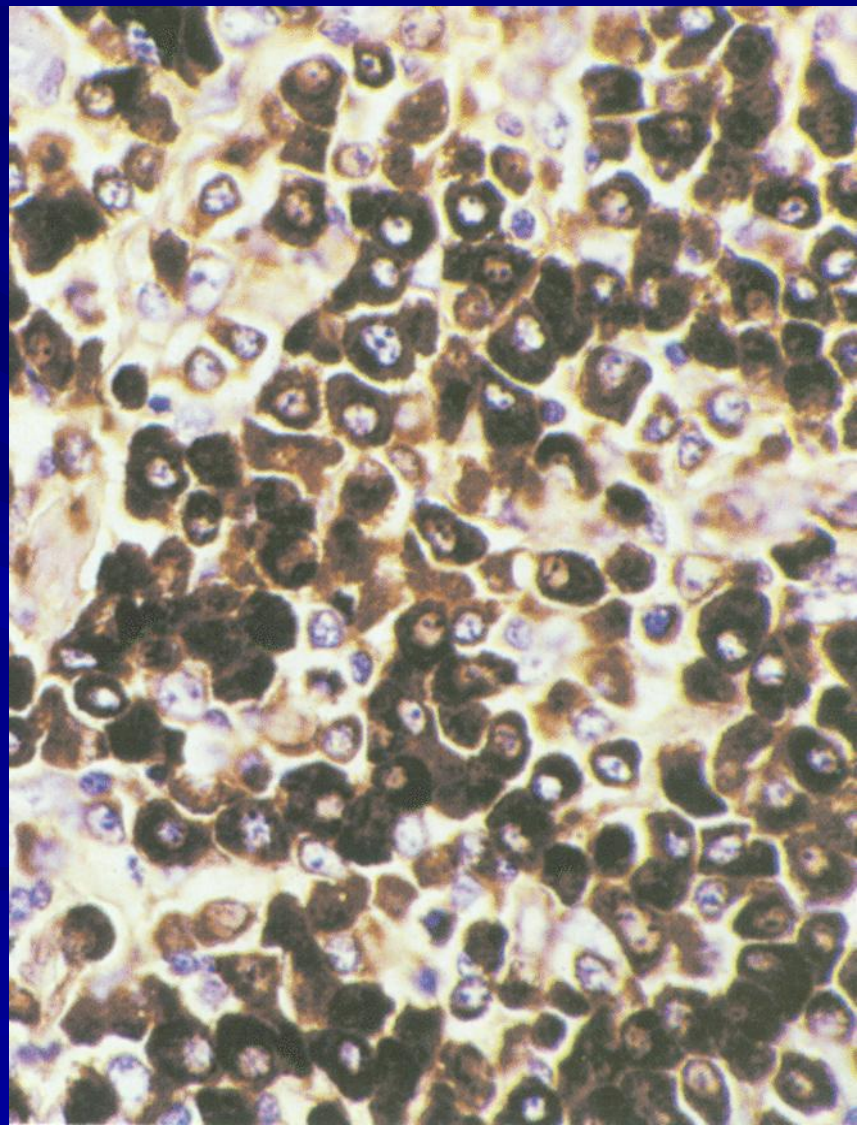


Gamma Heavy Chain Immunostain

Gamma-Heavy chain disease, H&E stain



Gamma-heavy chain stain



Gamma-HCD

- Most commonly, a chronic lymphocytic leukemia picture with blood involvement
- Predominantly plasmacytic proliferation
- Usually in extranodal locations
  - Thyroid, salivary glands
- Vascular proliferation
  - May mimic angioimmunoblastic lymphadenopathy

Associated Disorders

- Associated autoimmune disorder in 25%,

  Most frequently
  - – Rheumatoid arthritis
  - – Hemolytic anemia, TTP

  Others
  - SLE
  - Sjogren's
  - Myasthenia gravis
- Immune disease may precede detectable HC protein, malignant proliferation disease in years

Clinical Course

- Variable
- Asymptomatic to state of rapidly progressive malignancy
- Serum level of gamma-HCD follows state of malignant process
- Median survival- 12 months

Mu-heavy Chain Disease

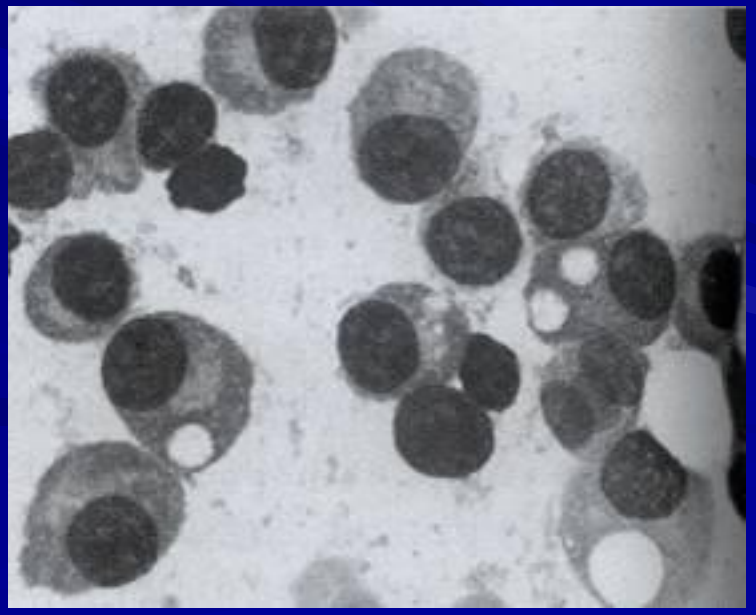
- Least common of HCDs
- Extremely rare
- Resembles CLL
- First described 1969, approximately 30 cases reported
- Wide age range: 15-80 y/o
- Defective light and heavy chain assemblage

Clinical Presentation

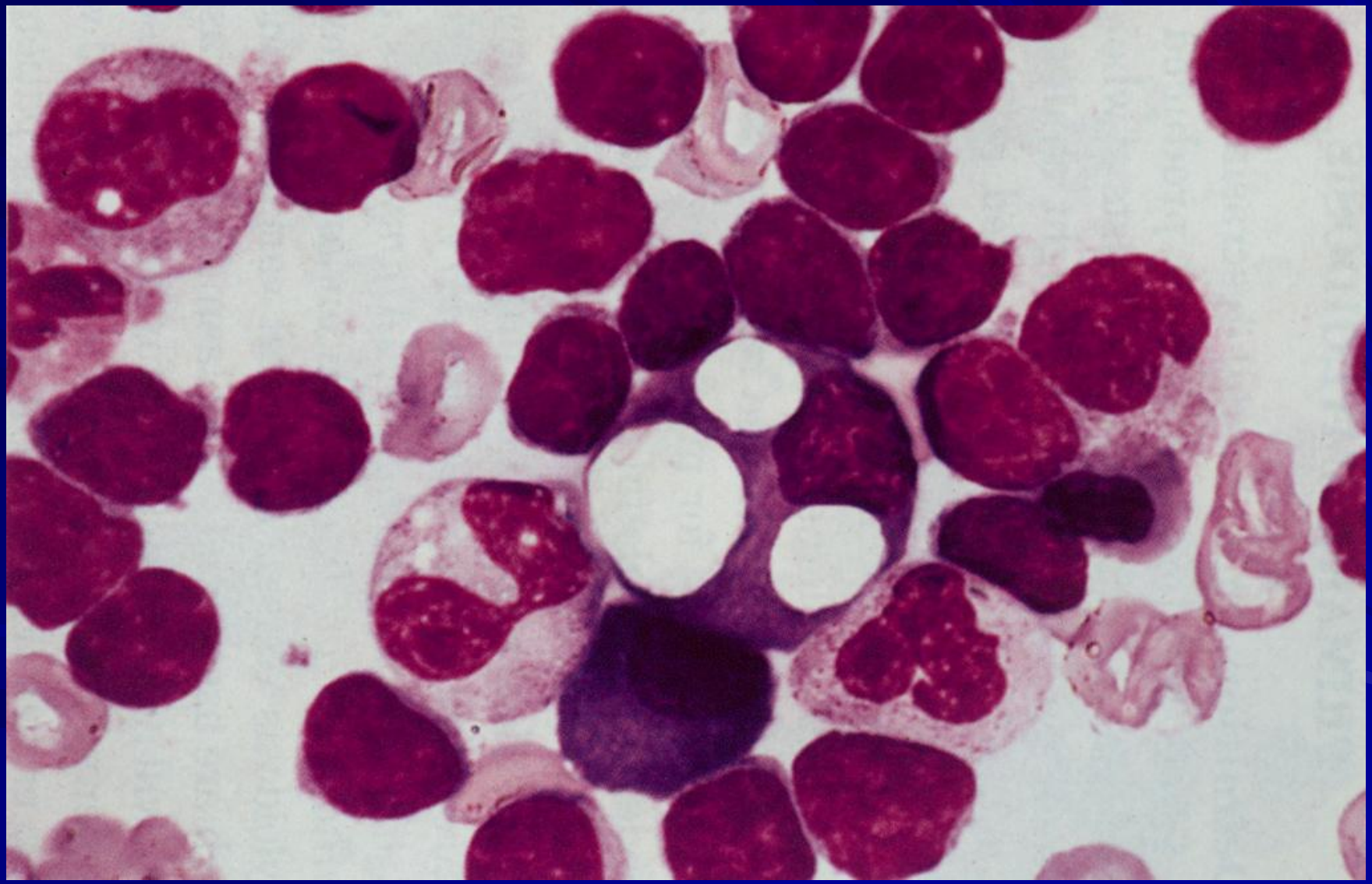
- Slowly progressive CLL
  - Differs in hepatosplenomegaly, lack of peripheral lymphadenopathy
- Bence-Jones proteinuria common, 50% of cases
- Usually kappa-light chain
- Lytic bone lesions, can mimic multiple myeloma
- Mu-HCD may be present without malignancy

Mu-heavy Chain Disease: Histology

- Characteristic vacuolated cytoplasm in plasma cells
- Admixes small, round lymphocytes, similar to CLL cells



Mu-Heavy Chain Disease



Clinical Course

- Slowly progressive
- Unclear survival range
  - < 1 month to > 10 years
- Treatment: same as for CLL