Histiocytic and Dendritic cell Neoplasms

Definition

- Neoplasms derived from phagocytes and dendritic cells

- WHO
  - Histiocytic sarcoma
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
  - Interdigitating dendritic cell sarcoma/tumor
  - Follicular dendritic cell sarcoma/tumor
  - Dendritic cell sarcoma, not otherwise specified

Incidence

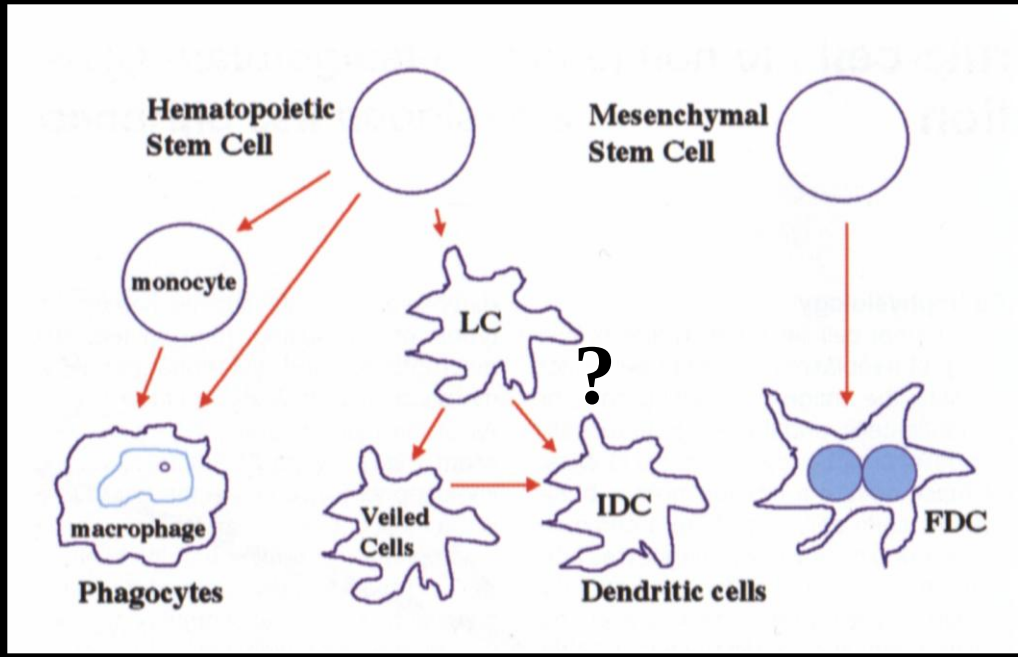
- < 1% of tumors presenting in lymph nodes
- Histiocytic malignancy; a “vanishing diagnosis”

Epidemiology

- Detailed data difficult to obtain because of disease rarity
- No significant geographical or racial differences in incidence

Pathophysiology

- Normal cellular counterparts
  - Phagocytic cells (antigen-processing)
  - Dendritic cells (antigen-presenting)
  - Common cellular origin (BM stem cell), except perhaps follicular dendritic cells
  - Independent lines of differentiation



Histiocytes/Macrophages

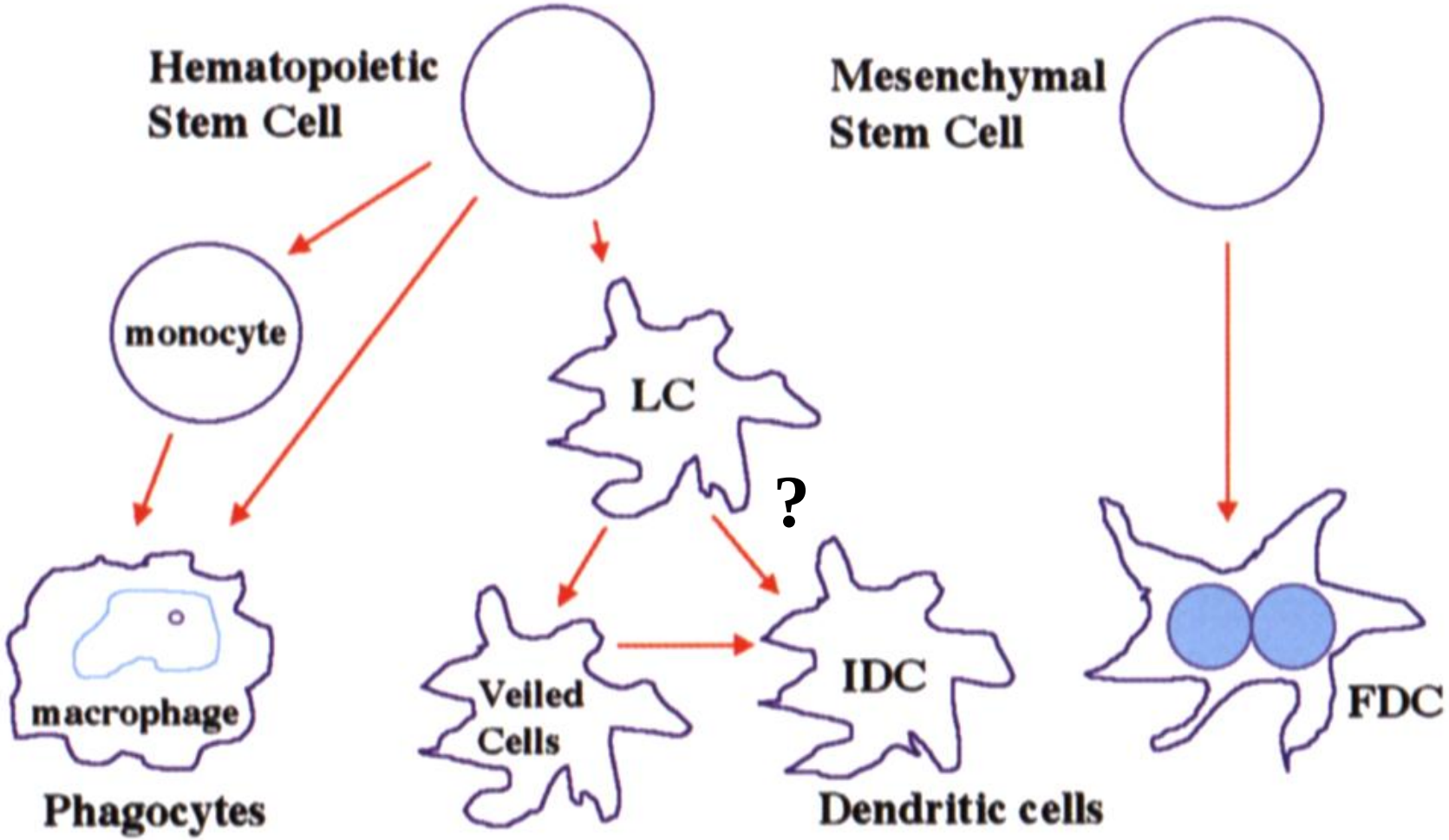
- Primary role: removal of particulate antigen
- Derived from the circulating blood monocyte pool
- Can demonstrate phagocytosis
  - Usually not a feature of histiocytic malignancies
  - More common in benign proliferations of histiocytes (hemophagocytic syndrome)

Histiocytes/Macrophages

- Markers
  - CD68
  - Acid phosphatase
  - Nonspecific esterases
  - Lysozyme (decreases with increase in phagocytosis)
  - Alpha-1-antitrypsin

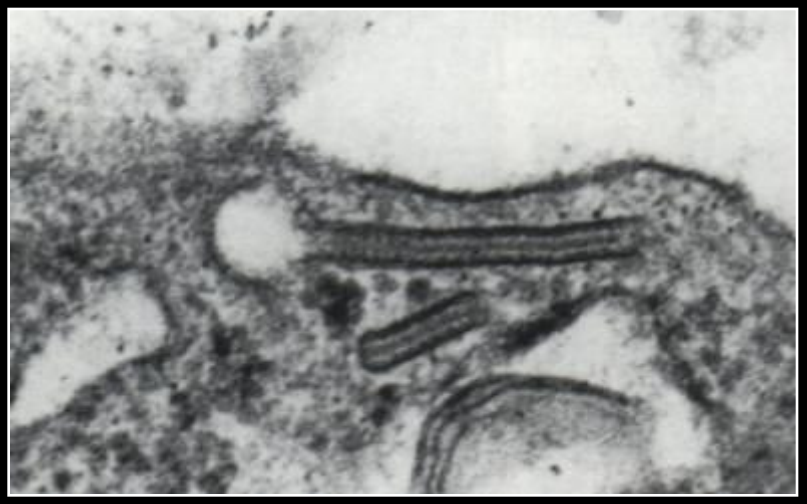
Histiocytes/Macrophages

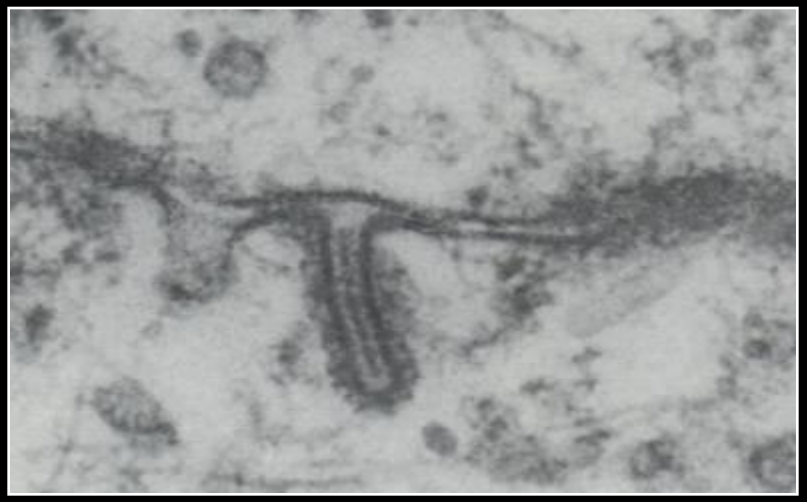
- Less specific markers
  - Antibodies to cell surface receptors for the Fc portion of IgG:
    - CD16, CD32, CD64
  - Complement receptors:
    - CD21, CD35
  - Cellular activation and adhesion molecules:
    - CD11a, CD11b, CD11c, CD14, CD18


Hematopoietic
Stem Cell
Mesenchymal
Stem Cell
monocyte
LC
?
macrophage
Veiled
Cells
IDC
FDC
Phagocytes
Dendritic cells

Langerhans Cells/Interdigitating Dendritic Cells

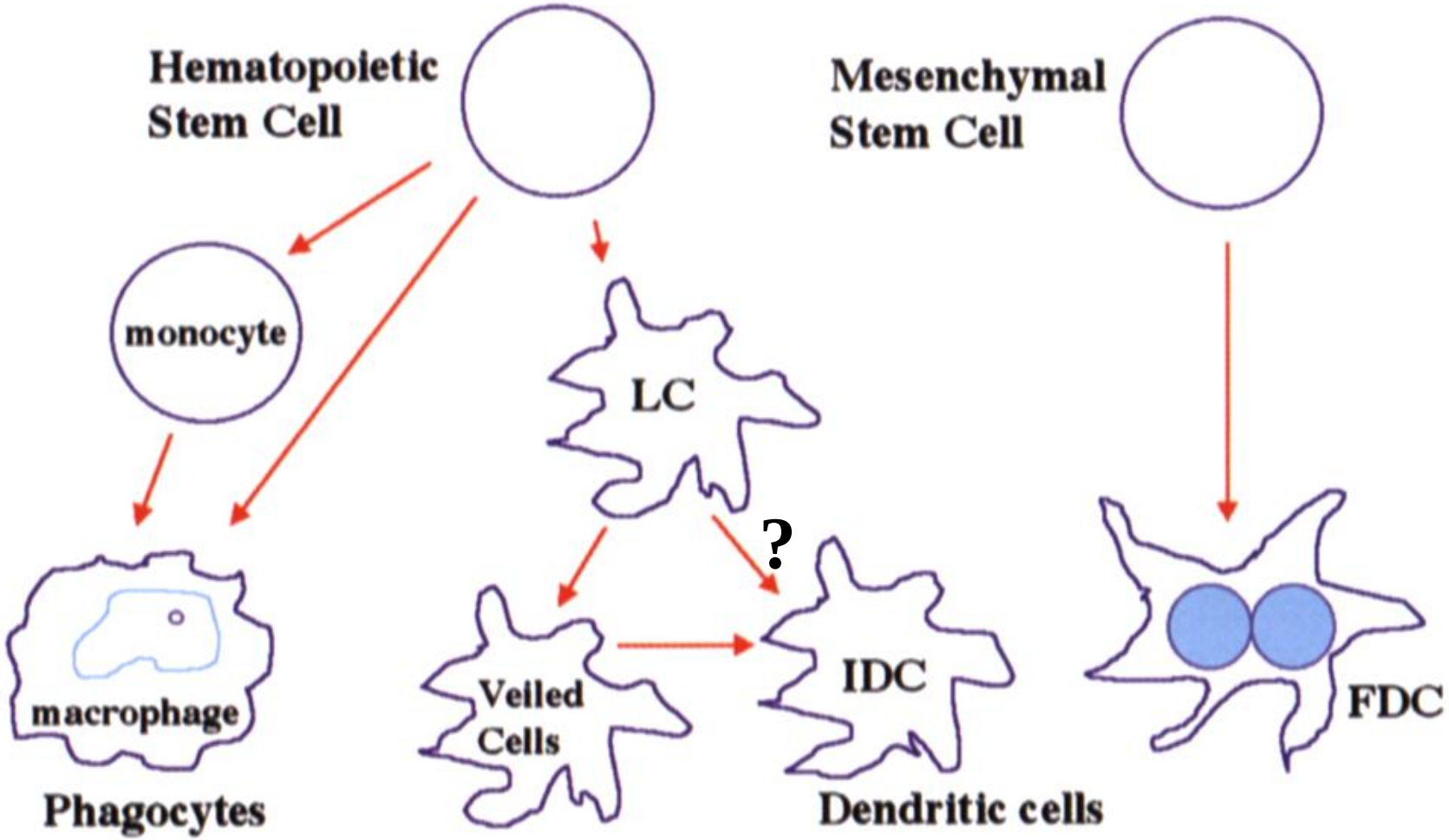
- Primary role: presenting antigens to T lymphocytes
- Langerhans cells (LC)
  - Birbeck granules
  - Found primarily in skin
  - Can migrate to PB (veiled cells)
  - Enter LNs via afferent lymphatics; reside in paracortex (interdigitating dendritic cells) **???**





Immunophenotype

- Langerhans cells (expression)
  - MHC Class II
  - S-100
  - CD1a
  - CD4
- Interdigitating dendritic cells
  - MHC Class II
  - S-100


Hematopoietic
Stem Cell
Mesenchymal
Stem Cell
monocyte
LC
?
macrophage
Veiled
Cells
IDC
FDC
Phagocytes
Dendritic cells

Follicular Dendritic Cells (FDC)

- Primary role: present antigens to B lymphocytes
- Most likely not of hematopoietic origin
- Found in follicles where they form a meshwork to trap antigens
- Contain iccosomes: antigen-antibody complexes in organelles
- Needed for B-cell activation
- CD21+
- CD23+
- CD35+

Fibroblastic Reticular Cells (FRC)

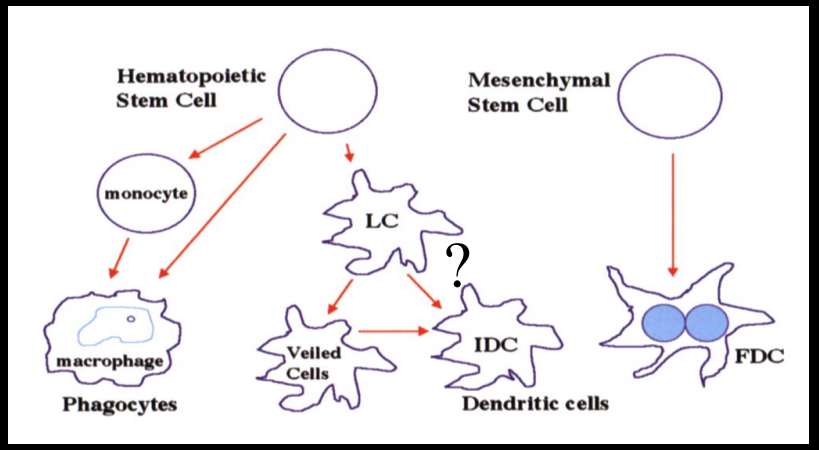
- Primary role: transport of cytokines and other mediators
- Mesenchymal origin
- Ensheathe post-capillary venules in lymph nodes

Fibroblastic Reticular Cells

- Neoplasms
  - Only few cases reported
  - Not in the WHO classification
  - Arise in Lymph nodes
    - Need to R/O IDC (S-100 +) and FDC (CD21/35 +) origin
  - Cells have features of myofibroblasts
  - Express
    - SMA
    - Desmin
    - Vimentin
    - Factor XIII

Survival

- Histiocytic sarcoma and IDC sarcoma
  - Aggressive
  - Potential for systemic spread
- FDC tumors
  - Localized
  - Potential for local invasion and recurrence
  - Distant metastases are infrequent
- LC histiocytosis
  - Wide spectrum of clinical behavior

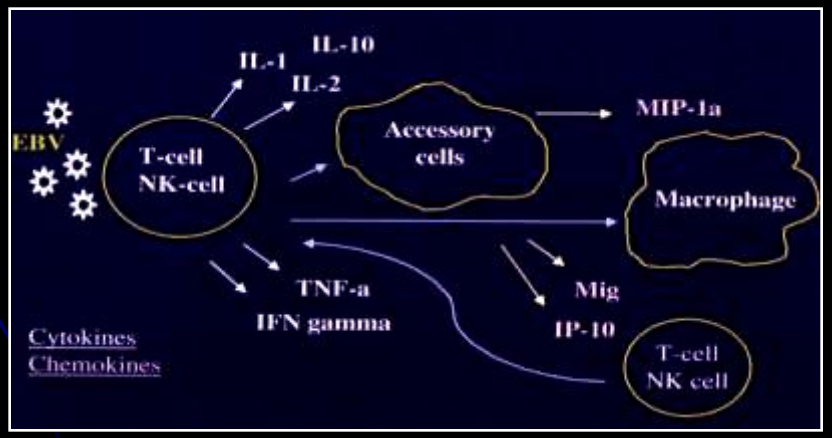


Hemophagocytic Syndrome (HPS)

- Scott and Robb-Smith (1939)
- Non-neoplastic, proliferative disorder of macrophages
- Important in DDX of histiocytic neoplasms
- More common than histiocytic neoplasms
- Immunodeficiency or other hematopoietic malignancies
- Fulminant clinical course (often fatal)

Pathogenesis of HPS

- Infection with EBV (or another virus) is a frequent precipitating event
- Excessive production of cytokines and chemokines (“cytokine storm”)
- Profound and uncontrolled macrophage activation with marked phagocytosis
- Pancytopenia



Histiocytic Sarcoma

- Definition
  - Malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes
  - Expression of one or more histiocytic markers (without dendritic cell markers)
  - Exclusion of extramyeloid manifestations of acute monocytic leukemia

Synonyms and Historical Annotation

- Virtually all “diffuse histiocytic lymphoma” cases are now DLBCL
- Most cases of “histiocytic medullary reticulosis” and “malignant histiocytosis” are now considered systemic ALCL or hemophagocytic syndrome

Epidemiology

- Rare (only few series of *bone fide* neoplasms)
- Wide age range (median 46 years)
- Male predilection (in some studies)
- Subset of cases associated with prior mediastinal germ cell tumors
- Other cases associated with malignant lymphoma (preceding or subsequent), or with myelodysplasia

Sites of Involvement

- 1/3: Lymph nodes
- 1/3: Skin, solitary or multiple lesions
- 1/3: Other extranodal sites (mostly GI)
- Some patients present with “malignant histiocytosis” (systemic, multiple sites of involvement)

Clinical Features

- Systemic symptoms (fever and weight loss), even in patients with solitary mass
- Skin manifestations vary widely
  - Benign-appearing rash
  - Solitary lesions
  - Innumerable tumors on trunk and extremities

Clinical Features

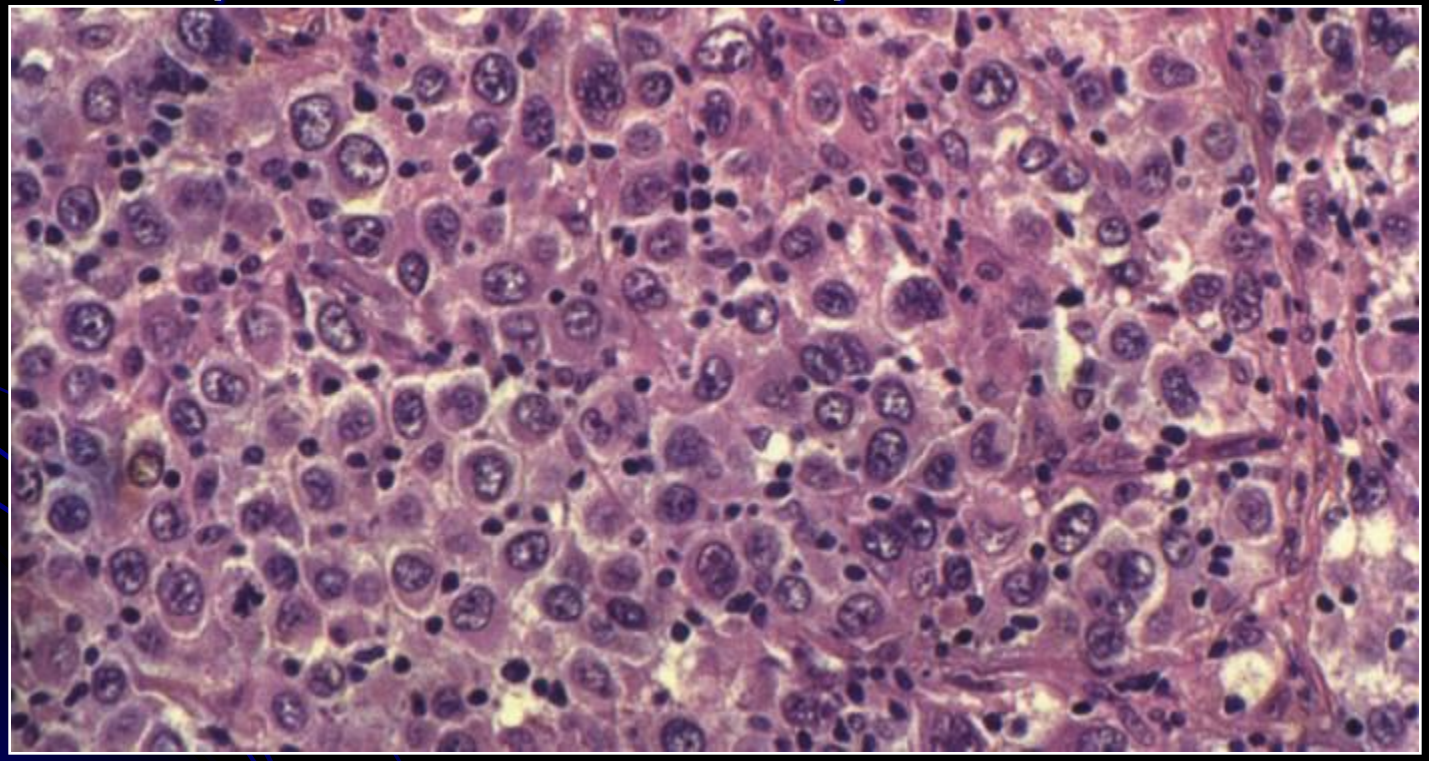
- GI lesions
  - Possible intestinal obstruction
- Hepatosplenomegaly (relatively common)
- Bone
  - Lytic lesions
- Bone marrow
  - Pancytopenia

Etiology

Unknown

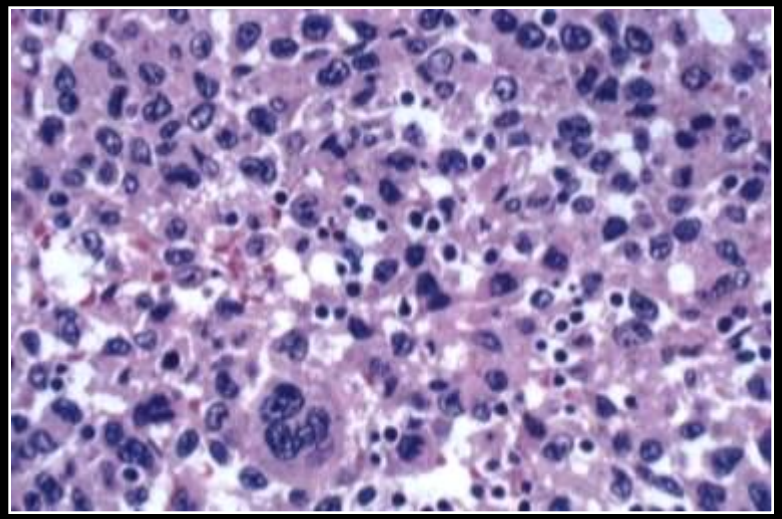
Morphology

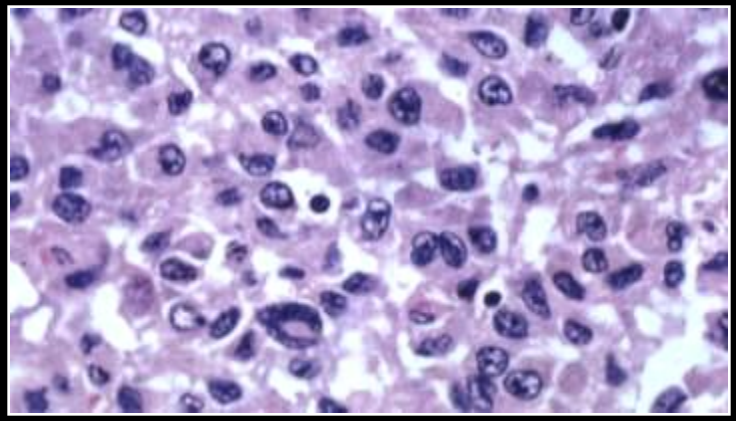
- Effacement of architecture by a diffuse, non-cohesive proliferation of neoplastic cells



Morphology

- Cells
  - Usually polymorphic
  - Large
  - Round to oval (spindling focally)
  - Cytoplasm
    - Abundant
    - Eosinophilic
    - May be foamy
  - Nuclei
    - Large
    - Round to oval
    - Eccentric
  - Large multinucleated cells (common)



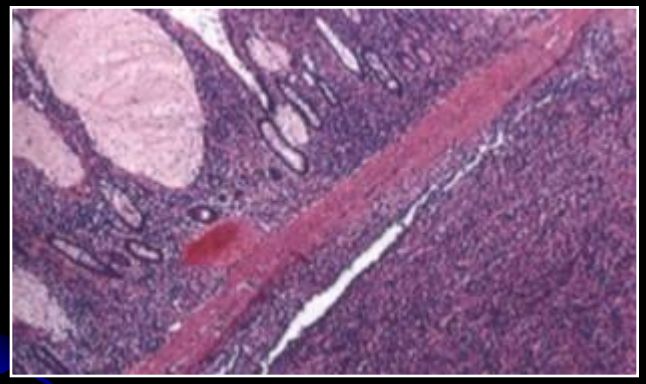


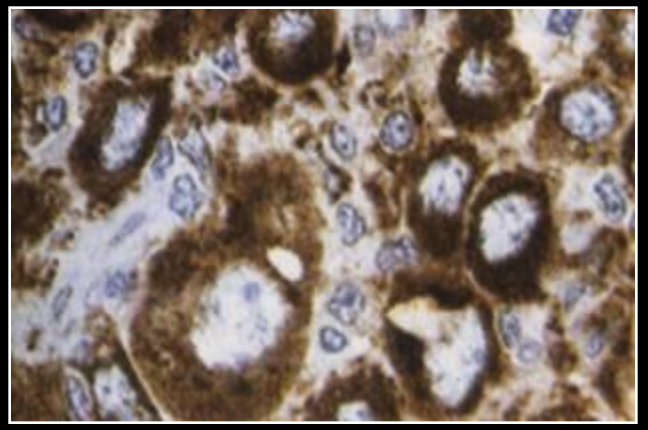
Morphology

- Vesicular chromatin
- Variable atypia
- Variable number of reactive cells
  - Small lymphocytes
  - Plasma cells
  - Benign histiocytes
  - Eosinophils

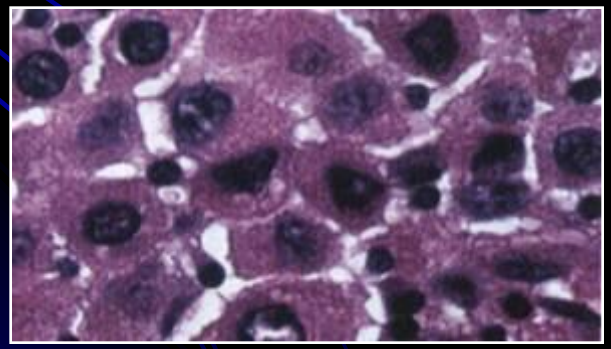
Morphology

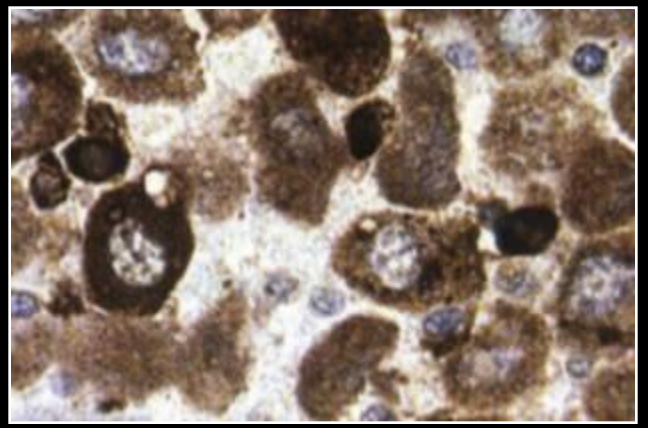
- May be indistinguishable from DLBCL or ALCL
- Markers necessary





CD68

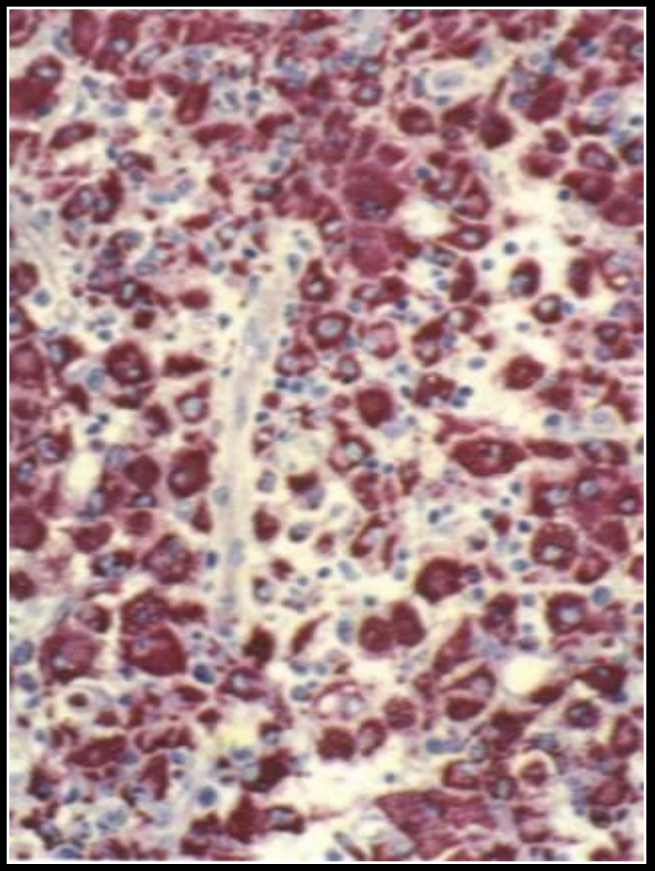




Lysozyme

Immunophenotype

- By definition
  - Presence of histiocytic markers
    - CD68
    - Lysozyme (Golgi pattern)
    - CD11c
    - CD14
  - Absence of specific myeloid markers
    - MPO
    - CD33
    - CD34



CD68

Immunophenotype

- Usually positive
  - CD45
  - CD45RO
  - HLA-DR
  - CD4
- S-100 may be positive (weak or focal)
- Ki67: variable (10-90%; mean 20%)

Immunophenotype

- Negative
  - B and T-cell markers
  - LC and IDC markers (CD1a, CD21, CD35)
  - CD30
  - HMB-45
  - EMA
  - CK

Genetics

By definition, no clonal immunoglobulin or TCR genes

Postulated Cell of Origin

Mature tissue histiocyte

Prognosis

- Aggressive neoplasm
- Poor response to therapy
- High clinical stage (III/IV) at presentation (70%)
- 60% die of progressive disease

WHO Interdigitating Dendritic Cell Sarcoma/Tumor

Definition

- Neoplastic proliferation of spindle to ovoid cells with phenotypic features of IDCs
- Term tumor/sarcoma is used because of the variable cytological grade and clinical behavior encountered in these neoplasms

Synonyms

- Reticulum cell sarcoma/tumor.
- Interdigitating cell sarcoma/tumor.

Epidemiology

- Extremely rare neoplasm
- Most studies represent single cases or very small series
- Mostly elderly adults with no sex predilection

Sites of involvement

- Solitary lymph node involvement is the most common
- Extranodal sites include skin, GI, soft tissue, liver and spleen

Clinical Features

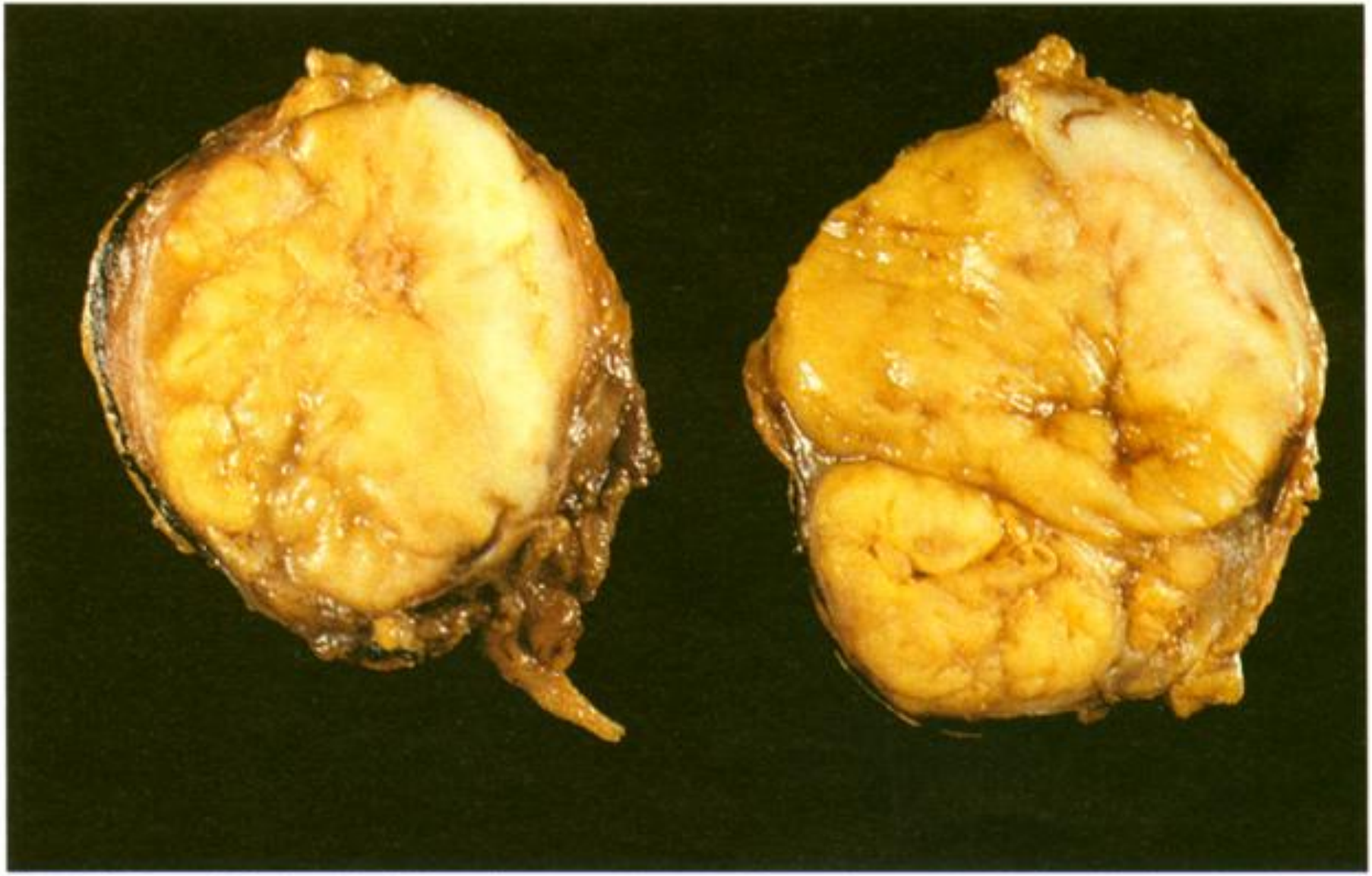
- Aymptomatic mass
- Systemic symptoms, when present, include fatigue, fever, and night sweats
- Complete remissions have been described following localized treatment

Etiology

- Unknown

Macroscopy

- Grossly lobulated and firm
- Cut surface tan, with focal areas of necrosis or hemorrhage



Interdigitating dendritic sarcoma, lymph node

Morphology

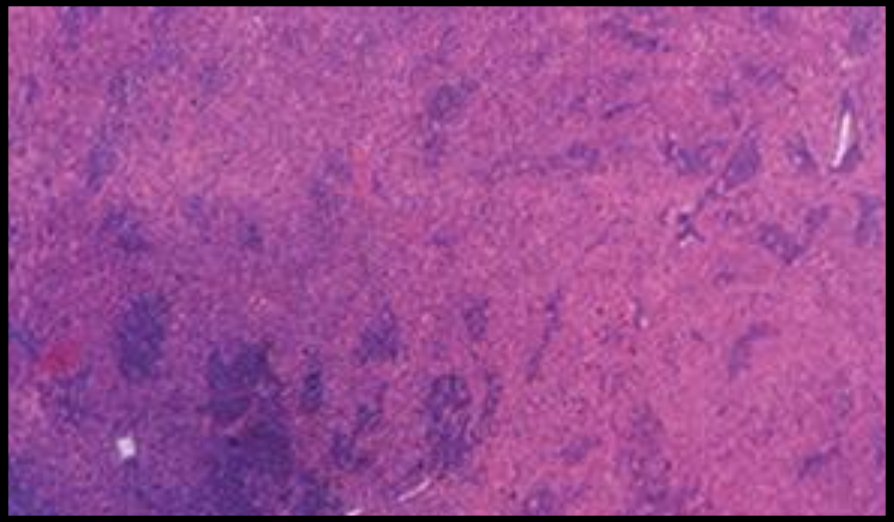
- In lymph nodes: paracortical distribution with residual follicles
- Fascicles, storiform pattern, whorls of spindle to ovoid cells
- Occasionally sheets of round cells
- Cytoplasm usually abundant, slightly eosinophilic; cell border often indistinct

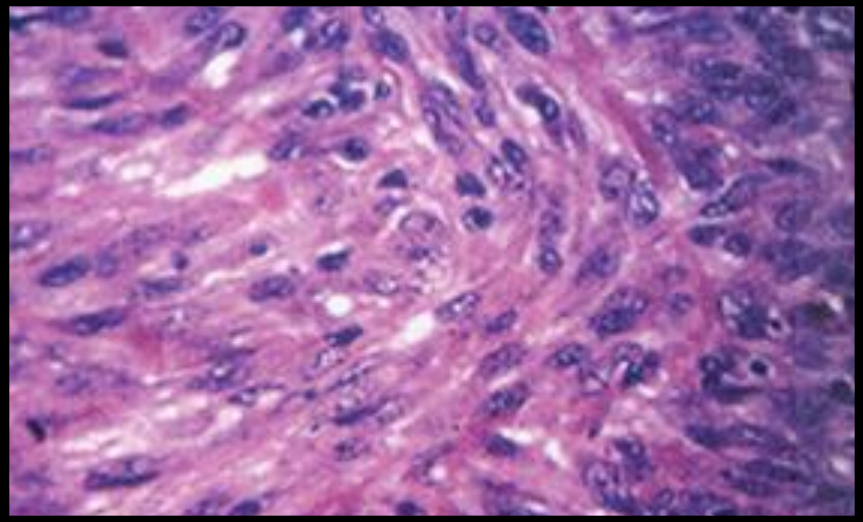
Morphology

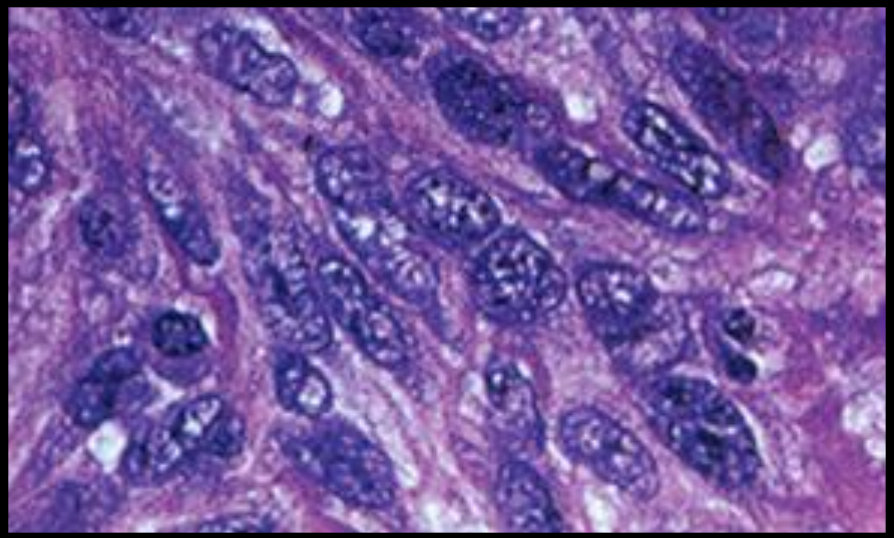
- Nuclei also spindled to ovoid
- Chromatin vesicular, with small to large distinct nucleoli
- Variable cytologic atypia
- Mitotic rate usually low, <5 per 10 HPF
- Necrosis usually absent
- Usually admixed lymphocytes, and less commonly, plasma cells

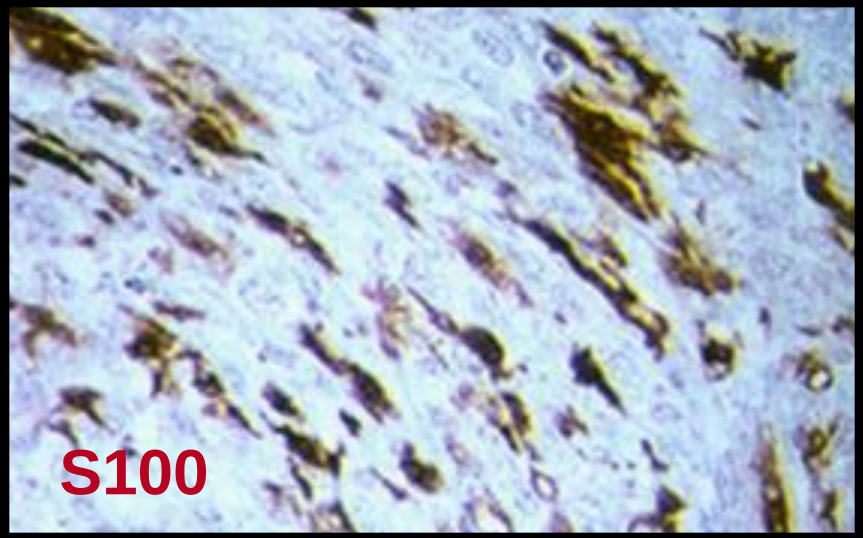
Morphology

- Histological appearance is sometimes indistinguishable from a follicular dendritic cell sarcoma/tumour and phenotyping may be necessary









Interdigitating dendritic sarcoma, lymph node

Ultrastructure

- The cells show complex interdigitating cell processes.
- Well formed desmosomes are not present.
- Birbeck granules are not seen.

Immunophenotype

- Neoplastic cells demonstrate the phenotype of non-neoplastic interdigitating dendritic cells
- S-100+
- Vimentin+
- CD1a negative
- Variable, weakly positive CD68, lysozyme and CD45

Immunophenotype

- Negative for FDC markers (CD21, CD35), MPO, CD34, specific B- and T-cell associated markers, CD30, EMA and cytokeratins
- Ki-67 index usually 10-20%
- Admixed lymphocytes almost always T-cell lineage; near absence of B cells

Genetic Features

- Ig heavy chain gene and the β, δ, and γ chain genes of the TCR are in germline configuration.

Postulated Cell of Origin

- The interdigitating dendritic cell of the paracortical region of the lymph node is the putative normal counterpart

Prognosis and Predictive Factors

- Variable clinical course ranging from benign localized disease to widespread lethal disease
- Visceral organs that are commonly affected include the bone marrow, spleen, skin, liver, kidney, and lung

Follicular Dendritic Cell Sarcoma/Tumor

Definition

- Neoplastic proliferation of spindle to ovoid cells showing morphologic and phenotypic features of follicular dendritic cells
- The term sarcoma/tumor is used because of the variable cytologic grade and indeterminate clinical behavior in many cases

Synonyms

- Reticulum cell sarcoma/tumor
- Dendritic reticulum cell sarcoma/tumor.

Epidemiology

- Rare neoplasm
- Most studies are single case reports or small series
- The largest series consisted of 13 and 17 cases
- Wide age range, with an adult predominance
- Equal sex distribution

Epidemiology

- Association with Castleman disease in 10-20% of the cases, usually hyaline vascular type
- Castleman disease may precede the tumor occur simultaneously
- May be an increased incidence in patients with treatment for longstanding schizophrenia

Sites of Involvement

- Lymph nodes in one-half to two-thirds
- Cervical nodes most often affected, as well as axillary, mediastinal, mesenteric and retroperitoneal lymph nodes
- Tonsils, spleen, oral cavity, GI tract, liver, soft tissue, skin and breast
- Common sites for metastasis include the lymph nodes, lung and liver

Clinical Features

- Most common presentation: slowly growing, painless mass
- Patients with abdominal disease may present with abdominal pain
- Systemic symptoms are unusual

Etiology

- None known in most cases
- A high proportion a FDC sarcoma/tumor showing features of inflammatory pseudotumor have been associated with EBV
- In these cases EBER has been found in all or virtually all the spindle cells. Southern blot studies demonstrate virus in monoclonal episomal form

Precursor Lesions

- In some cases of Castleman disease there is proliferation of FDCs outside the follicles forming clusters and small sheets
- The neoplasm therefore may evolve via intermediate steps of hyperplasia and dysplasia of follicular dendritic cells

Macroscopy

- Tumors range from 1 to 20 cm, with a median of 5 cm
- Cervical lymph nodes: smallest tumors
- Retroperitoneal lymph nodes: largest tumors
- Most are well-circumscribed masses, and solid tan-grey on cut section; larger tumors may show necrosis or hemorrhage

Morphology

- Spindle to ovoid cell proliferation.
- Fascicles, storiform patterns, whorls – at times similar to meningioma (360º) pattern
- Uncommonly, fluid-filled cystic spaces in perivascular location as in thymoma
- Amyloid changes

Morphology

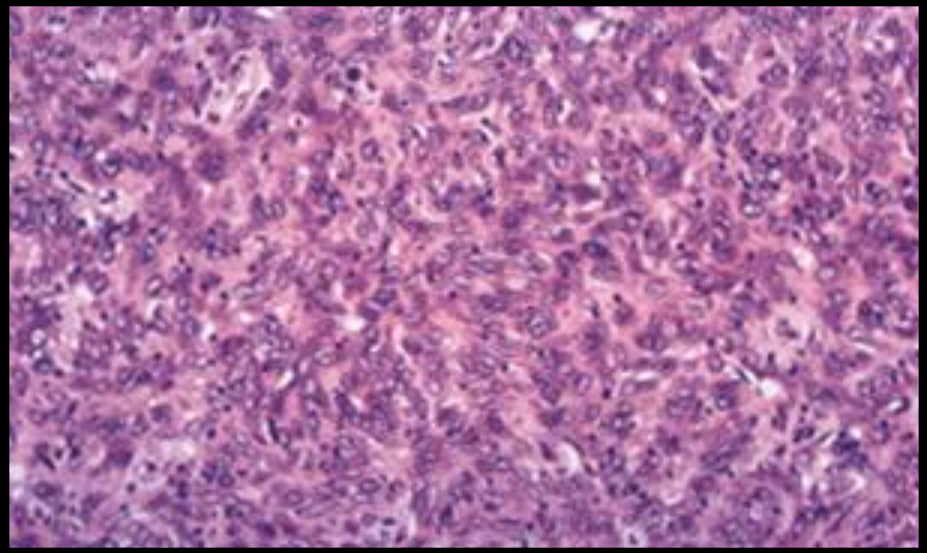
- Cells have a plump, slightly eosinophilic cytoplasm with indistinct cell borders
- Elongated nuclei
- Vesicular or granular finely dispersed chromatin; small but distinct nucleoli; delicate nuclear membrane
- Occasional multinucleated cells may be seen, sometimes resembling Warthin-Finkeldy giant cells

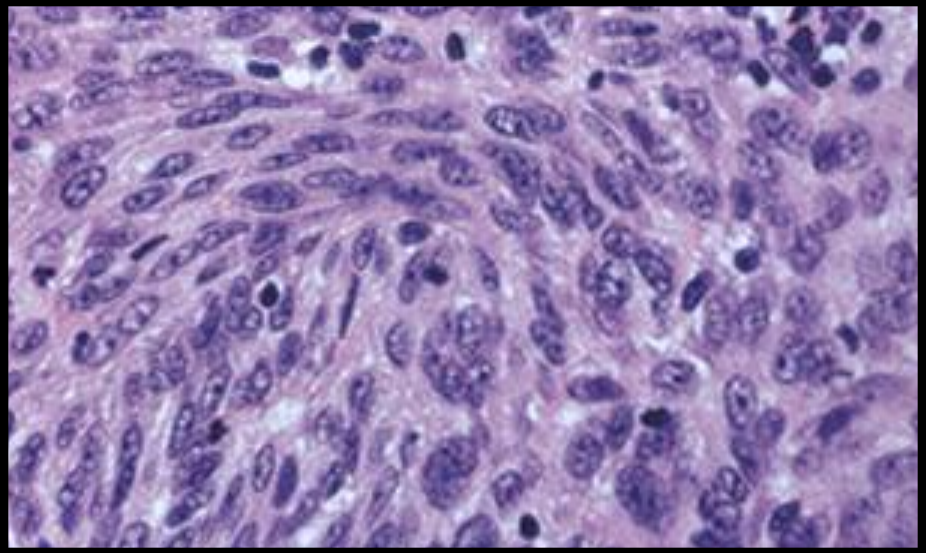
Morphology

- Pseudonuclear inclusions may be seen
- Cytologic features usually bland, cytologic atypia in a subset of cases
- Mitotic rate 0-10/10 HPF
- Cases with cytologic atypia may have much higher mitotic rate (>30/10 HPF) and atypical mitoses

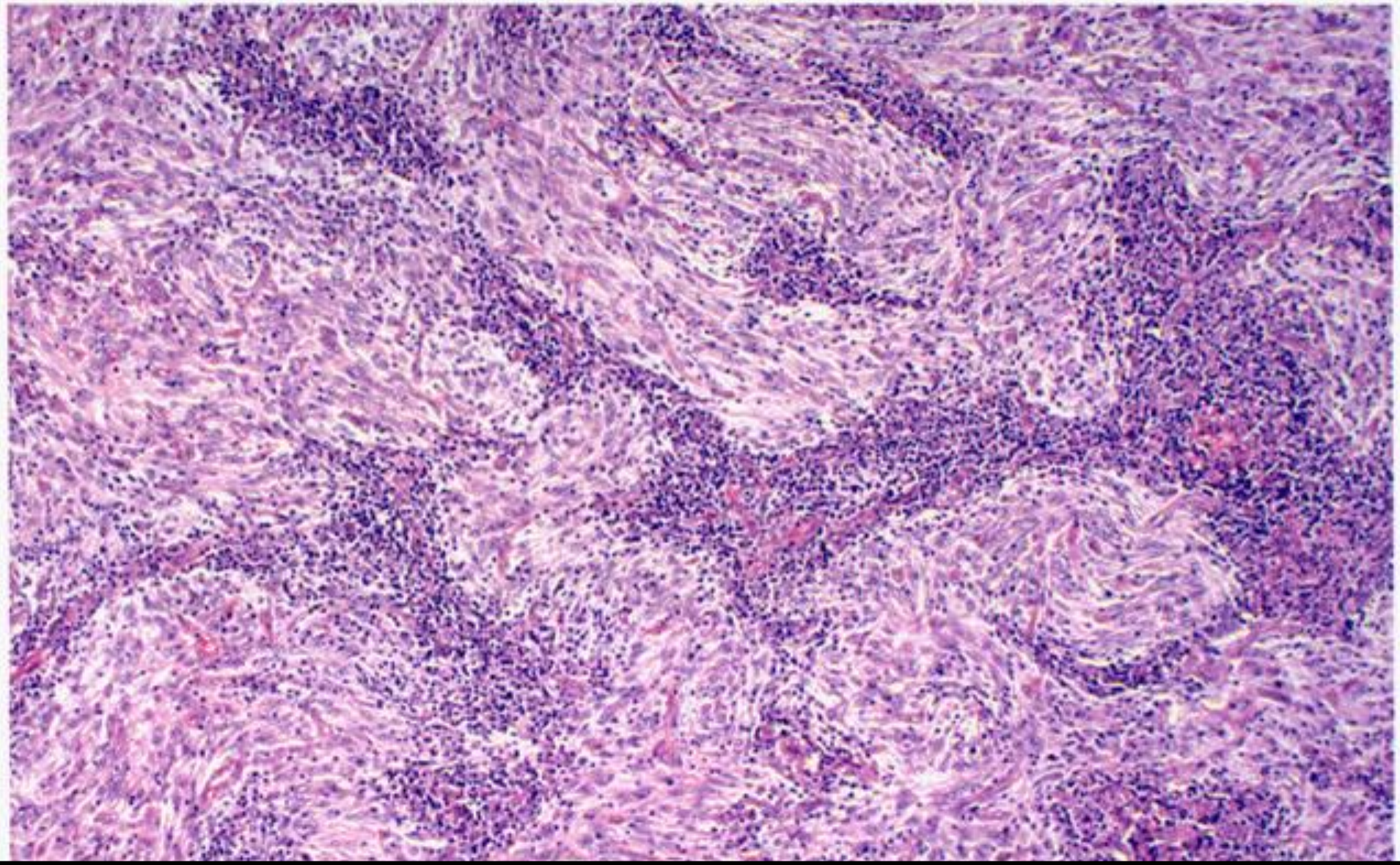
Morphology

- Uninvolved residual lymph node tissue is often present as residual germinal centers, or clusters of small lymphocytes or plasma cells, particularly in a perivascular location
- In lesion itself there may be scattered small lymphocytes; focal necrosis may also be present
- Rarely, epithelioid cells may be seen

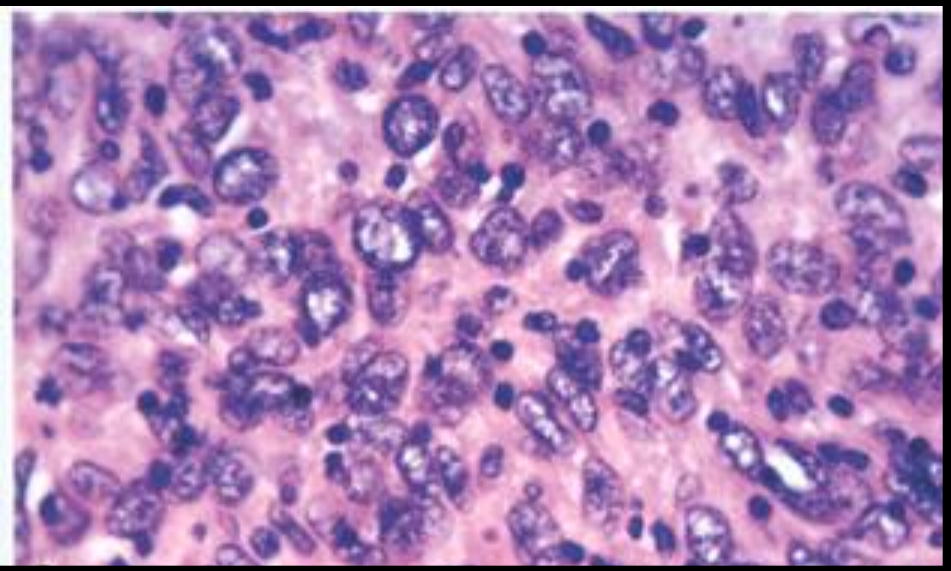


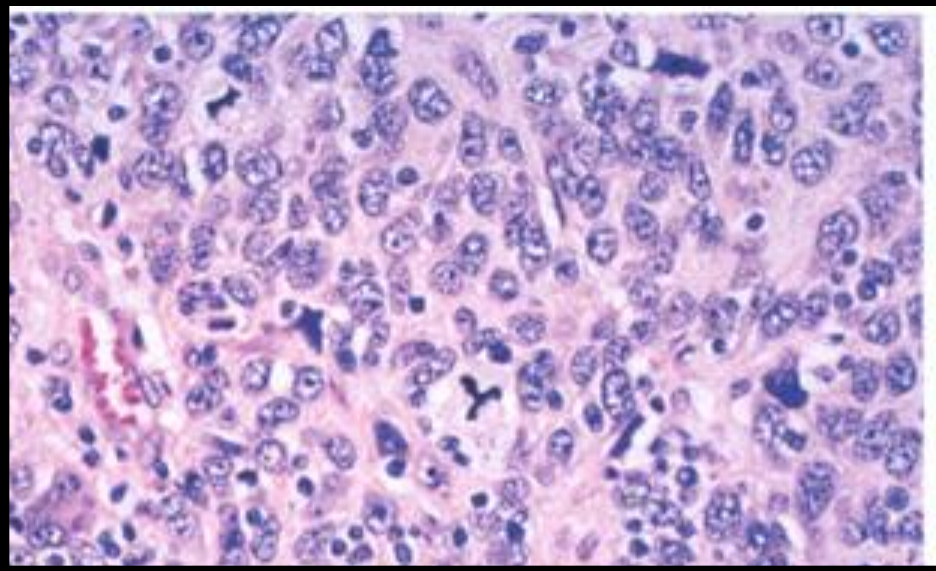


Follicular dendritic cell sarcoma



Follicular dendritic cell sarcoma

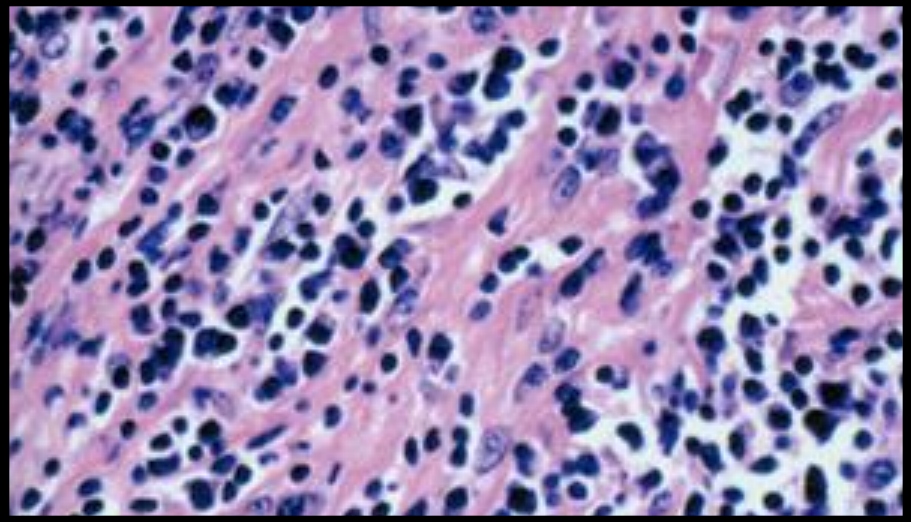


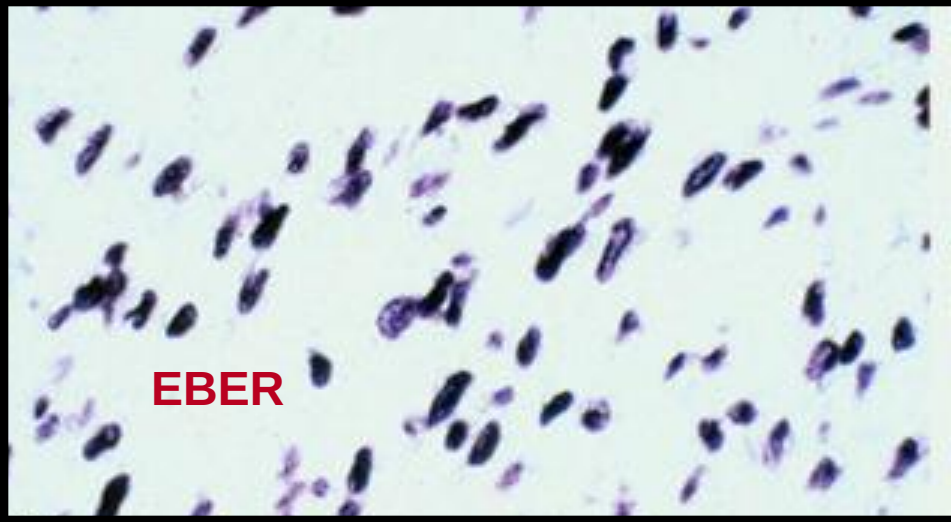


Follicular dendritic cell sarcoma

Morphology

- Putative cases of FDC sarcoma of liver and spleen often are morphologically more consistent with inflammatory pseudotumor.
- In these benign cases the spindle cells are not as cohesive, and are often obscured by a prominent lymphoplasmacytic reaction
- Cells have a vesicular chromatin pattern, with variable nuclear atypia and may contain prominent nucleoli

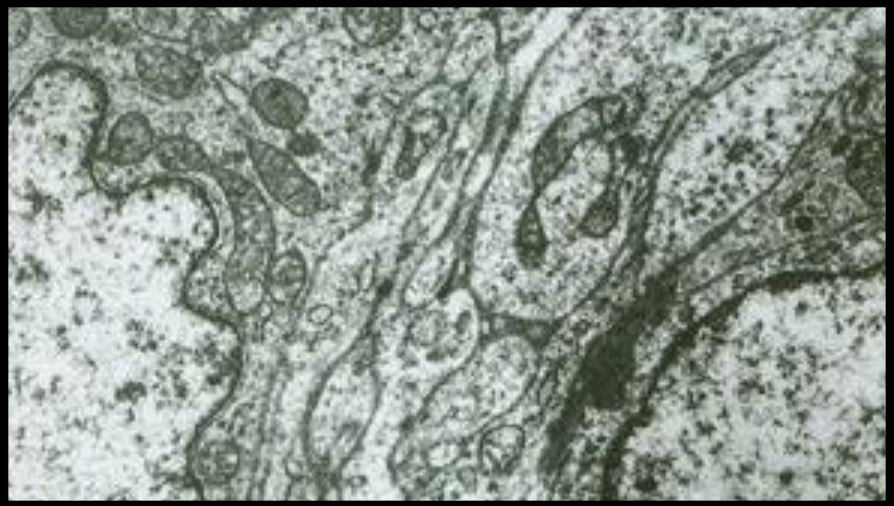




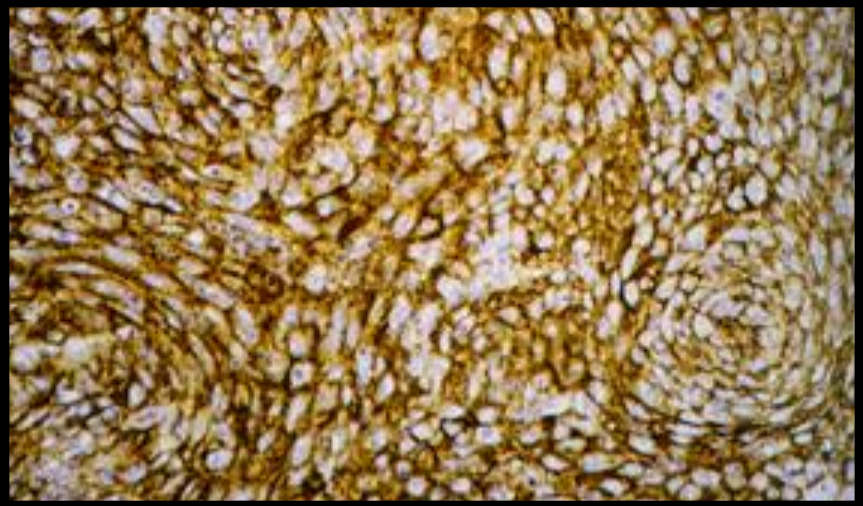
Follicular dendritic cell sarcoma, liver

Ultrastructure

- The cells have elongated nuclei, often with cytoplasmic invagination
- The cytoplasm often contain numerous polysomes.
- Distinctive feature: numerous long, slender cytoplasmic processes, often connected by scattered, mature desmosomes
- Birbeck granules and numerous lysosomes are not seen



EM



CD21

Follicular dendritic cell sarcoma

Immunophenotype

- Neoplastic cells demonstrate the phenotype of non-neoplastic follicular dendritic cells
- CD21+, CD35+, and CD23+
- Positive for desmoplakin, vimentin, fascin, HLA-DR, and often EMA
- Variable positivity for S-100 and CD68
- Occasional positivity for CD45 and CD20

Immunophenotype

- Negative for CD1a, lysozyme, MPO, CD34, CD3, CD79a, CD30, HMB-45, and cytokeratins
- Ki-67 positivity 1-25%, mean 13%
- Small lymphocytes sometimes B-cell phenotype; T cells predominate in other cases
- Muscle specific actin: currently associated more with fibroblastic reticular cell tumors with myofibroblastic features

Immunophenotype

- In putative cases of FDC sarcoma/tumor of liver and spleen with inflammatory pseudotumour, the FDC markers are often weak and focal

Genetic features

- Ig heavy chain gene and the β, δ, and γ chain genes of the TCR are in germline configuration

Postulated Cell of Origin

- The follicular dendritic cell of the follicle is the putative normal counterpart

Prognosis and Predictive Factors

- Typically indolent behavior, like a low grade tissue sarcoma
- Most patients treated with complete surgical excision, with or without adjuvant radio- or chemotherapy
- Local recurrences 40-50%
- Metastases 25%, often after local recurrence

Prognosis and Predictive Factors

- Poorer prognosis: intra-abdominal presentation, significant cytologic atypia, extensive coagulative necrosis, high prolferation index, tumor size >6 cm, and lack of adjuvant therapy
- 10-20% of patients die of disease

Dendritic Cell Sarcoma, Not Otherwise Specified

Definition

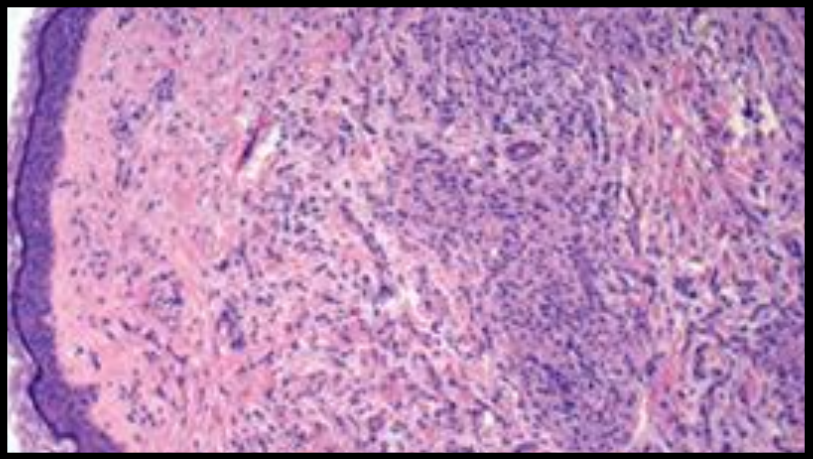
- Occasional dendritic cell neoplasms do not fall into well-defined categories, as defined in the previous sections

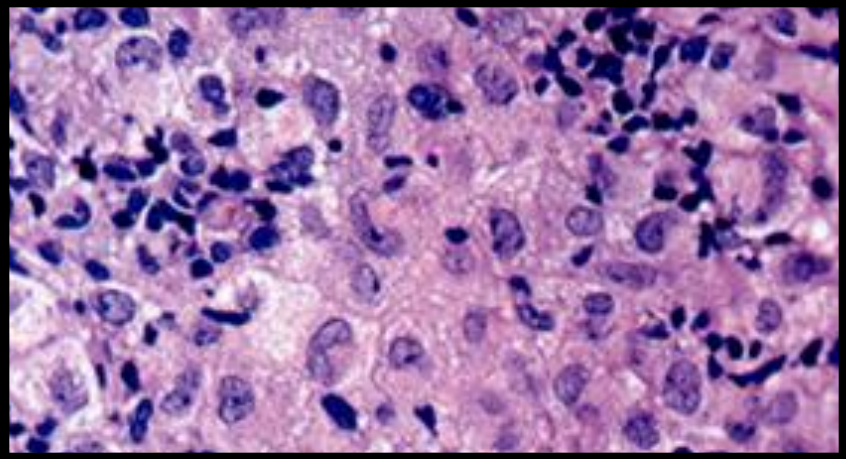
General Comments

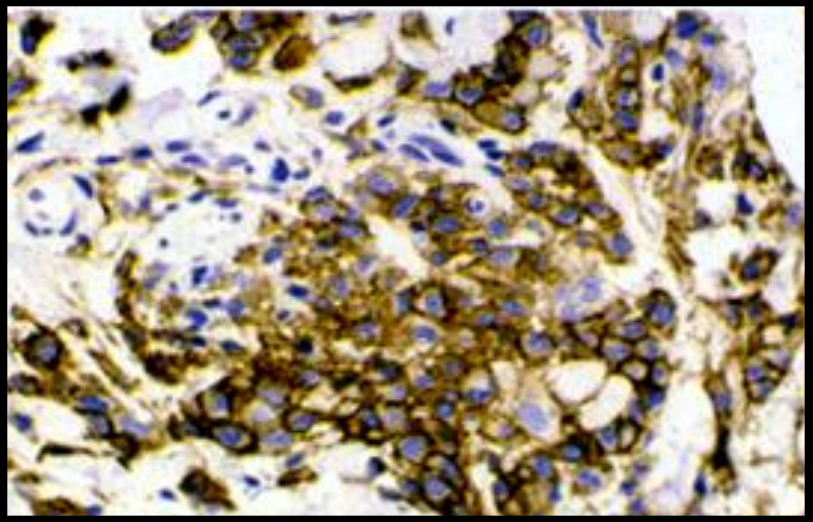
- Have been called indeterminate cell sarcoma/tumor
- Extremely rare cases reported
- Dx of exclusion, not well characterized morphologically and immunophenotypically

General Comments

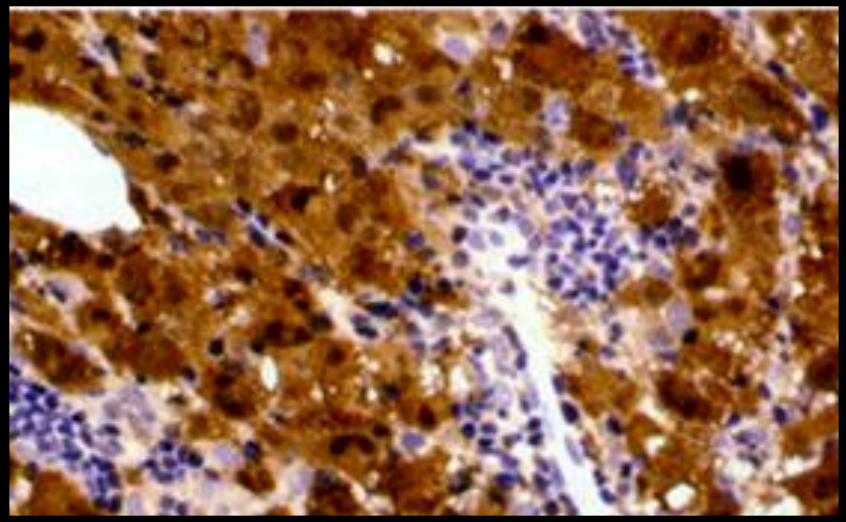
- Tumors positive for CD1a and S-100 protein but without Birbeck granules have been called indeterminate neoplasms said to derive from a cell in transition between a Langerhans cell and an interdigitating dendritic cell
- In a recent large series with multiple markers and EM no cases of this category were found







CD1a



S100

Dendritic cell sarcoma, NOS

Langerhans Cell Histiocytosis (LCH)

Definition

- Neoplastic proliferation of Langerhans cells
- CD1a+
- S-100+
- Birbeck granules on EM

Synonyms

- Histiocytosis X (Lichtenstein, 1953)
- Langerhans cell granulomatosis
- Eosinophilic granuloma
- Hand-Schüller-Christian disease
- Letterer-Siwe disease

Epidemiology

- About 5 per million
- Childhood
- Male:female ratio 3.7:1
- Northern Europe
- Possible association with ALL and lymphoma
- LCH of lung in adults (probably represents a separate entity, a reactive condition to tobacco and marijuana), innumerable bilateral nodules

Sites of Involvement

- Unifocal disease (solitary eosinophilic granuloma)
- Bones (skull, femur, pelvis, ribs)
- (Less often lymph nodes, skin, lung)

Sites of Involvement

- Multifocal, unisystem disease (Hand-Schüller-Christian disease)
- Several sites of involvement in one organ system, usually bone

Sites of Involvement

- Multifocal, multisystem disease (Letterer-Siwe disease)
- Multiple organ systems
- Bone, skin, liver, spleen, lymph nodes

Clinical Features

Unifocal Disease

- Older children, adults
- Lytic bone lesions (diaphysis) with erosion into soft tissues

Clinical Features

Multifocal, Unisystem Disease

- Young children
- Multiple destructive bone lesions, adjacent soft tissue masses
- Skull often involved (exophthalmos and diabetes insipidus)

Clinical Features

Multifocal, Multisystem Disease

- Infants
- Fever, skin manifestations, hepato-splenomegaly, lymphadenopathy, bone lesions, pancytopenia

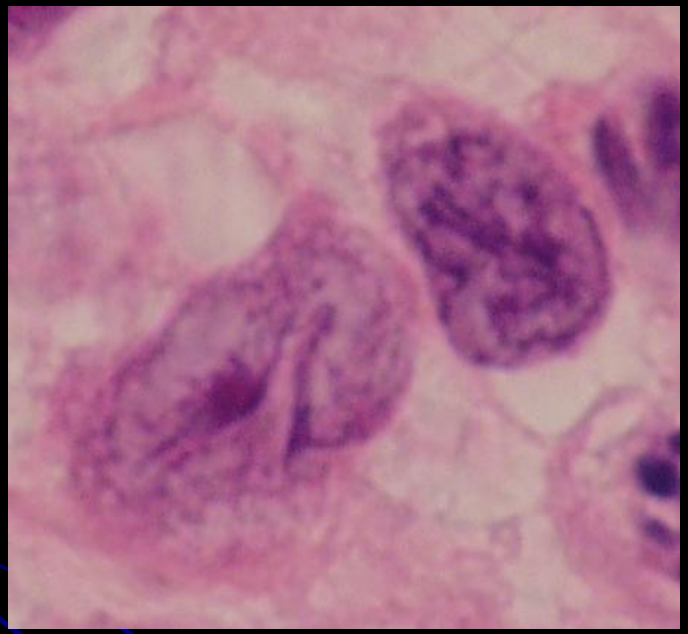
Etiology

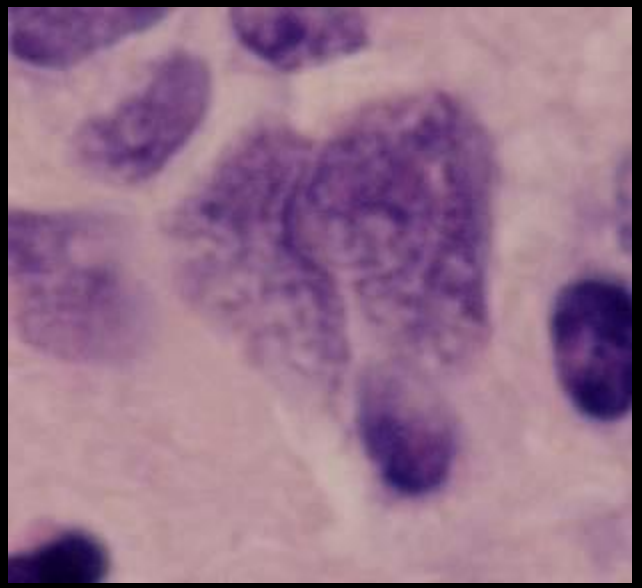
- Unknown
- No convincing evidence for viruses

Morphology

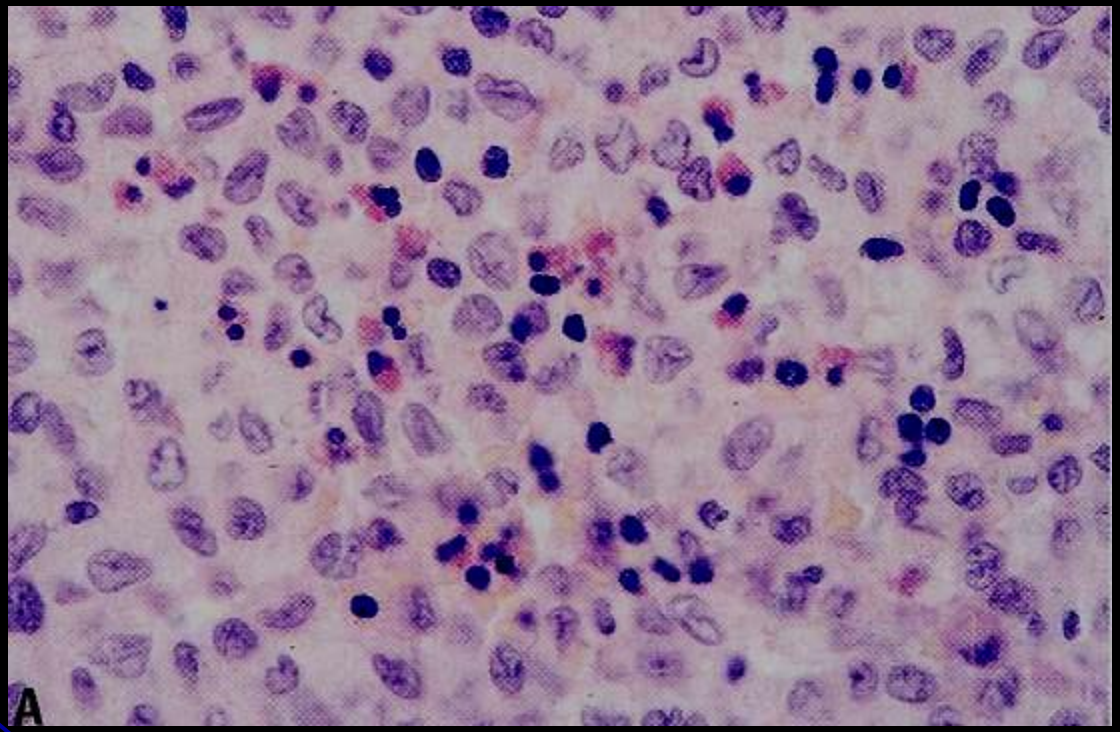
- Langerhans cells in appropriate *milieu*
- Longitudinal nuclear grooves (twisted, whelk-shaped), inconspicuous nucleoli
- Inflammatory background of histiocytes, eosinophils, neutrophils, and lymphocytes
- Necrotic foci, occasionally
- Sinuses in lymph nodes, followed by paracortex
- Red pulp in spleen

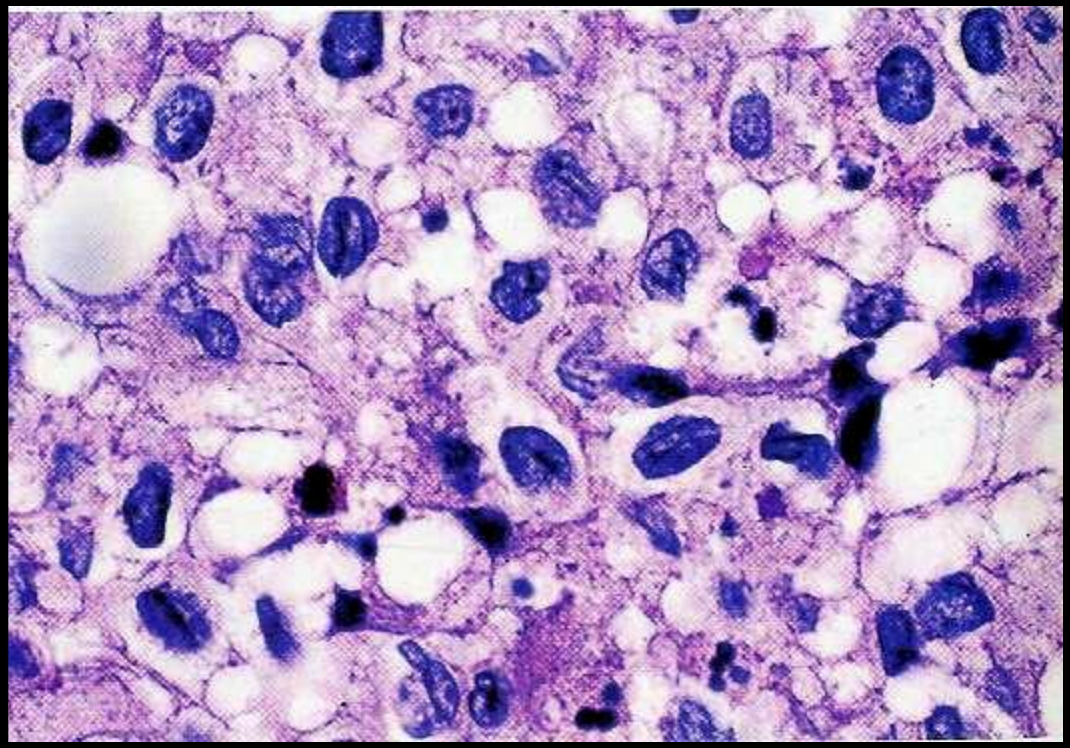
Langerhans Cell

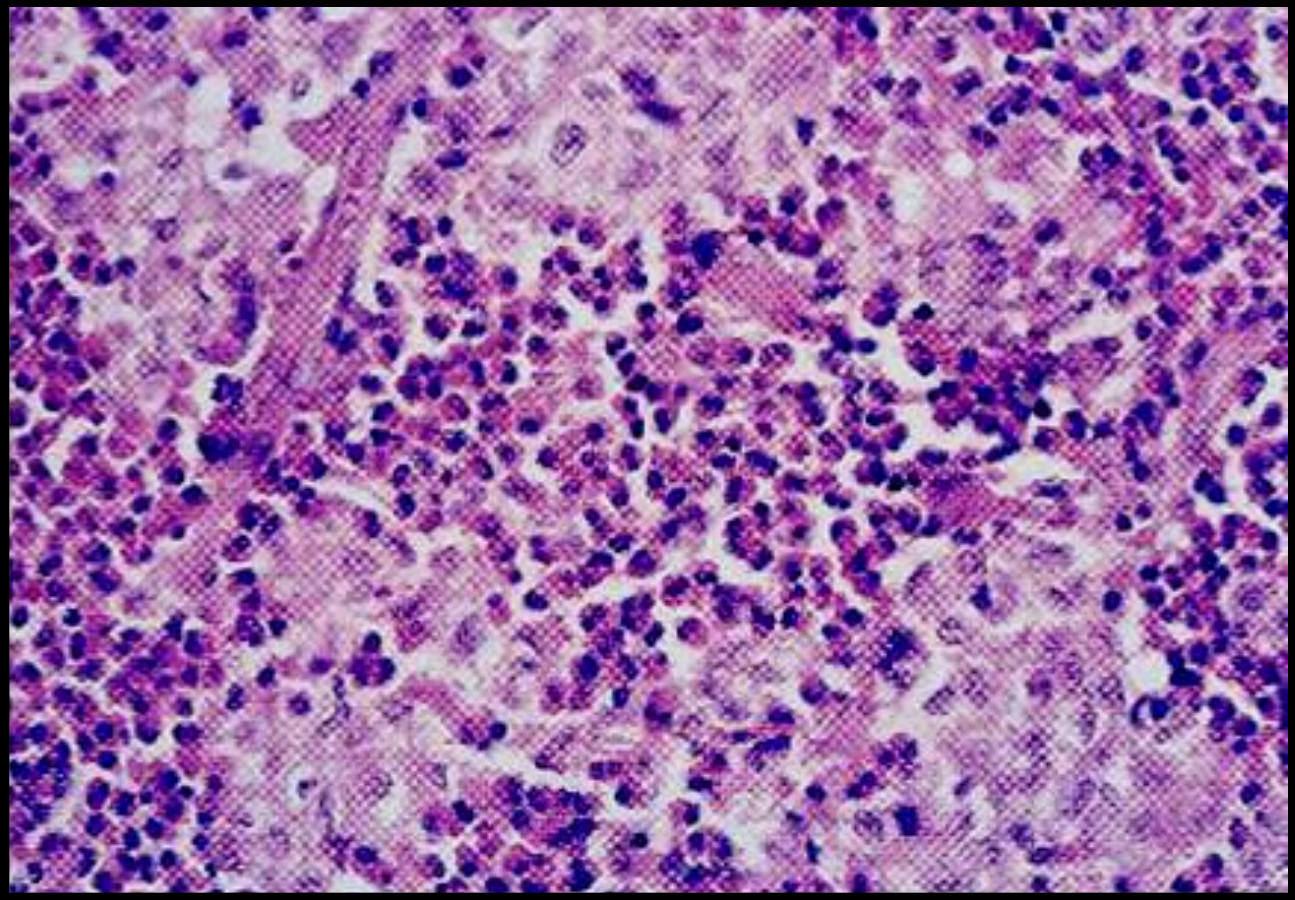


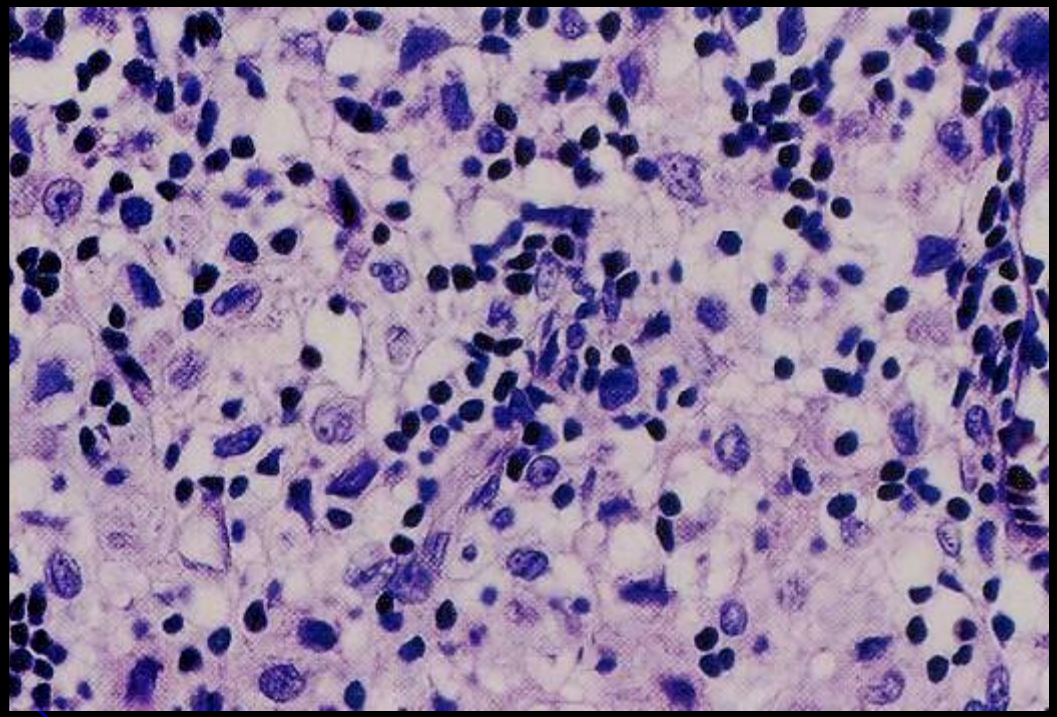


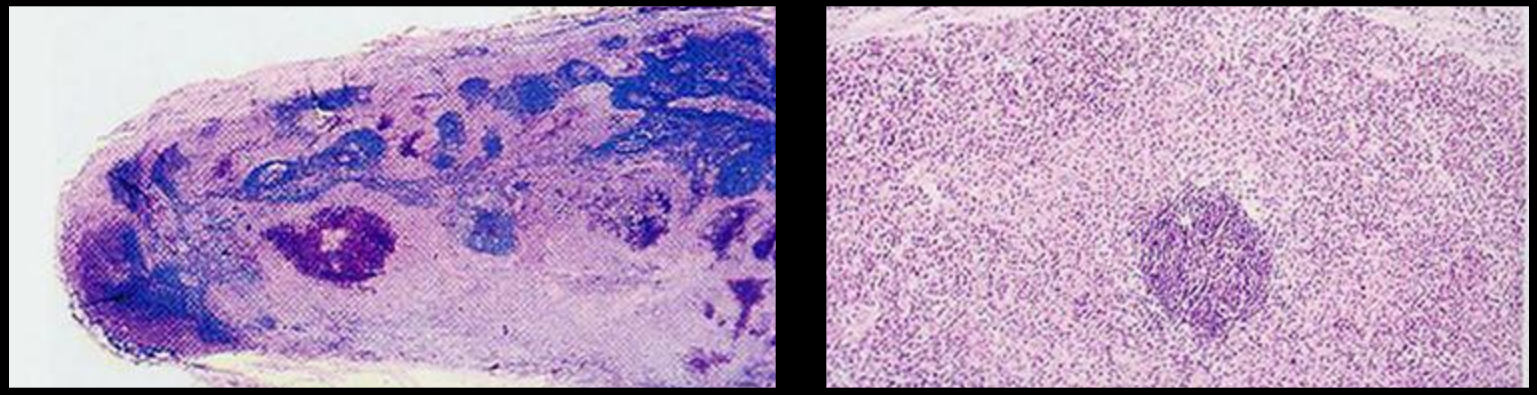
Langerhans Cell Histiocytosis











LCH, Lymph node

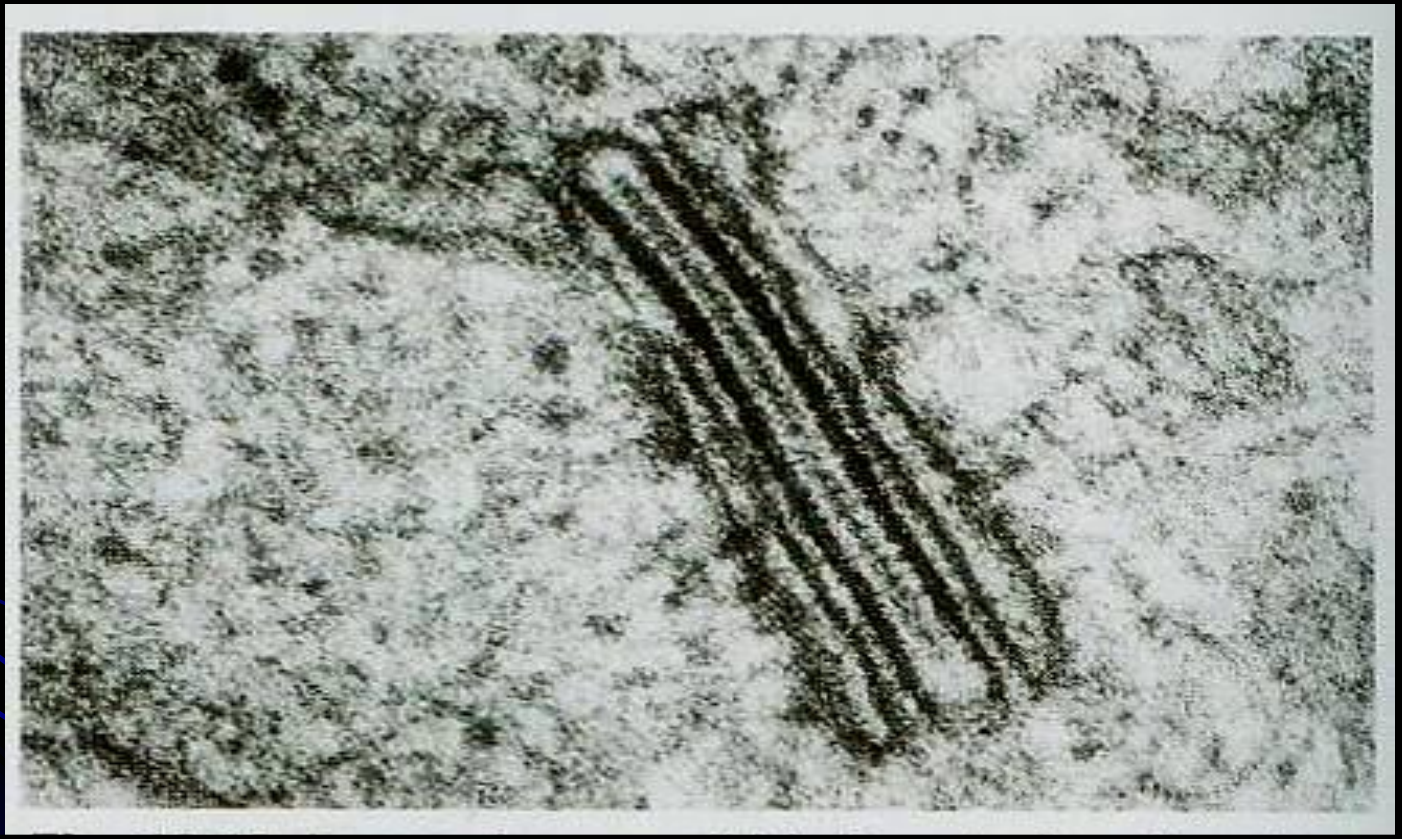
Grading

- Degree of atypia does not correlate with outcome

Ultrastructure

- Birbeck granule
  - Tennis racket shaped
  - 200-400 nm in length; 33 nm in width
  - Can be absent in 25%
- Lysosomes present
- Cell junctions absent

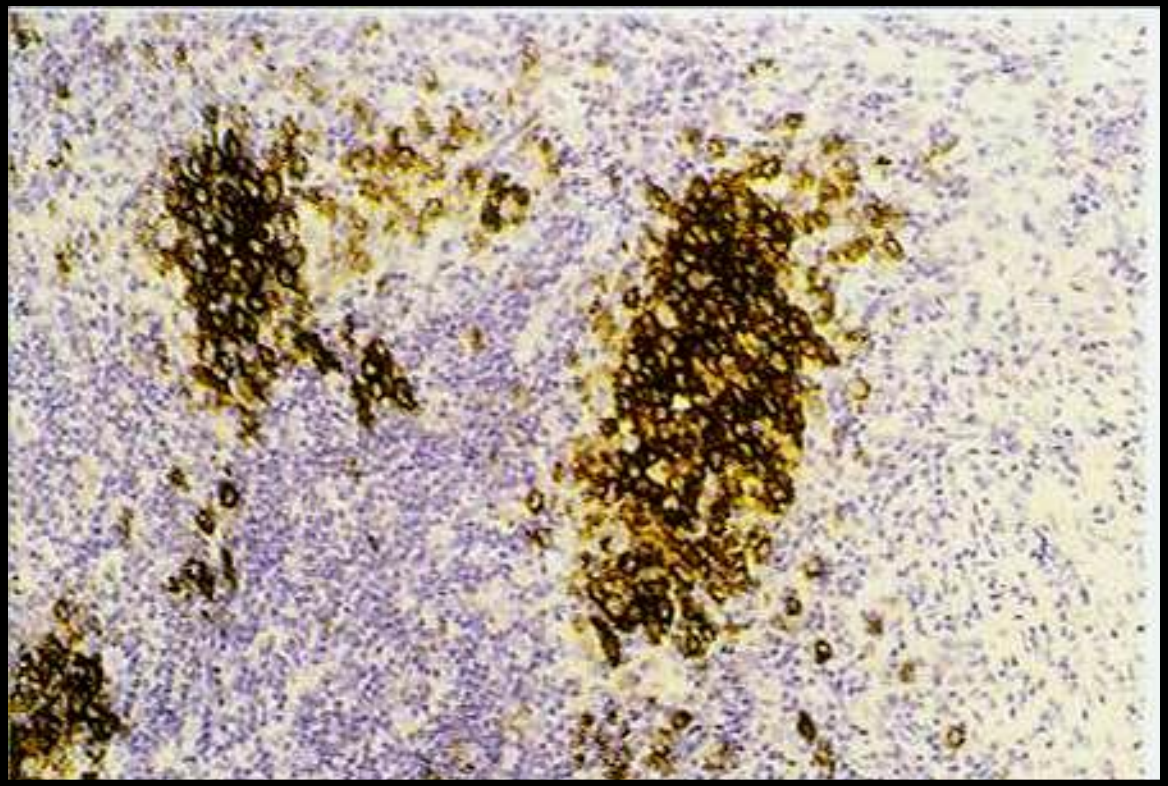
Birbeck Granule



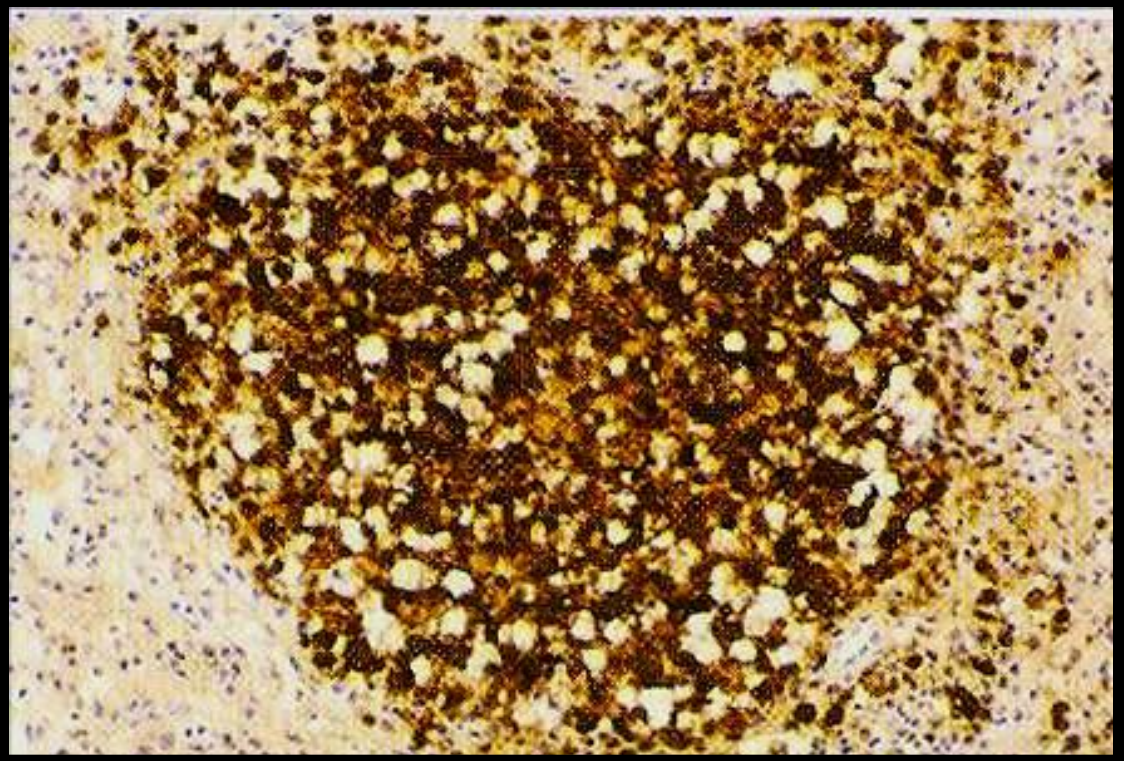
LCH: Birbeck granule, EM

Immunophenotype

- CD1a+ & S100+
- Vimentin+, CD4+
- Placental alkaline phosphatase+ (only neoplastic LCs – normal LCs are negative)
- Variable stain for CD45, CD68, lysozyme
- (CD34, CD30, MPO negative)
- Surface adhesion molecules different in neoplastic and non neoplastic LCs



LCH, CD1a



S-100

Enzyme Cytochemistry

- Positive for adenosine triphosphase, α-naphthyl acetate esterase, α-naphthyl butyrate esterase, and acid phosphatase
- Negative for TRAP, peroxidase, and chloroacetate esterase

Genetics

- Monoclonal
- IgH gene, and beta, gamma, and delta chain genes are germline

Prognosis

- Related to organs involved
- Absence of bone lesions with multiorgan involvement is poor prognostic sign
- Progression of unifocal to multisystem disease in about 10%
- Unifocal disease >95% survival
- 75% survival when 2 organs involved

Prognosis

- Prompt response to therapy better prognosis
- LCH of lung can regress after cessation of smoking

Langerhans Cell Sarcoma

Definition

- Neoplastic proliferation of Langerhans cells
- Overtly malignant cytologic features
- Can present *de novo* or progress from antecedent LCH

Epidemiology

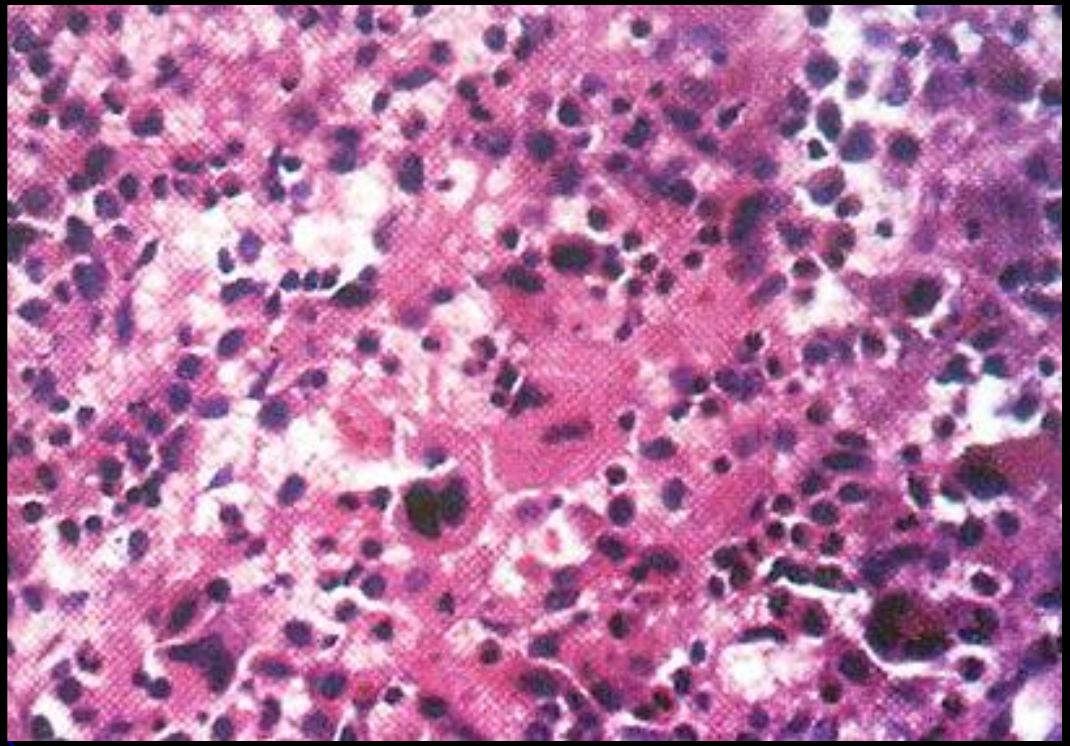
- Rare
- Adults and children (median age 41 years)
- Female predominance (in contrast to LCH)

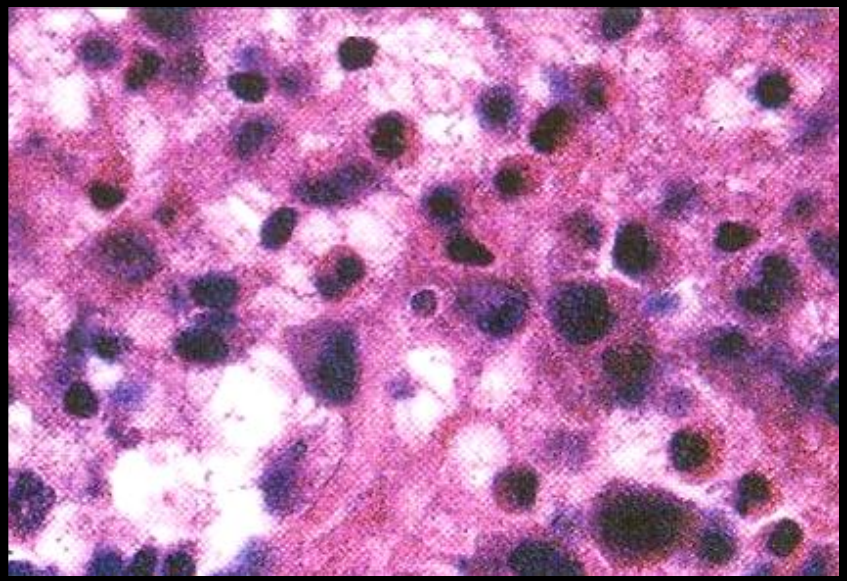
Sites of Involvement

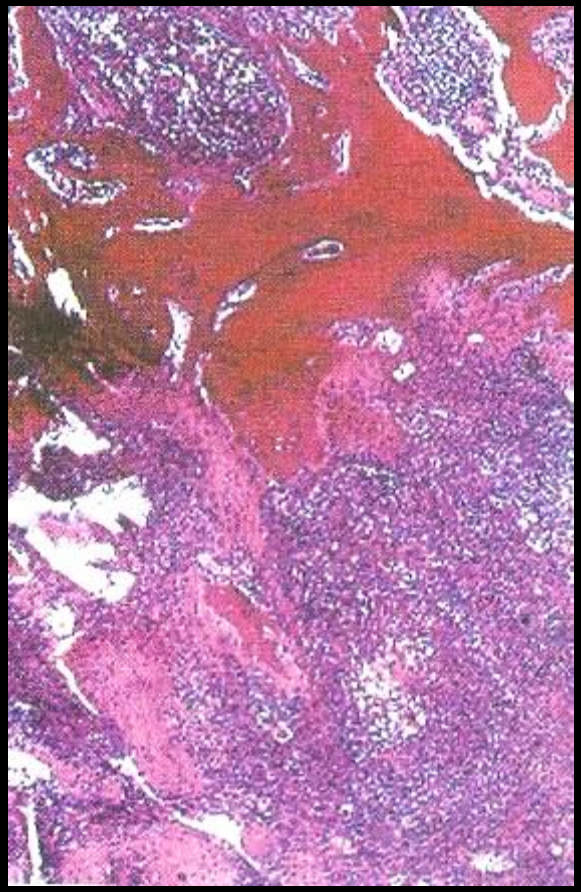
- Multiorgan involvement
- Lymph nodes, liver, spleen, lung and bone

Morphology

- Large malignant cells
- Nuclei with occasional grooves, prominent nucleoli
- Mitoses high (>50/10 HPF)
- Rare eosinophils (prominent inflammatory infiltrate absent)
- Sinusoidal pattern in lymph nodes





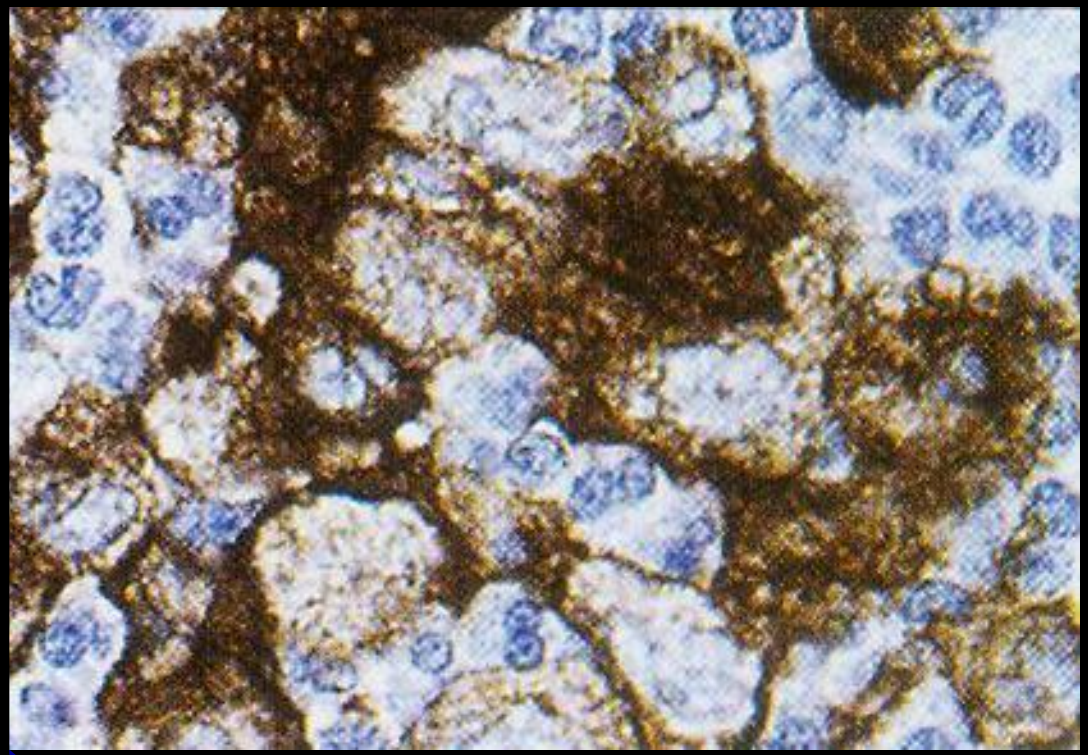


Ultrastructure

- Birbeck granules can be identified

Immunophenotype

- CD1a+ & S100+
- CD1a may be focal
- Some expression of CD68, CD45 & lysozyme
- Ki-67 ranges from 10% to 60%



CD1a

Prognosis

- Aggressive
- Overall survival about 50%