Histiocytic Disorder in Bone Marrow

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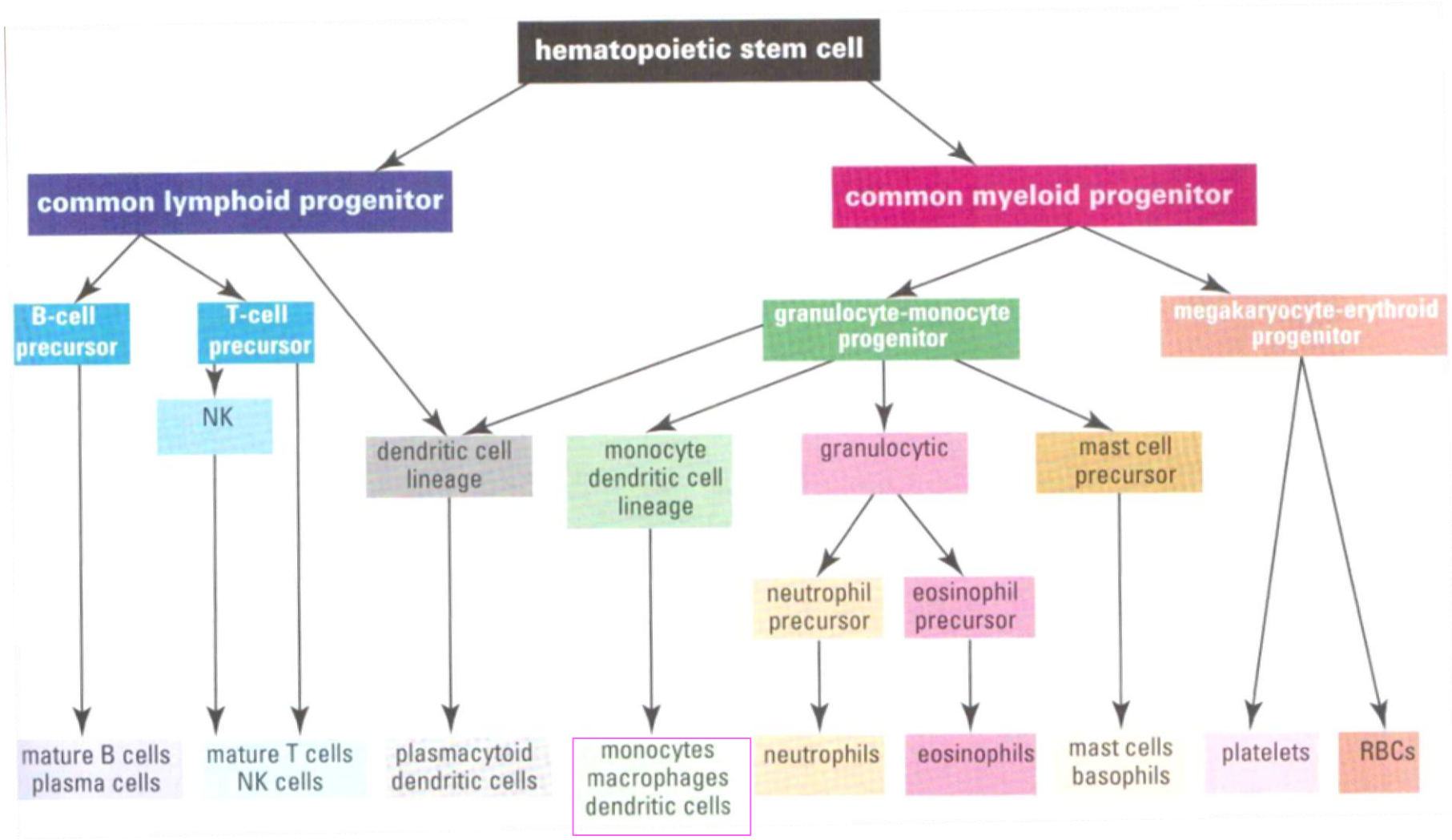
Disorders In this chapter

Focus on histiocytic/macrophage and dendritic cell infiltration

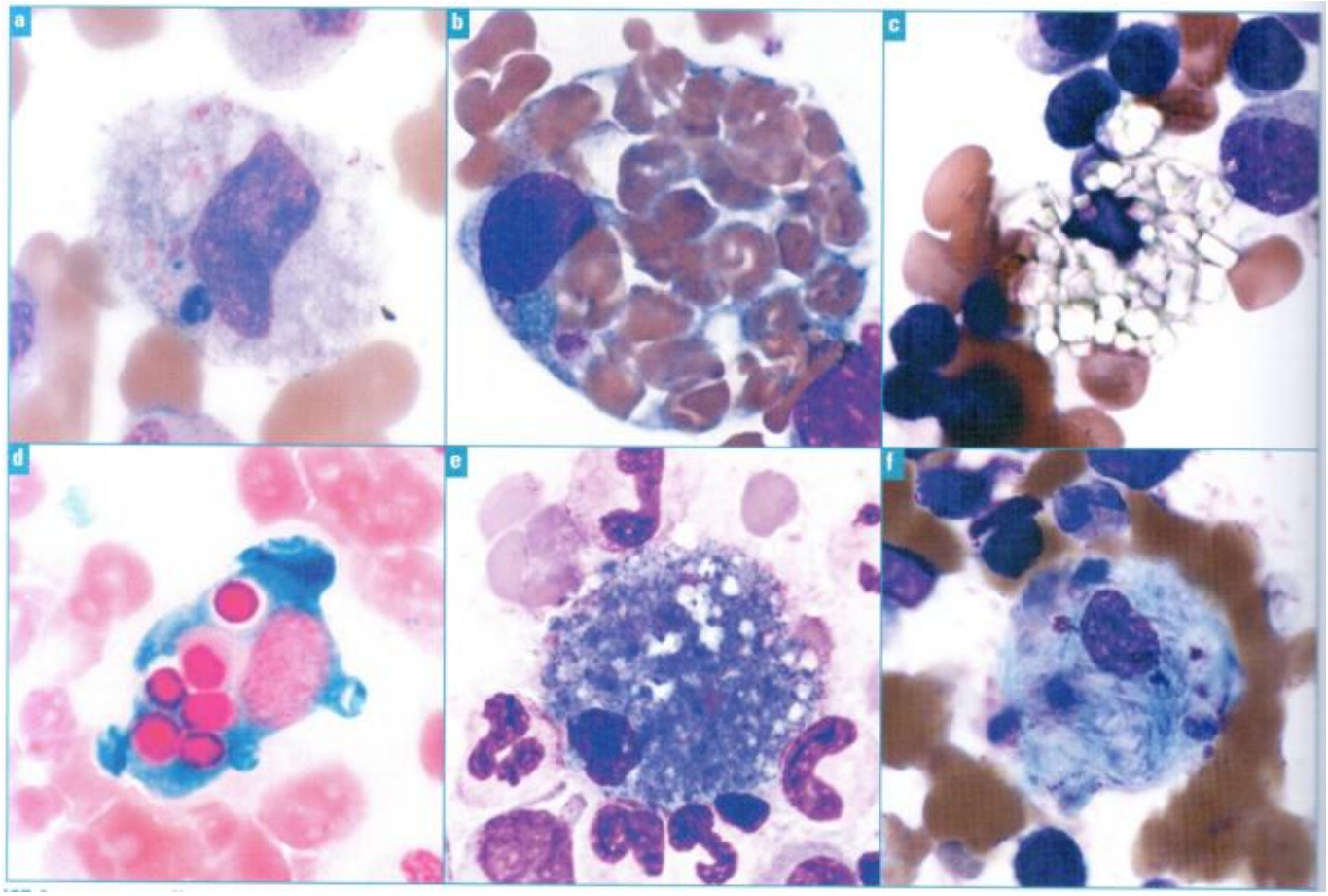
1. Bone marrow granuloma
2. Diffuse histiocytoses
   - Familial hemophagocytic lymphohistiocytosis
   - Secondary hemophagocytic lymphohistiocytosis
   - Lysosomal storage diseases
   - Miscellaneous reactive histiocytic disorders
3. Clonal diffuse histiocytic disorders: rare
   - Langerhans cell histiocytosis
   - Malignant histiocytosis/disseminated histiocytic sarcoma
   - Rare systemic histiocytic disorders of uncertain clonality

❖ Covered in other chapters: monocyte-related neoplasm, blastic plasmacytoid dendritic cell neoplasm

Monocyte, macroghages, dendritic cells, plasmacytoid dendritic cell



Spectrum of histiocytes



A. Normal histiocyte

B. Hemophagocytic histiocyte

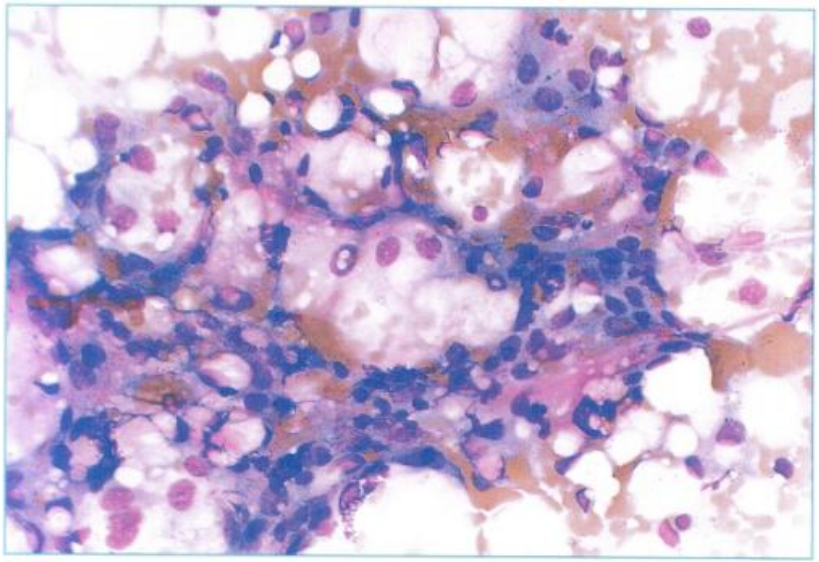
C. Histiocyte containing crystals from a patient with cystinosis

D. Iron-laden histiocyte

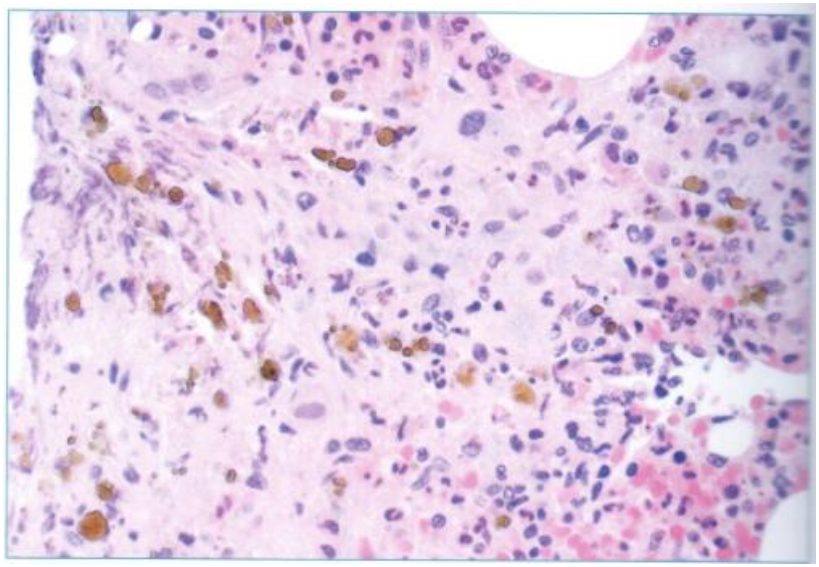
E. Sea-blue histiocyte

F. Gaucher type histiocyte

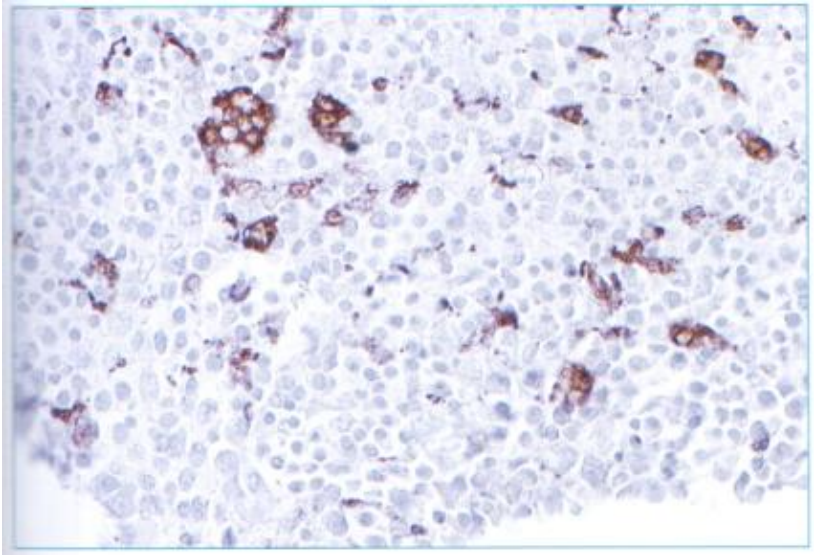
Histiocytes on bone marrow aspirate smear and biopsy section



Normal macrophages concentrated within BM particles



Fibrosis, hemosiderin-laden histiocytes



Immunoperoxidase stain for CD68
Diffusely distributed macrophages

Histiocytic Disorders in Bone Marrow

Pattern	Morphology	Comments
Localized	Granulomatous infiltrates	Many types of granulomas Caseating, epithelioid, or lipogranulomas Many specific and nonspecific disease associations
Diffuse	Increased histiocytes throughout bone marrow parenchyma; variable morphologic and cytologic features	Non-neoplastic diffuse histiocytoses include: increased cell turnover systemic infections/collagen vascular diseases following therapy hemophagocytic syndromes lysosomal storage diseases secondary histiocytoses in various Hodgkin and non-Hodgkin lymphomas and other neoplasms distinctive clinical syndromes such as Kikuchi disease and Rosai-Dorfman disease
		Clonal diffuse histiocytic disorders include: Langerhans cell histiocytosis plasmacytoid dendritic cell neoplasms various myelomonocytic leukemias rare histiocytic/dendritic sarcomas

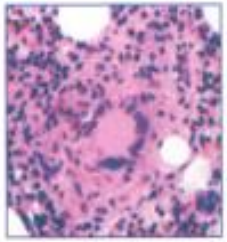
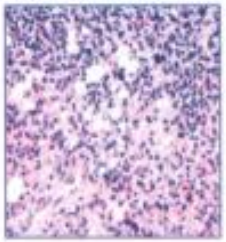
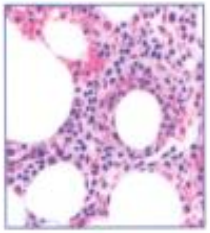
References: [Chand 2003, Florena 2002, Huang 2006, Jiang 2006, Onciu 2004, Sumiyoshi 1992, Vellodi 2005, Weitzman 2005]

Granuloma

- Lipogranulomas

- Epithelioid granuloma
  - Caseating granuloma
  - Ring granuloma
  - Foreign body granuloma

Morphologic Types of Bone Marrow Granulomas

Caseating granuloma		Epithelioid granuloma with central eosinophilic, caseating necrosis May contain multinucleated histiocytes Abundant histiocytes, variable numbers of eosinophils, neutrophils, lymphocytes
Epithelioid granuloma		Discrete collection of histiocytes May contain multinucleated giant cells Abundant histiocytes, variable numbers of eosinophils, neutrophils, lymphocytes
Lipogranuloma		Foamy histiocytes predominate within granuloma May be seen in conjunction with lymphoid aggregates Lipid vacuoles vary greatly in size; both intracellular (within histiocytes) and extracellular lipid present Become more epithelioid as lipid is resolved
Ring granuloma		Epithelioid granuloma with collar of histiocytes surrounding central empty space Variable numbers of other inflammatory cells Central region occasionally will contain lipid, but typically empty
Foreign body granuloma		Epithelioid granuloma with multinucleated foreign body-type giant cells Polarizable material may be present (eg, keratin in sternal bone marrow from previous heart surgery) Crystal deposition disorders may also elicit a foreign body giant cell reaction*

General Features of Bone Marrow Granulomas

Type of Granuloma	Features/Comments
Lipogranuloma	Common finding in up to 10% of BM biopsy sections Etiology unknown, often associated with lymphoid aggregates More common in elderly patients Generally considered insignificant
Disorders with epithelioid granulomas*	
Tuberculosis†	Tend to be large with central caseation, frequent giant cells Organisms rare
Histoplasmosis†	Variably size; ~50% show caseation and/or giant cells Organisms rare to moderately abundant
Mycobacterium avium-complex†	Variably size, generally noncaseating Organisms usually abundant
Viral	Small, poorly delineated clusters of histiocytes lacking either caseation or giant cells Rare ring-shaped granulomas described Dominant finding is abundance of lymphocytes, plasma cells, immunoblasts
Other infections	In patients with brucellosis, rickettsial infections, and other fungal infections "Donut ring" granuloma with central lipid core in Q fever, brucellosis, typhoid fever, and rare viral infections Distinctive finely vacuolated (Virchow cells) characterize BM granuloma in leprosy

General Features of Bone Marrow Granulomas

Disorders with epithelioid granulomas*

Non-Hodgkin lymphoma	Epithelioid granulomas may be admixed with lymphomatous infiltrates
Hodgkin lymphoma	2% from staging evaluations contain small epithelioid granulomas Epithelioid granulomas can also be admixed with overt infiltrates of classical Hodgkin lymphoma
Other neoplasms	Epithelioid granulomas may be admixed with leukemic and carcinomatous infiltrates
Post-therapy/other conditions	Linked to many medications and recombinant therapies Immune disorders (rare ring forms) Rare granulomas after bone marrow transplantation or after either chemotherapy or bacille Calmette-Guérin therapy

*Epithelioid granulomas are occasionally found in patients with drug reactions, sarcoidosis, collagen vascular disease, and solid tumors (see Chapter 34 and Volume 1, Chapter 9)
†In immunosuppressed patients, diffuse increase in histiocytes may be present; organisms are generally present (see Chapter 33)

References: [Brunning 1994, Eid 1996, Farhi 1985, Krober 2004, Mukhopadhyay 2004, Swerdlow 1983]

Diffuse Histiocytoses: 1. Hemophagocytic lymphohistiocytosis

- Clinical and laboratory criteria

Diagnostic Criteria (5 of 8 Required)
1. Fever
2. Splenomegaly
3. Bicytopenia
4. Hypertriglyceridemia *or* hypofibrinogenemia
5. Hemophagocytosis
6. Low/absent NK activity
7. Hyperferritinemia
8. High soluble interleukin-2-receptor levels
*Stringent criteria ***not*** required if positive family history ***or*** positive molecular findings of HLH

- Primary vs. Secondary
- Only increased histiocytes with prominent hemophagocytosis on BM

  -> should be reported as evidence of hemophagocytic Syndrome

  -> rare histiocytes showing hemophagocytosis are common in BM

Hemophagocytic Lymphohistiocytosis

Types of Hemophagocytic Lymphohistiocytosis

Primary (Familial Hemophagocytic Lymphohistiocytosis and Other Constitutional Disorders*)

Familial, autosomal recessive; genetically heterogeneous

Perforin gene mutations in 40% of cases

Other constitutional immunodeficiency disorders linked to hemophagocytic syndromes:

- Chédiak-Higashi syndrome, Griscelli syndrome
- X-linked lymphoproliferative syndrome, Wiskcott-Aldrich syndrome

Secondary to Infection (Infection-Associated Hemophagocytic syndrome)

In patients with underlying immunodeficiency often secondary to immunosuppressive therapy

Overwhelmingly caused by viral infections (EBV by far most common)

but occasionally triggered by many other types of infections

Secondary to Malignancy (Maligancy-Associated Hematophagocytic Syndrome)

Overlap with infection-associated subtype since immunosuppressive therapy

- may render patient susceptible to systemic viral infection

Also seen in patients with NK- or T-cell neoplasms in which cytokines released from neoplastic cells

- initiate hemophagocytosis; rarely reported in B-cell neoplasms

Rarely linked to therapies for neoplasms (eg, G-CSF)

Secondary to Systemic Autoimmune Disorders

Collagen vascular disorders (without underlying infection)

Hemophagocytic Lymphohistiocytosis

Mechanism and Finding of Hemophagocytic Lymphohistiocytosis

Mechanisms Causing Systemic Hemophagocytosis

Common mechanism for all types :

- T- or NK-cell dysfunction leads to macrophage activation
- Increased levels of many cytokines released by macrophages or T cells
  - initiate systemic hemophagocytosis (hyperinflammatory syndrome/macrophage activation syndrome)

Clinical/Laboratory Features

Fever, severe constitutional symptoms

Hepatosplenomegaly, lymphadenopathy, Abnormal liver function tests, high triglycerides

Coagulopathy, common; frequent DIC picture

Variable skin rash, Neurologic symptoms(more common in familial cases)

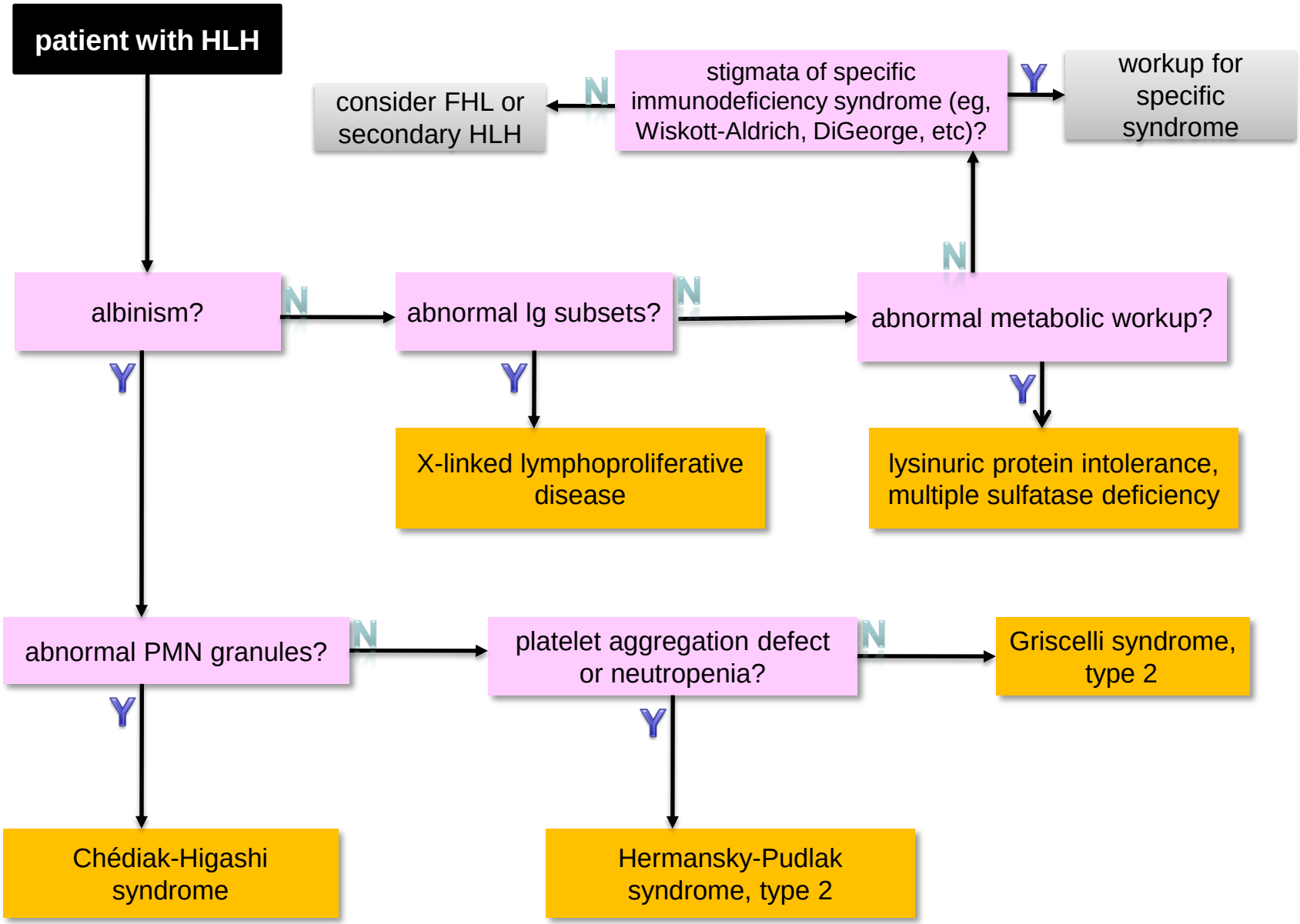
Blood/Bone Marrow Findings

Blood: bi-or trilineage cytopenias

Bone marrow: variable bone marrow cellularity

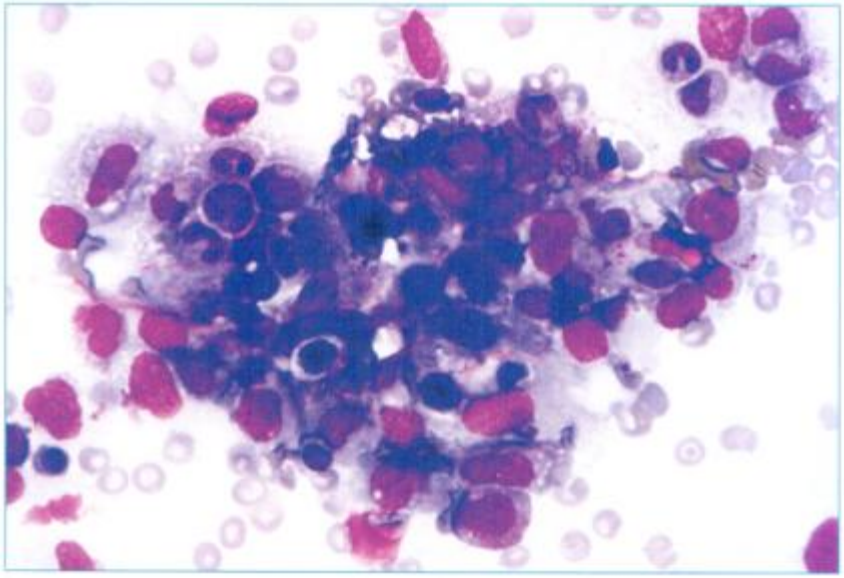
- granulocytic and erythroid lineages often decreased
- megakaryocytic hyperplasia
- histiocytic hyperplasia with prominent hemophagocytosis of mature/immature hematopoietic cells
- variable numbers of plasma cells and immunoblasts, sometimes pronounced
- mild reticulin fibrosis, variable
- mild dyserythropoiesis, occasional granulomas, occasional necrosis

Algorithm for identification of main genetic syndromes associated with HLH

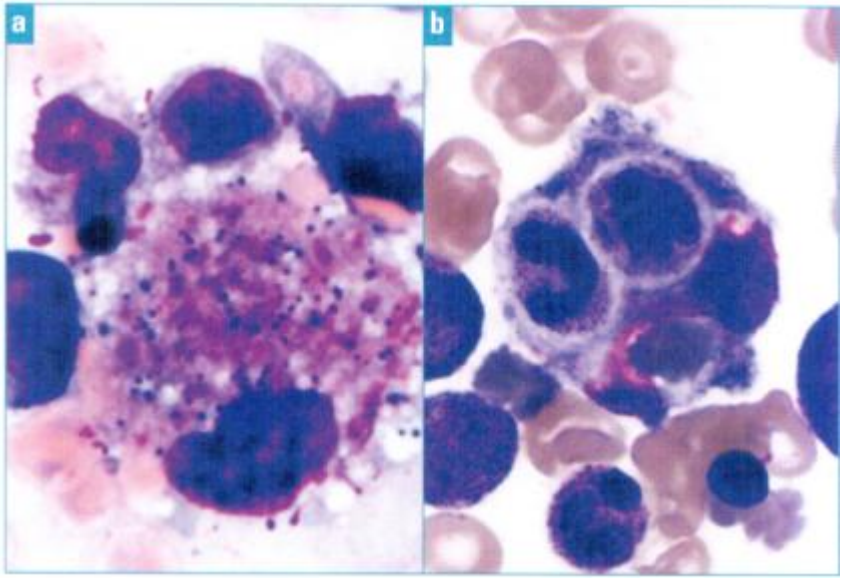


Familial Hemophagocytic Lymphohistiocytosis

- Differentiation hemophagocytic histiocytes from clonal histiocytes in clonal histiocytic disorder
  - Morphologic feature
    - Histiocytes in hemophagocytic syndrome: mature, lack atypia
    - Clonal histiocytes: nuclear atypia, minimal phagocytosis

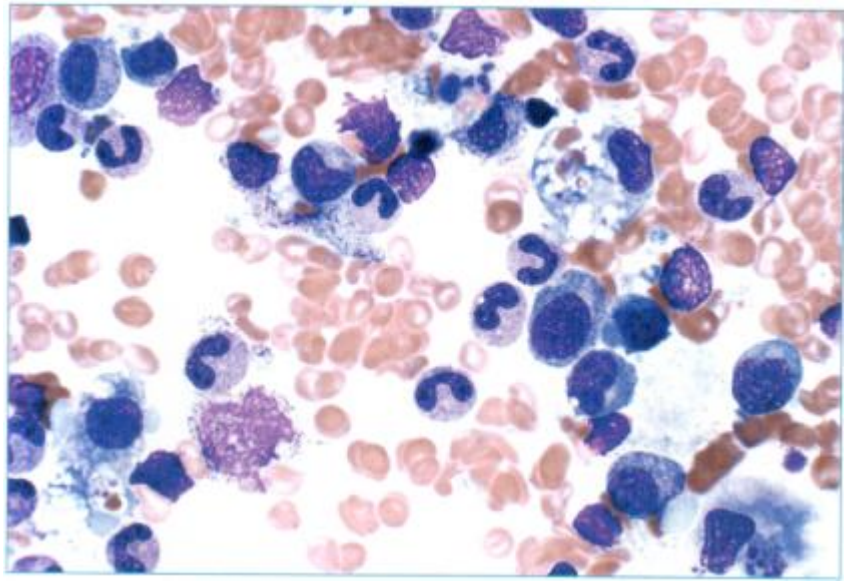


Marked increase in histiocytes concentrated in and near BM particles

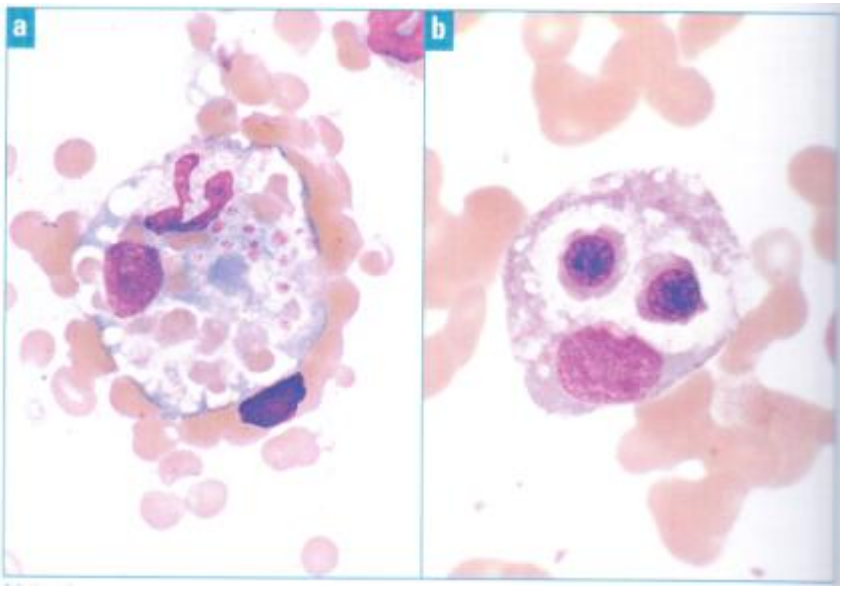


A. Histiocyte with prominent dark granules and relatively nonphagocytic
B. Histiocytes show marked hemophagocytosis

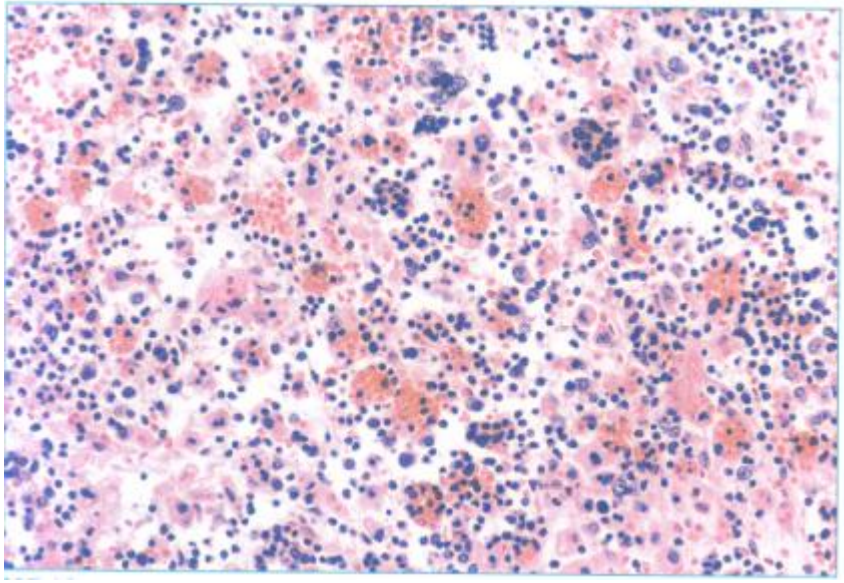
Secondary Hemophagocytic Lymphohistiocytosis



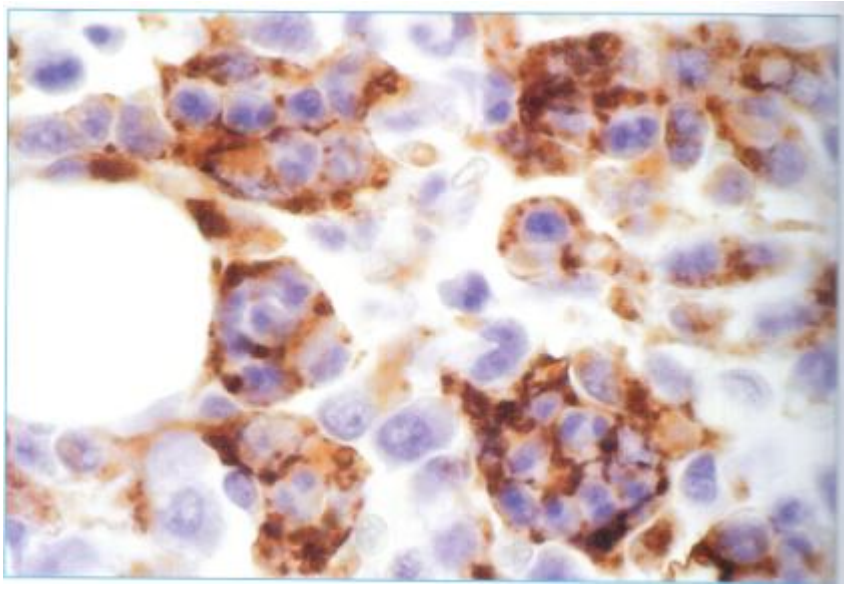
EBV-associated hemophagocytic syndrome



Infection-associated hemophagocytic syndrome
Ingested mature and immature cells

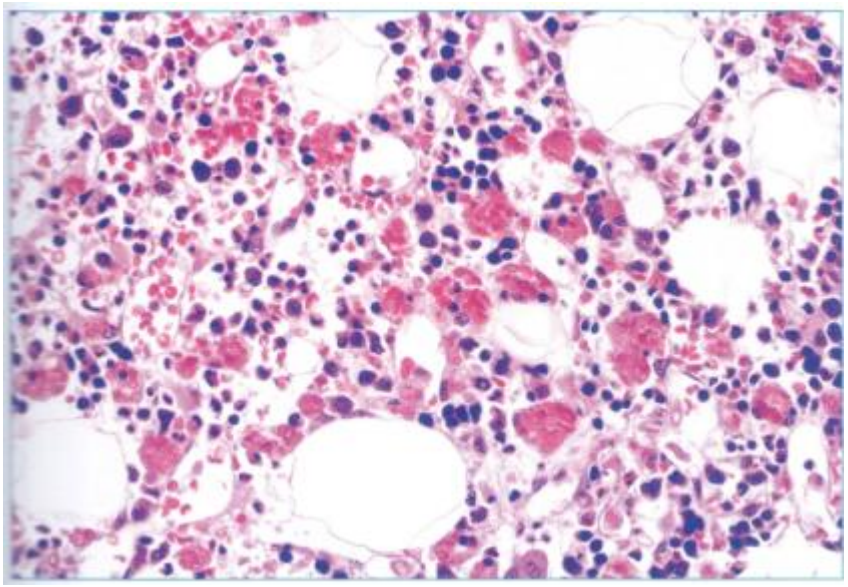


"Sack-like" appearance to histiocytes

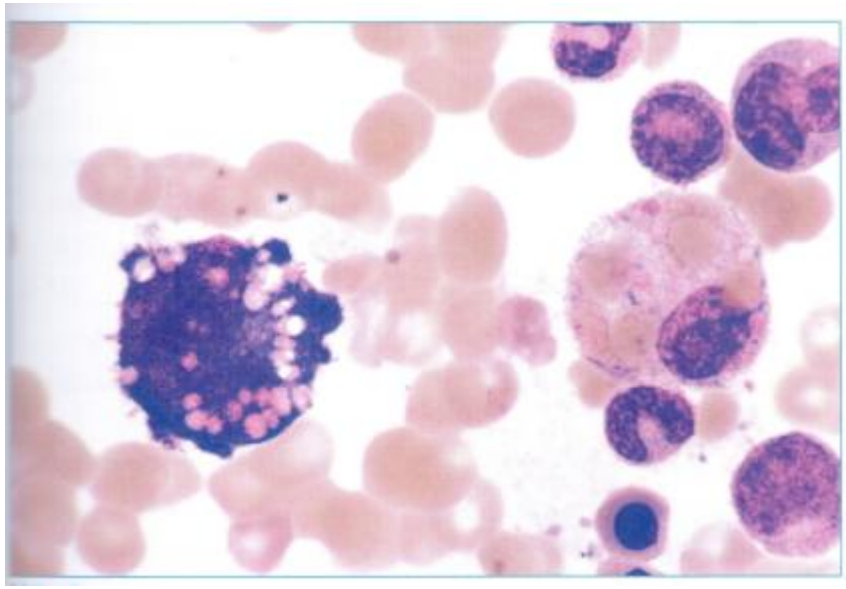


CD68 immunohistochemical staining

Secondary Hemophagocytic Lymphohistiocytosis



Primary cutaneous γδ T-cell lymphoma



Disseminated histiocytic sarcoma
Neoplastic histiocyte (left), benign phagocytic histiocyte (right)

Diffuse Histiocytoses: 2. Lysosomal storage disease

- Rare genetic disorders linked to specific lysosomal enzyme defects
- Multiple general categories of enzyme defects
  - Sphingolipidoses/sulfatidoses (eg, Gaucher disease, Niemann-Pick)
  - Glycoproteinoses (eg, mannosidosis)
  - Mucolipidoses (eg, sialidosis, mucolipidosis II, IV)
  - Mucopolysaccharidoses (eg, Hunter disease, Morquio disease)
  - Other defects (eg, cystinosis, Pompe disease)

General Features of Lysosomal Storage Disorder

Lysosomal enzyme defect or deficiency; generally autosomal recessive disorder

Usually get systemic accumulation (within lysosomes) of protein that is substrate for deficient enzyme (exceptions include Niemann-Pick in which multiple types of lipids accumulate)

Disease manifestations relate to anatomic sites of accumulation of substrate

Most storage diseases exhibit multiple clinical forms with variable age of onset and severity

Vacuolated blood lymphocytes may be seen in sphingolipidoses, glycogenoses, mucopolysaccharidoses, sialidosis

Distinctive **storage cells (macrophages) of various morphologic types** may be present **in BM (**eg, **Niemann-Pick, Gaucher, sea-blue histiocytes**†)

BM involvement usually prominent;

typically much more extensive than acquired conditions with “pseudo” storage disease cells

Diagnosis must be confirmed by enzymatic/molecular testing (*not* a morphology only diagnosis)

†Sea-blue histiocytosis is a variant of Niemann-Pick disease

References: [Mais 2008, Taddei 2009, Vellodi 2005]

Causes of Increased "Storage Disease" Type Histiocytes in BM

Foamy Vacuolated Histiocytes

Niemann-Pick
Fat necrosis/infarct
Lipogranulomas
Other storage diseases (Hurler, Tangier)
Hypercholesterolemia
Hyperlipoproteinemia
Polyvinylpyrrolidine plasma expander use
Many other constitutional enzyme deficiency disorders

Sea-Blue Histiocytes*

Niemann-Pick
Other lysosomal storage disorders
Myeloproliferative neoplasms, especially CML
Myelodysplasia
Acute leukemias
Other neoplasms: Hodgkin lymphoma, myeloma
Immune thrombocytopenic purpura
Constitutional anemias: thalassemia, sickle cell anemia
Collagen vascular disorders
Hyperlipoproteinemia
Hypercholesterolemia
Total parenteral nutrition

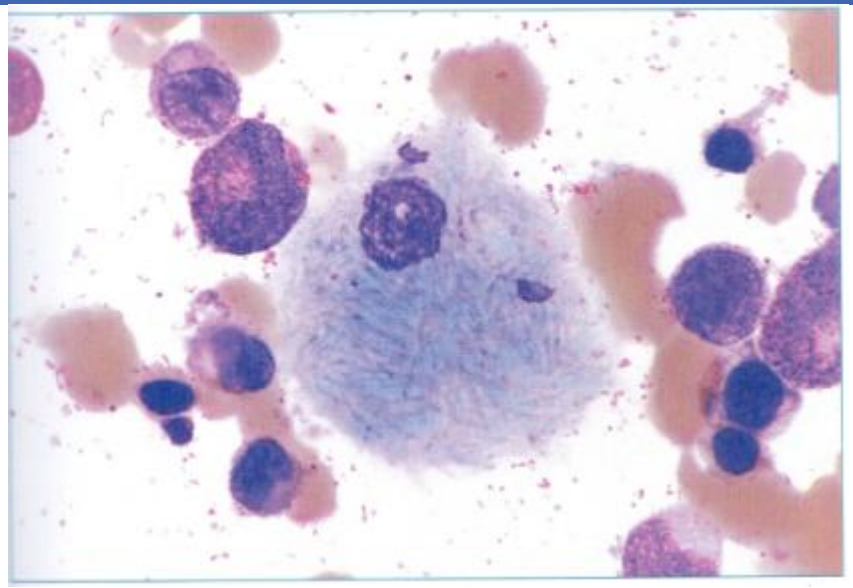
Gaucher-Type Cells*

Gaucher's disease
Chronic infections; systemic bacilli Calmette-Guerin infection following immunization
Myeloproliferative neoplasms, especially CML
Constitutional anemias: thalassemia, sickle cell anemia, CDA
Other neoplasms: Hodgkin lymphoma

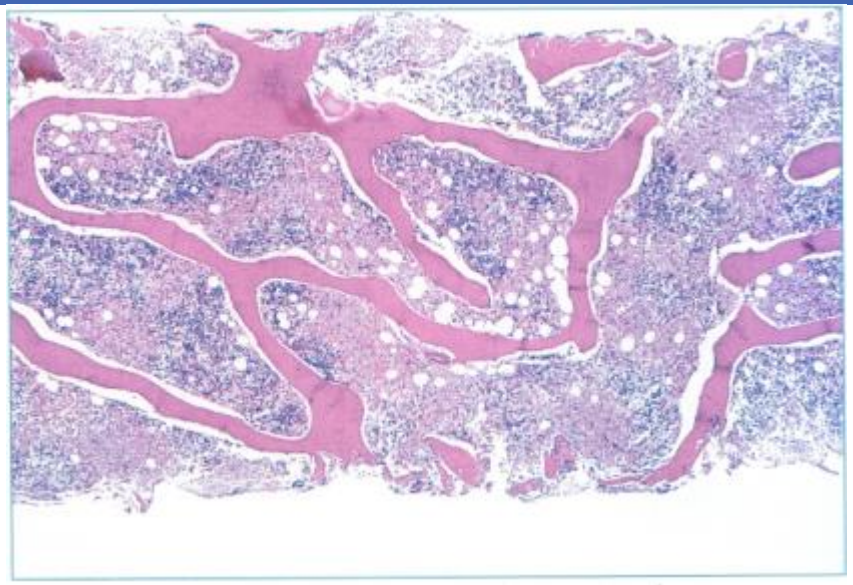
*Increased in conditions of high cell turnover in bone marrow
CDA = congenital dyserythropoietic anemia

References: [Bigorgne 1996, Brunning 1970, Ganguly 2004, Gesundheit 2006, Kumar 2005]

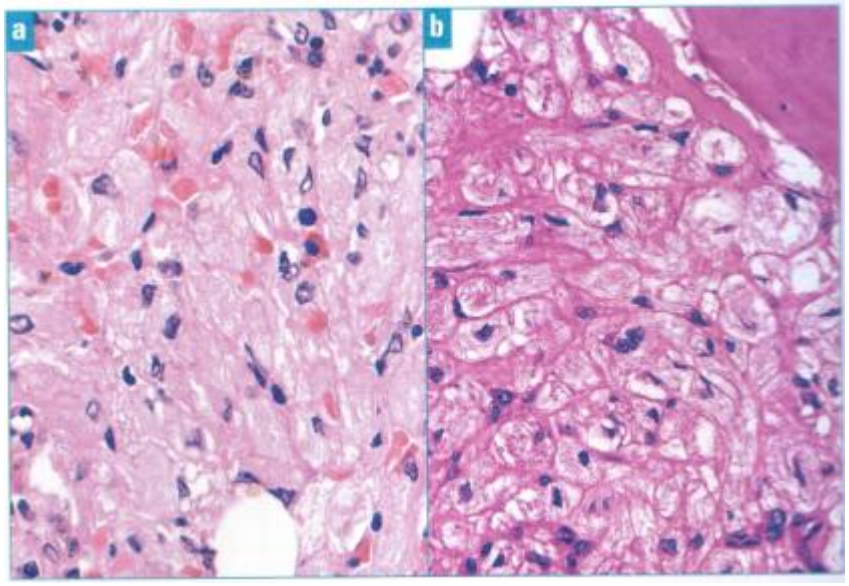
Gaucher Cells in Gaucher Disease



Voluminous cytoplasm with subtle striations

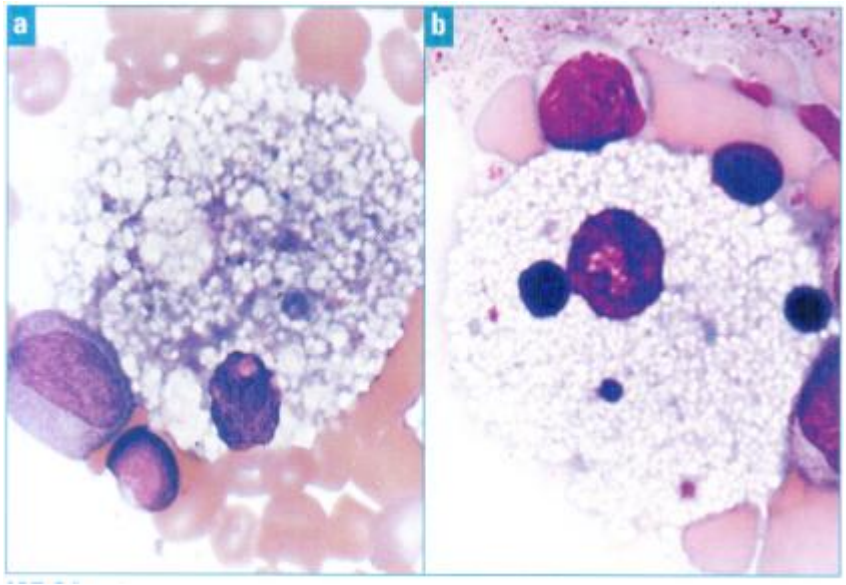


Extensive eosinophilic infiltrates

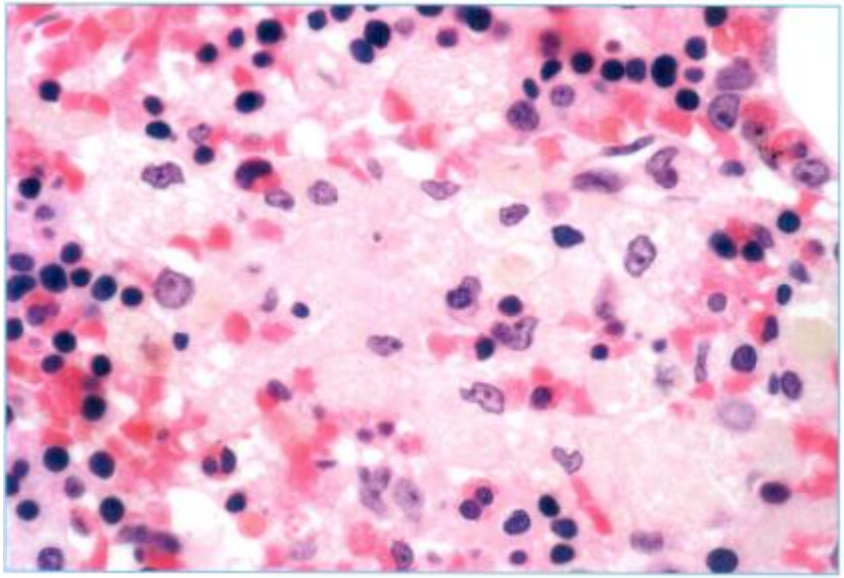


Crinkled, striated appearance of Gaucher cells

Niemann-Pick Histiocyte in Niemann-Pick Disease

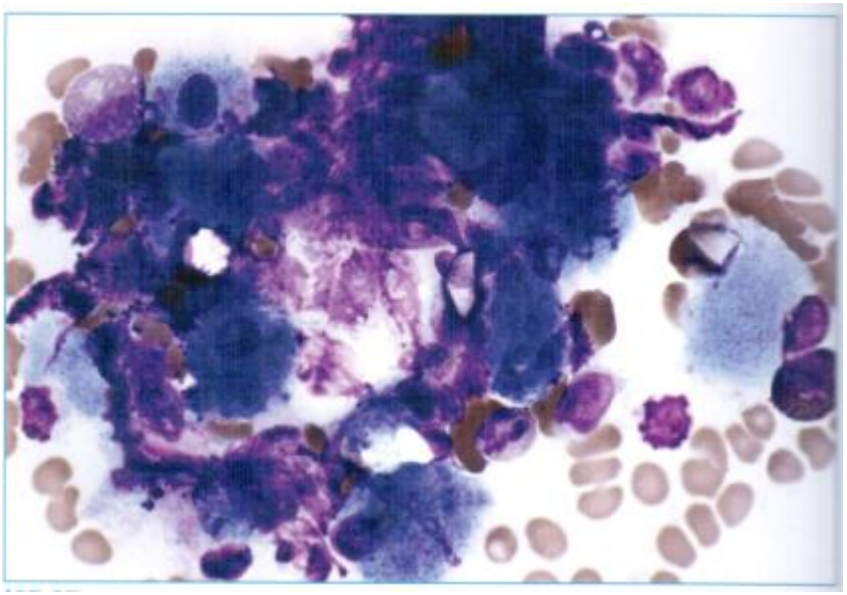


2 Niemann-Pick type histiocytes with prominent fine cytoplasmic vacuolization

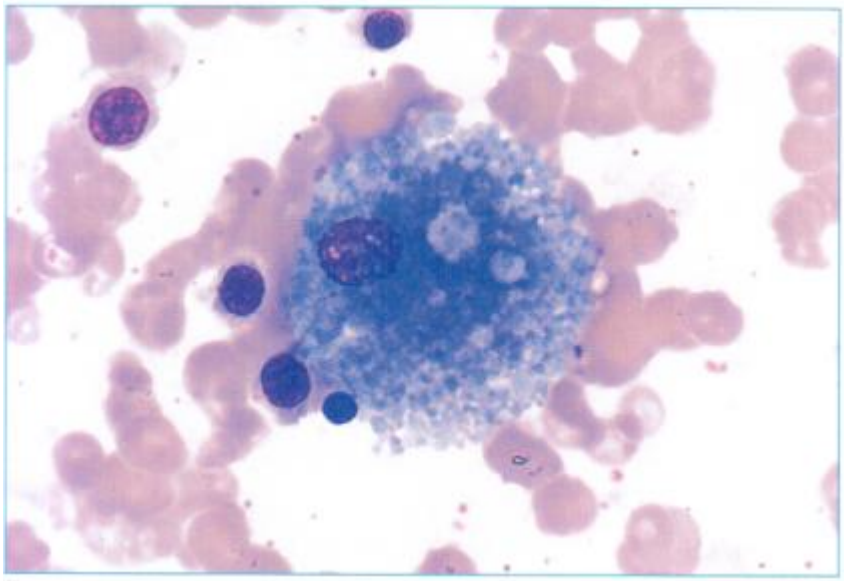


Significant BM involvement by Niemann-Pick disease

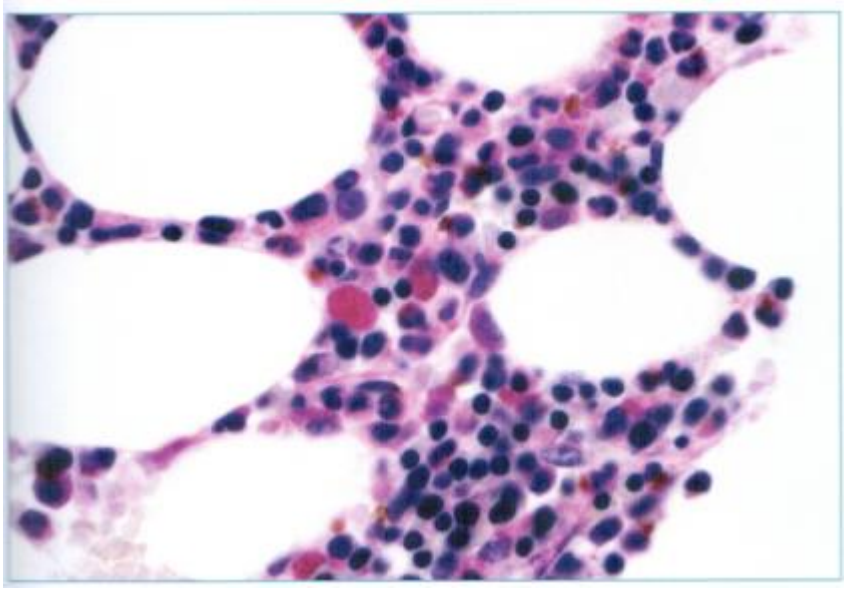
Sea-blue Histiocyte in Subtype of Niemann-Pick Disease



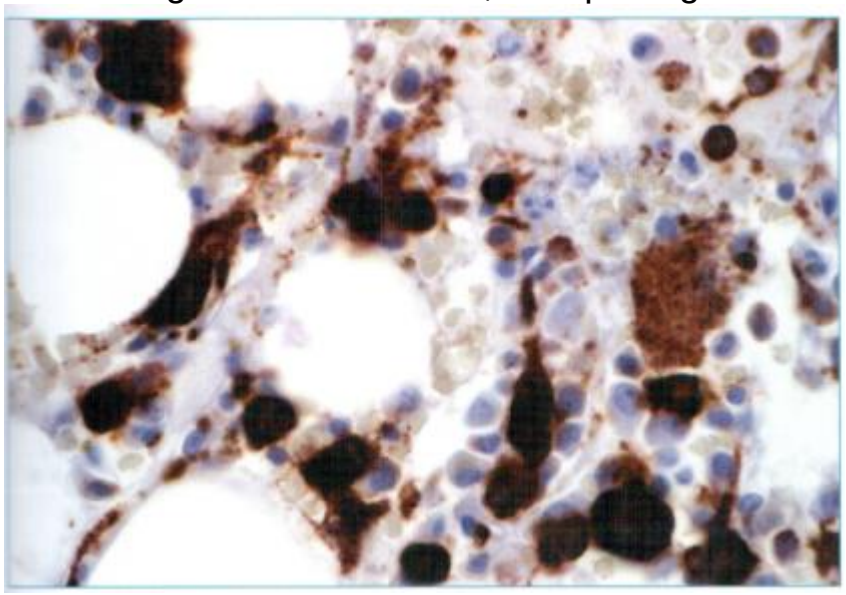
Sea-blue histiocytes



Typical sea-blue histiocyte with cytoplasm containing numerous coarse, basophilic granules

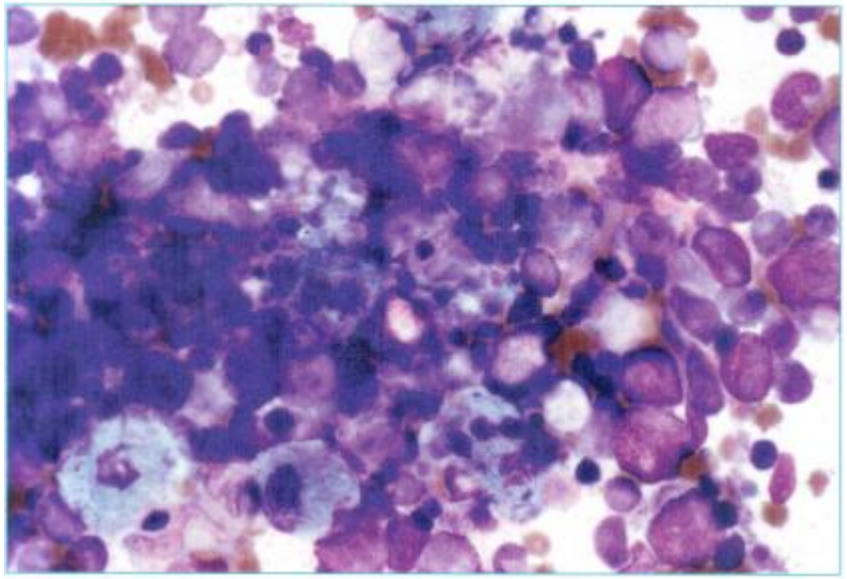


PAS positive sea-blue histiocytes

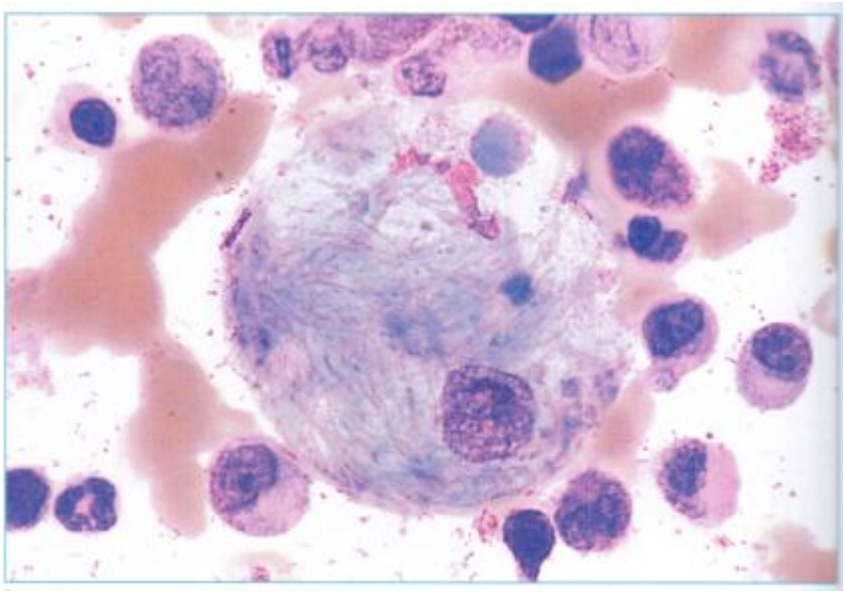


CD68 positive sea-blue histiocytes

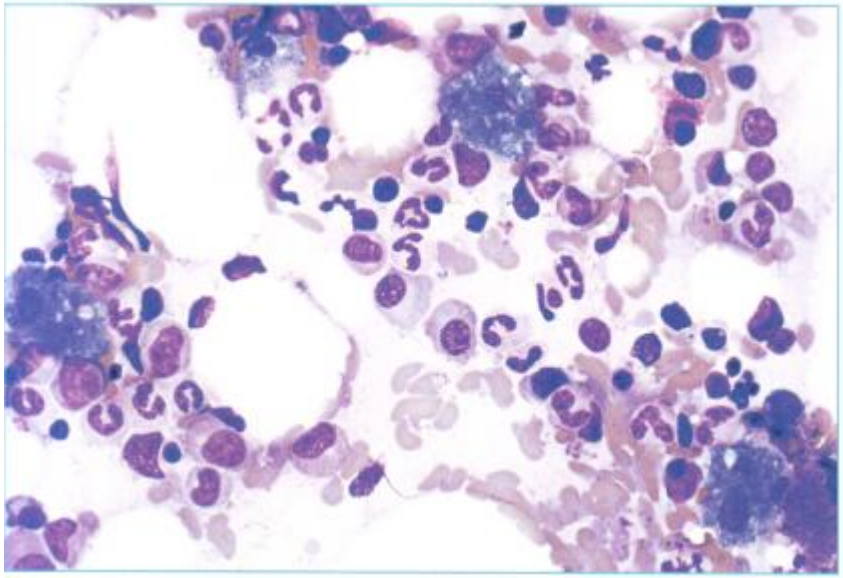
Gaucher Cells, See-blue Histiocyte in other diseases



CML
Pseudo-Gaucher cells



CML
Pseudo-Gaucher cells



Collagen vascular disease
Sea-blue histiocytes

Diffuse Histiocytoses: 3. Miscellaneous Reactive Histiocytic Disorders

- Increased BM histiocytes (benign histiocytosis)

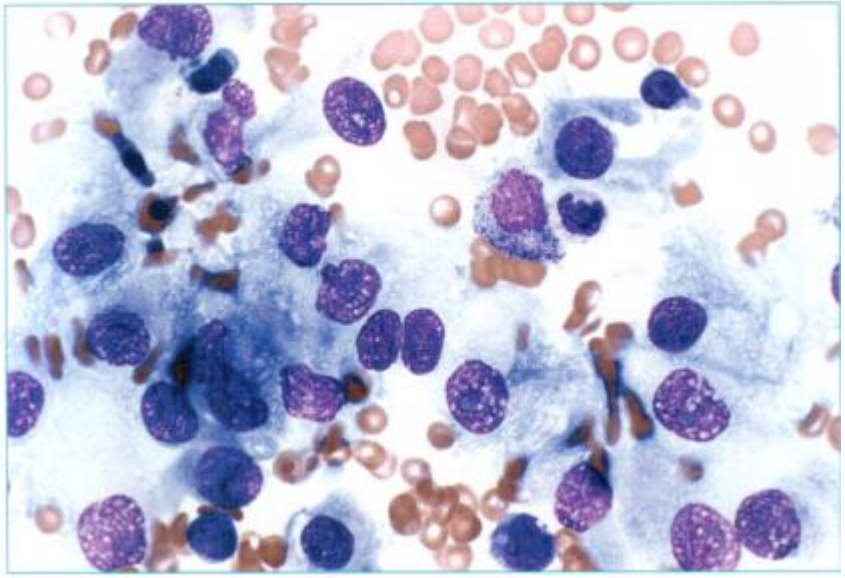
1. Myeloablative therapy
2. Fat necrosis
3. After BM transplantation
4. Non-Hodgkin lymphoma, Hodgkin lymphoma, Aggressive NK cell leukemia, T cell lymphoma

   -> histiocytic proliferation masking lymphoma in some cases
5. Sinus histiocytosis with massive lymphadenopathy, Kikuchi syndrome in rare cases

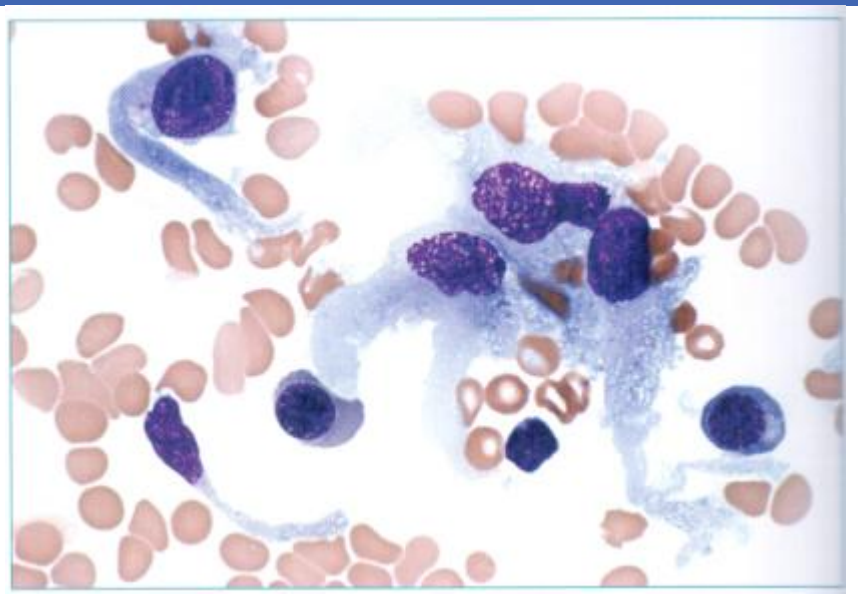
Clonal Diffuse Histiocytic Disorders: Langerhans Cell Histiocytosis

- Langerhans cell; BM derived type of dendritic cell that is localized primarily to skin and mucosal surfaces, normal constituent of BM
- Langerhans cell histiocytosis
  - Extent of BM involvement (20%): from minimal to massive
  - Morphologic feature: often have long stellate cytoplasmic projection in aspirate smear, characteristic linear nuclear groove are not prominent in air dried preparation
  - Immunologic or ultrastructural technique for diagnosis
    - S100(positive on normal BM elements), CD1a, and langerin coexpression
    - Birbeck granules
  - Also occur with either ALL, AML

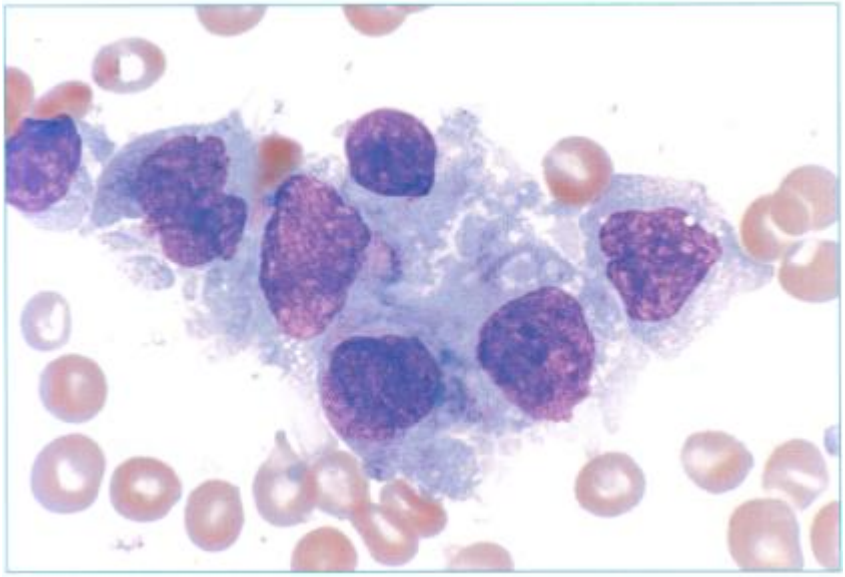
Langerhans Cell Histiocytosis on aspirate smear



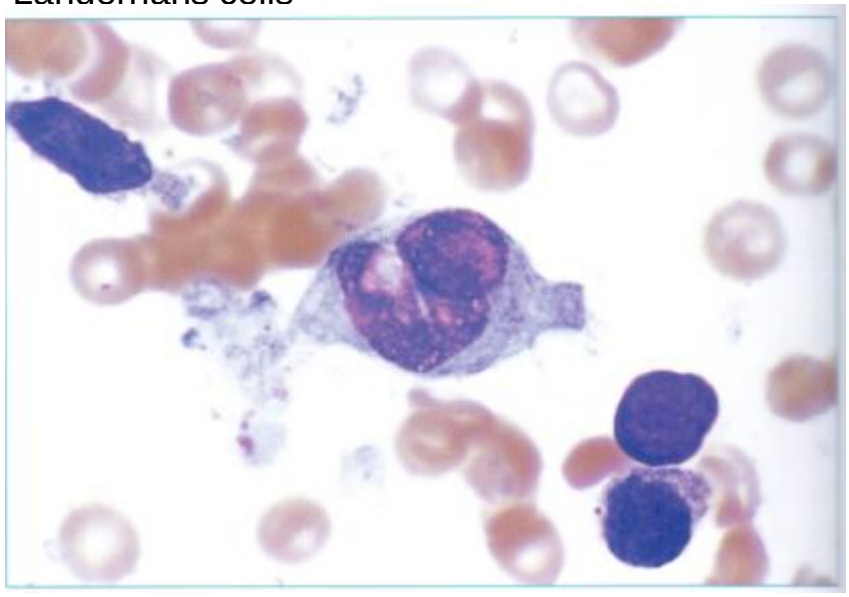
Complete effacement by Langerhans cell histiocytosis



Strikingly elongate dendritic processes of Langerhans cells

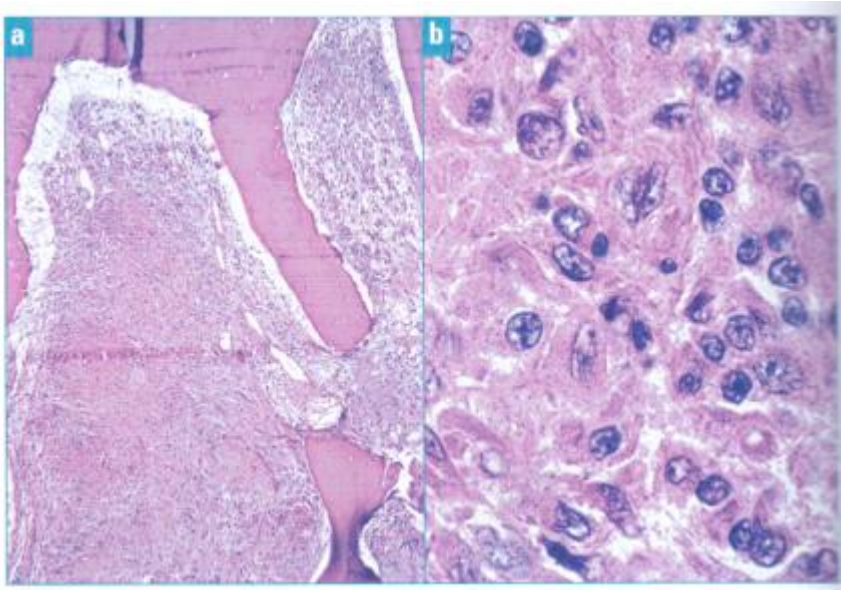


Variable appearance of Langerhans cells

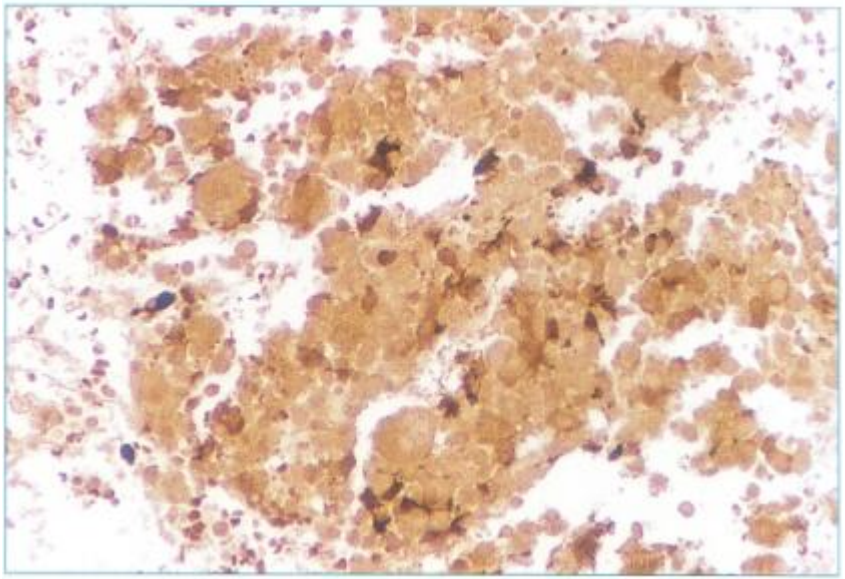


Langerhans cell with linear nuclear folding

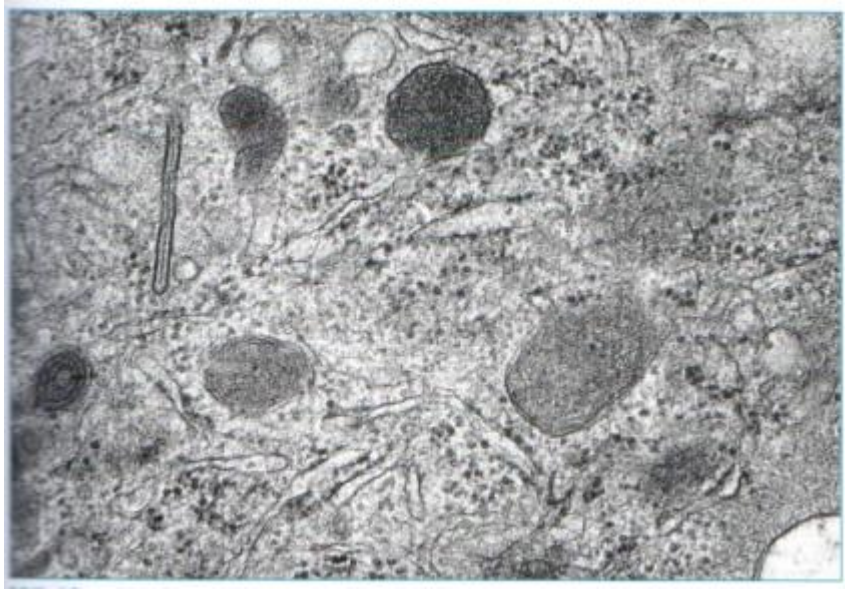
Langerhans Cell Histiocytosis



Extensive bone marrow effacement



S100 stain of BM clot section

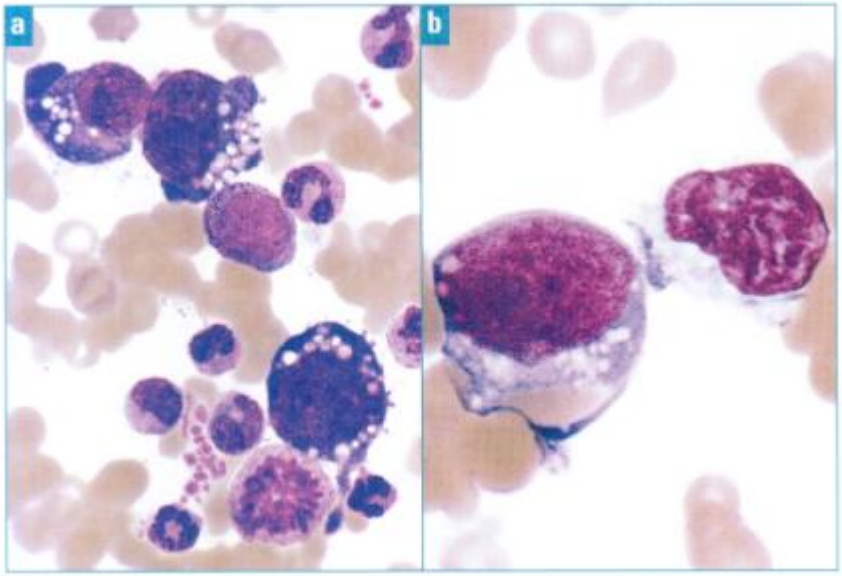


Electron micrograph, classic Birbeck granule

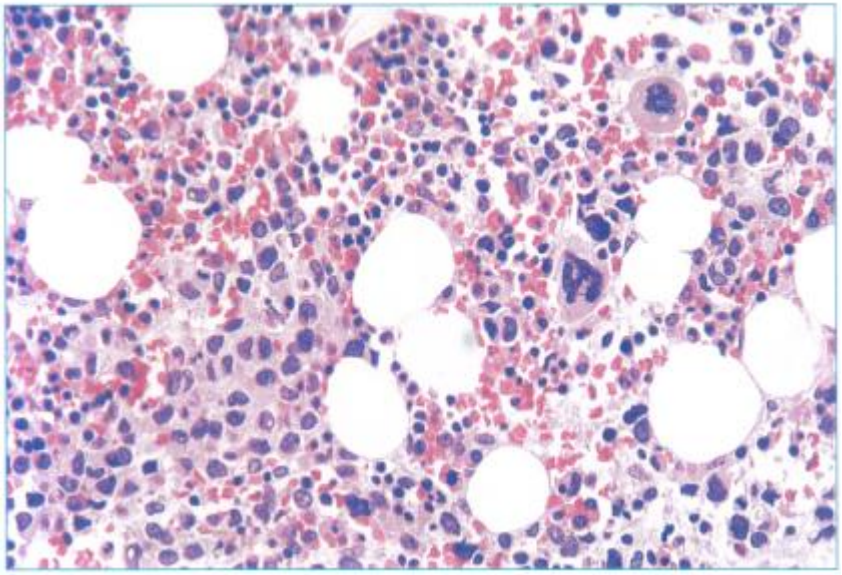
Clonal Diffuse Histiocytic Disorders: Disseminated Histiocytic Sarcoma

- BM infiltration of histiocytic sarcoma
  - Rare
  - Disseminated histiocytic sarcoma(=malignant histiocytosis)
  - Morphologic feature
    - very large overall cell size and nuclear atypia
    - minimal phagocytosis
  - This diagnosis can be rendered only when anaplastic large cell lymphoma, monocytic leukemias, aggressive NK cell leukemia, T-cell lymphomas, and B-cell lymphomas have been definitively excluded.

Disseminated Histiocytic Sarcoma



Scattered neoplastic histiocytes, minimal erythrophagocytosis



A subtle infiltrate of clustered and individually dispersed atypical cells

Components of Diagnostic Interpretation in BM Histiocytic Disorders

Provide evidence (usually immunophenotypic) that disorder is histiocytic
and specify cell type: macrophage vs dendritic cell

If primary leukemic process,
classify according to current recommendations for acute myeloid leukemia and chronic myelomonocytic leukemia

Provide evidence to establish process as
a neoplastic histiocytic disorder vs various secondary histiocytoses(such as hemophagocytic syndrome)

If bone marrow involvement by malignant histiocytosis/disseminated histiocytic sarcoma is considered,
provide data used to exclude lymphomatous processes such as anaplastic large cell lymphoma as well as myeloid/NK leukemias

NK = natural killer

Components of Diagnostic Interpretation in BM Histiocytic Disorders

Be aware that an extensive benign histiocytic infiltrate (often, but not always, with hemophagocytosis)
- can mask morphologically occult classical Hodgkin and non-Hodgkin lymphomas and NK-cell neoplasms

Routine immunohistochemical staining for B, T, NK and Reed-Sternberg cells is recommended *if* there is a clinical suspicion of an underlying neoplasm

Comment on extent of bone marrow effacement

Comment on other lineage abnormalities

Recommend additional tests as appropriate

NK = natural killer

감사합니다.