

2.

# Neoplastic Proliferations of White Cells

## ~ Histiocytic Neoplasms

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# Langerhans Cell Histiocytoses

- ▶ Histiocytosis is an “umbrella” designation for a variety of proliferative disorders of **dendritic cells or macrophages**.
- ▶ Some are highly malignant neoplasms (very rare histiocytic sarcomas), others are completely benign & reactive such as most histiocytic proliferations in lymph nodes
- ▶ Between these two extremes lie a group of uncommon tumors comprised of Langerhans cells, **the Langerhans cell histiocytoses**.

# Langerhans Cell Histiocytoses

- ▶ Langerhans cells are a special type of **immature** dendritic cell that are found in the epidermis; similar cells are found in many other organs.
- ▶ Function → to capture antigens and display them to T cells.

Dendritic cells



Cxs: 43 (GJCs, HCs), 45

Panxs: 1 (HCs?)

Follicular dendritic cells



Cxs: 43 (GJCs)

Panxs: 1 (HCs?)

Monocyte/macrophages



Cxs: 37 (HCs), 43 (GJC, HCs)

Panxs: 1 (HCs)

Kupffer cells



Cxs: 43 (GJCs)

Panxs: 1

Osteoclast



Cxs: 43 (HCs and GJCs)

Panxs: 1? 3?

Microglia



Cxs: 32 (HCs), 36, 43

(GJCs, HCs), 45

Panxs: 1 (HCs)

Neutrophils



Cxs: 37 (HCs), 40, 43

(GJCs?, HCs)

Panxs: 1 (HCs)

B cells



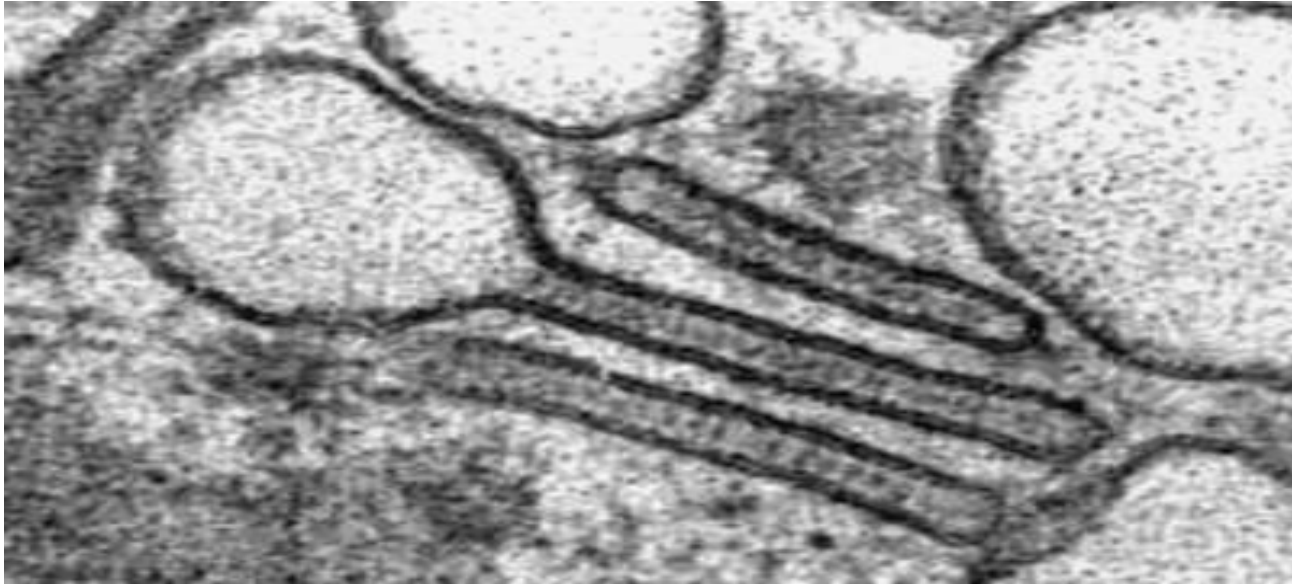
Cxs: 40, 43 (GJCs)

Panxs: 1 (HCs?)

# Langerhans Cell Histiocytoses

- ▶ Langerhans cell proliferations take on different clinical forms, but **all are believed to be variations of the same basic disorder.**
- ▶ The proliferating Langerhans cells express **MHC class II antigens, CD1a, and langerin.**
- ▶ **Langerin:** is a transmembrane protein found in Birbeck granules.
- ▶ **Birbeck granules:** cytoplasmic rodlike tubular structures, they have a characteristic electron micrographs tennis racket appearance.

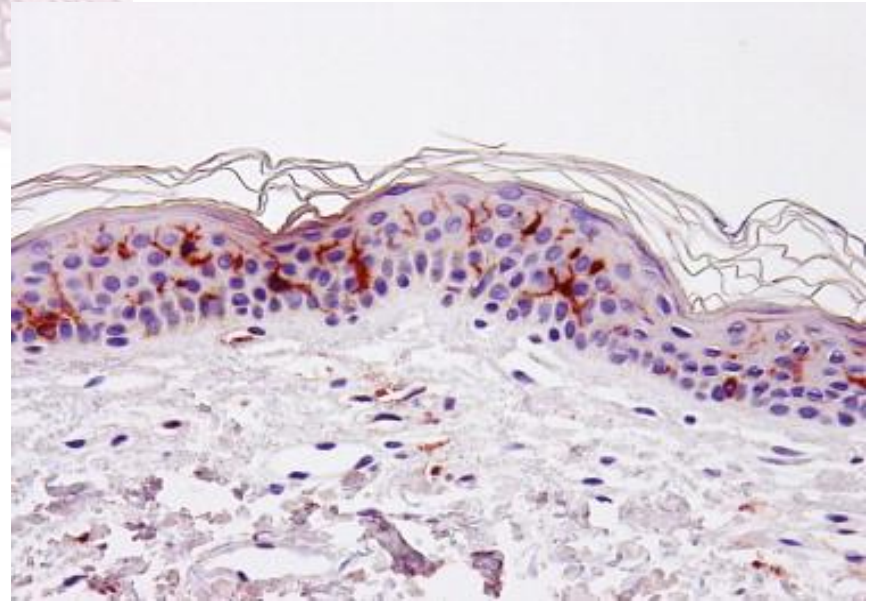
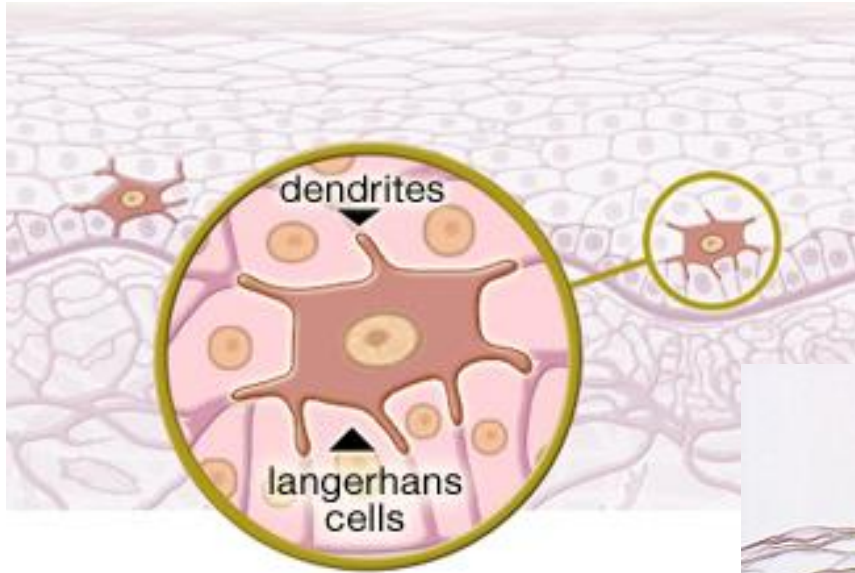
# Langerhans Cell Histiocytoses - Birbeck granules

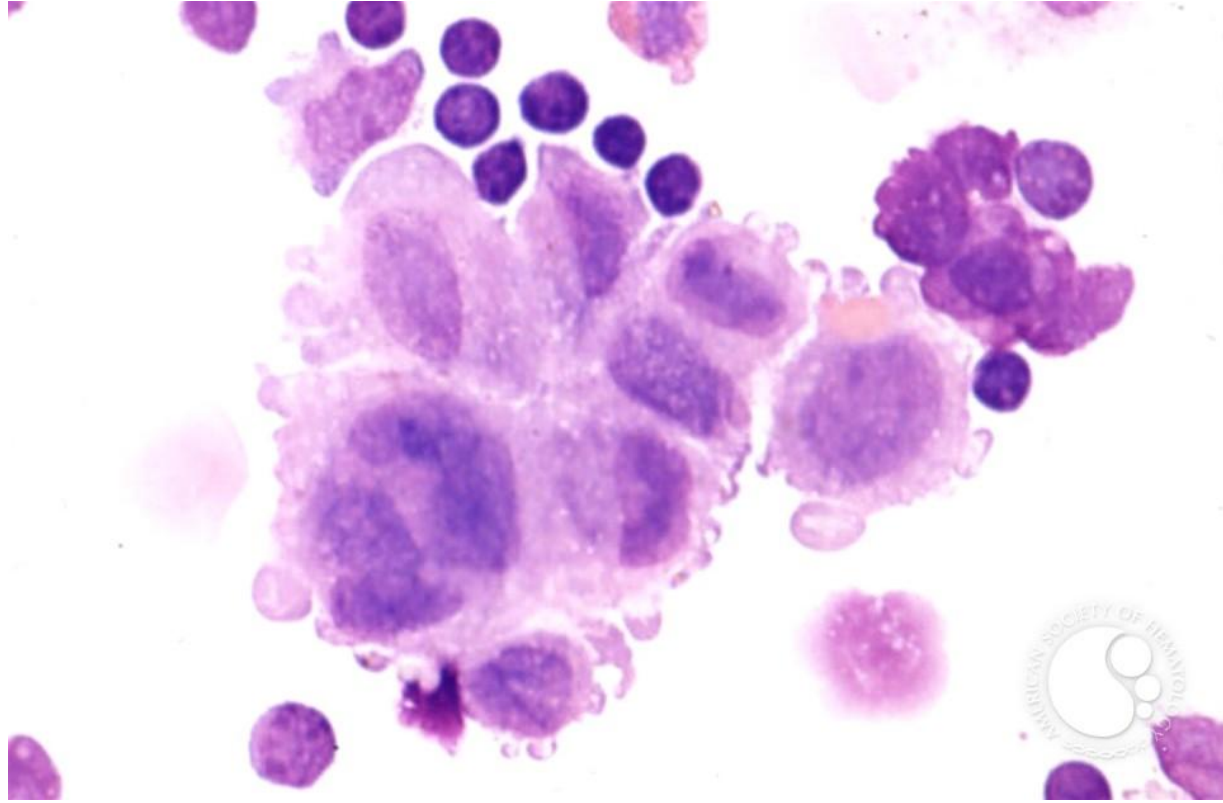


Electron microscope

# Langerhans Cell Histiocytoses

- ▶ Under the light microscope, the proliferating Langerhans cells do not resemble their normal dendritic counterparts.
- ▶ They have abundant, often vacuolated cytoplasm and vesicular nuclei, an appearance more akin to that of tissue macrophages (histiocytes)— hence the term Langerhans cell histiocytosis.





## Langerhans Cell Histiocytoses – Pathogenesis

- The different clinical forms are frequently associated with an acquired mutation in the kinase BRAF → hyperactivity of the kinase.
- This same mutation is found in a variety of other tumors, including; benign nevi, malignant melanoma, papillary thyroid carcinoma, and some colon cancers.

# Langerhans Cell Histiocytoses

- ▶ Langerhans cell histiocytoses can be grouped into two major relatively distinctive clinicopathologic entities:

# Multisystem Langerhans cell histiocytosis (Letterer-Siwe disease)

- Children younger than 2 years of age.
- Manifests with multifocal cutaneous lesions that grossly resemble seborrheic skin eruptions.
- Most affected patients have hepatosplenomegaly, lymphadenopathy, pulmonary lesions, and (later in the course) destructive osteolytic bone lesions.

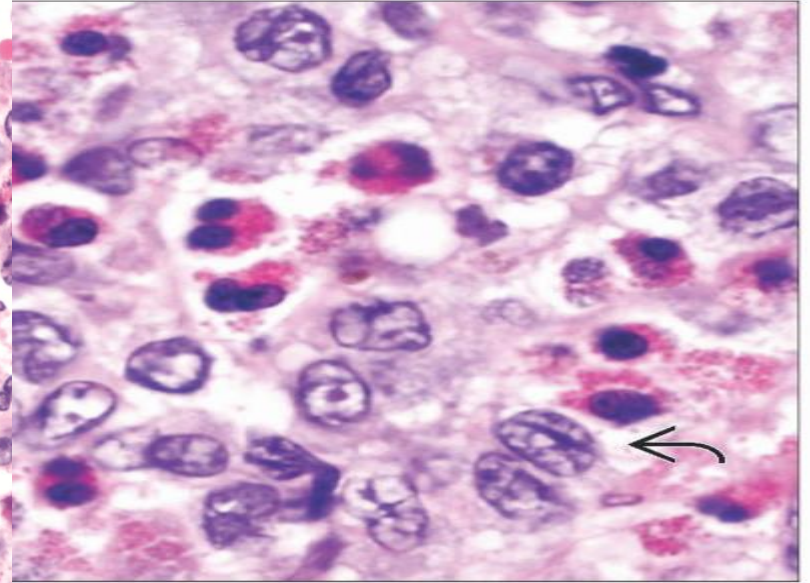
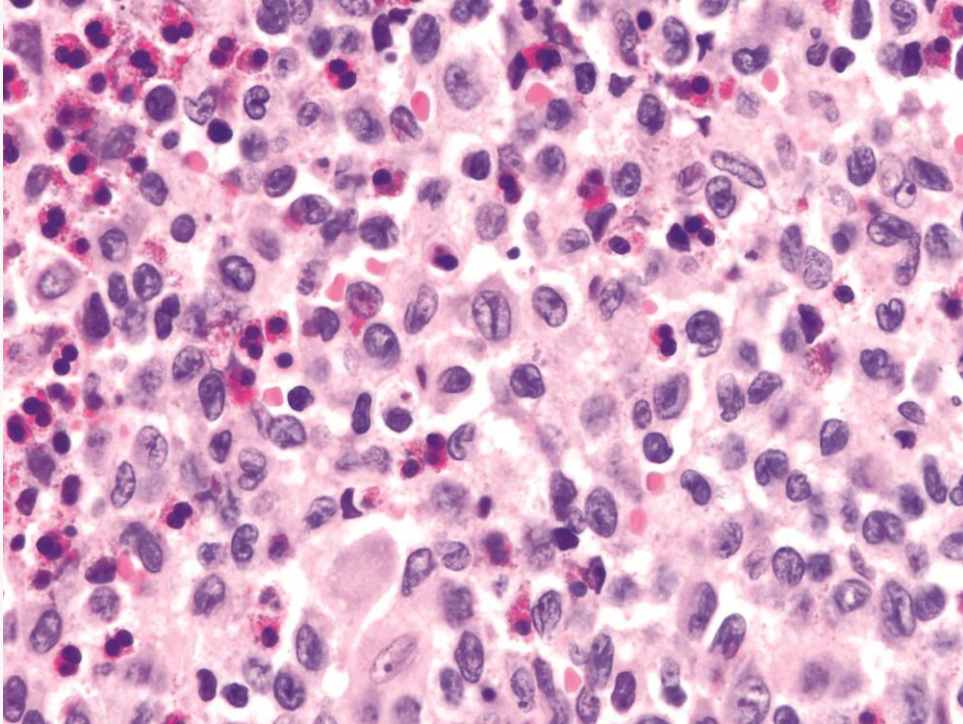
# Multisystem Langerhans cell histiocytosis (Letterer-Siwe disease)

- Extensive marrow infiltration often leads to pancytopenia.
- The disease is **rapidly fatal** if untreated.
- With intensive chemotherapy, 50% of patients survive 5 years.

# Unisystem Langerhans cell histiocytosis (eosinophilic granuloma)

- Unifocal or multifocal.
- Characterized by expanding accumulations of Langerhans cells, usually within **the medullary cavities of bones** or less commonly in the skin, lungs, or stomach.
- The Langerhans cells are admixed with variable numbers of lymphocytes, plasma cells, neutrophils, & **eosinophils (prominent)**.
- Virtually any bone may be involved; the calvaria, ribs, and **femur are most commonly affected**.

# Unisystem Langerhans cell histiocytosis (eosinophilic granuloma) - morphology



# Unisystem Langerhans cell histiocytosis (eosinophilic granuloma) - **Unifocal**

- **Unifocal** disease most often involves a single bone.
- Asymptomatic or cause pain, tenderness, and pathologic fracture.
- It is an **indolent** disorder that may heal spontaneously or be cured by local excision or irradiation.

# Unisystem Langerhans cell histiocytosis (eosinophilic granuloma) - Multifocal

- **Multifocal** unisystem disease usually affects children
- Typically manifests with multiple erosive bony masses that sometimes extend into soft tissues.
- In about 50% of cases, involvement of the posterior pituitary stalk of the hypothalamus leads to diabetes insipidus.
- Many patients experience **spontaneous regressions**; others are treated effectively with chemotherapy.

# 3.

## Disorders of the Spleen and Thymus

# Spleen - SPLENOMEGALY

- The spleen is frequently involved in a wide variety of systemic diseases.
- In virtually all instances the spleen responds by enlarging (**splenomegaly**)
- **Symptoms**; dragging sensation in the left upper quadrant & discomfort after eating.
- **Hypersplenism**; chronically enlarged spleen removes excessive numbers of one or more of the formed elements of blood, resulting in anemia, leukopenia, or thrombocytopenia.
- **Platelets** are particularly susceptible to sequestration in the of the red pulp → thrombocytopenia is more prevalent and severe in persons with splenomegaly than is anemia or neutropenia

## SPLENOMEGALY - Disorders

➤ According to the degree of splenomegaly they are grouped:

1. Massive splenomegaly (weight > 1000 g)

Myeloproliferative neoplasms (CML, primary myelofibrosis);  
indolent leukemias (CLL and hairy cell leukemia); lymphomas;  
infectious diseases(e.g., malaria); Gaucher disease

## SPLENOMEGALY - Disorders

2. Moderate splenomegaly (500–1000 g) Chronic congestive splenomegaly (portal hypertension or splenic vein obstruction); acute leukemias; extravascular hemolysis (hereditary spherocytosis, thalassemia major, autoimmune hemolytic anemia; many infections, including infective endocarditis, tuberculosis, & typhoid; metastatic disease.
3. Mild splenomegaly (< 500 g): Acute splenitis; acute splenic congestion; infectious mononucleosis; septicemia, and intraabdominal infections

# SPLENOMEGALY - Disorders

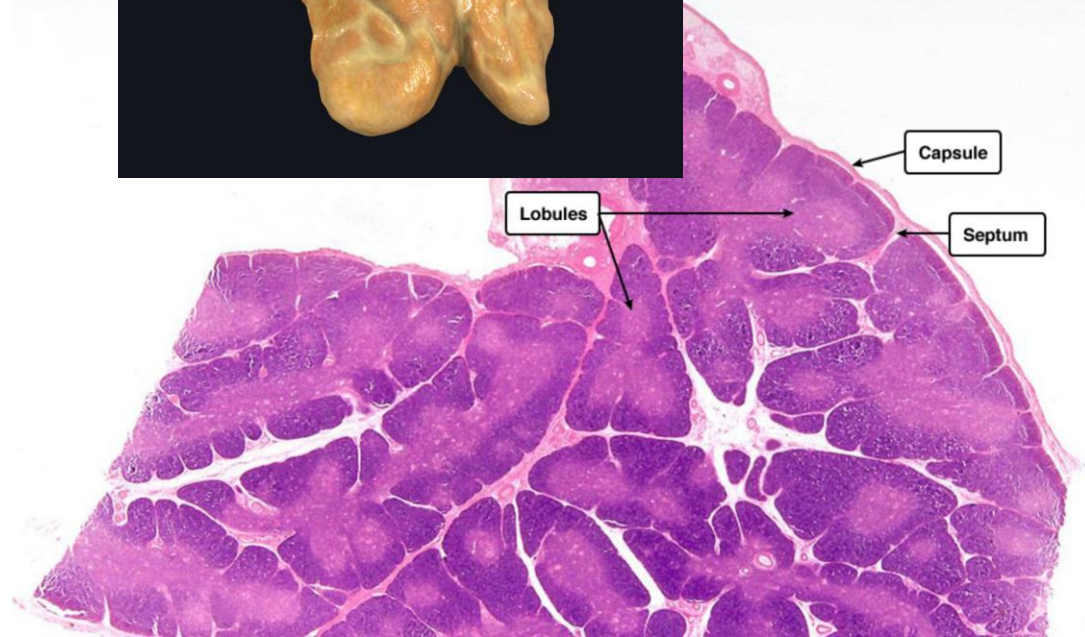
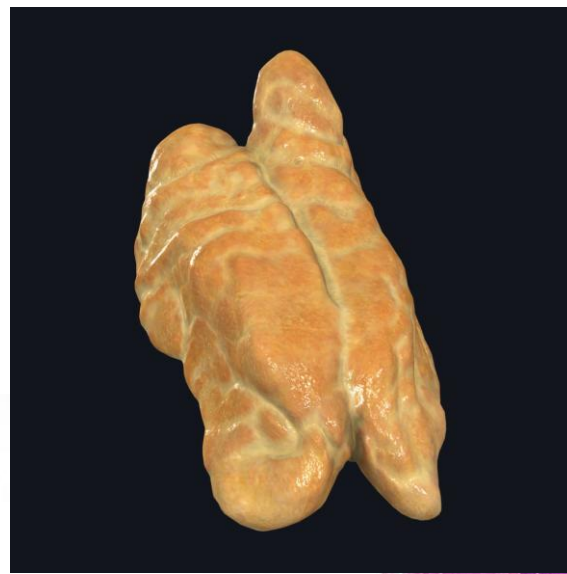


Normal



# THYMUS

- Thymus has a crucial role in T-cell maturation.
- Can be involved by lymphomas, particularly those of T-cell lineage.



## THYMUS – Thymic hyperplasia

- Thymic enlargement often is associated with the presence of lymphoid follicles, or germinal centers, in the medulla.
- These germinal centers contain reactive B cells, which are only present in small numbers in normal thymuses.
- Thymic follicular hyperplasia is found in most patients with myasthenia gravis and sometimes in other autoimmune diseases, such as systemic lupus erythematosus & rheumatoid arthritis.
- Removal of the hyperplastic thymus is often beneficial early in the disease.

# THYMUS – Thymomas

- Tumors of thymic epithelial cells.
- Several classification systems for thymoma based on cytologic & biologic. One simple & clinically Classification:

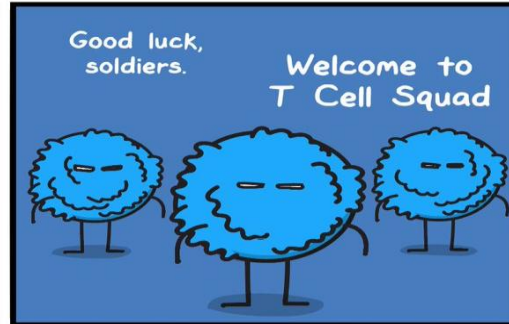
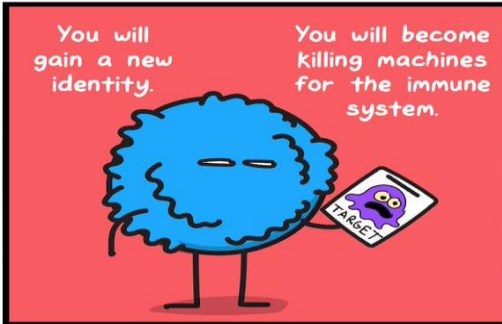
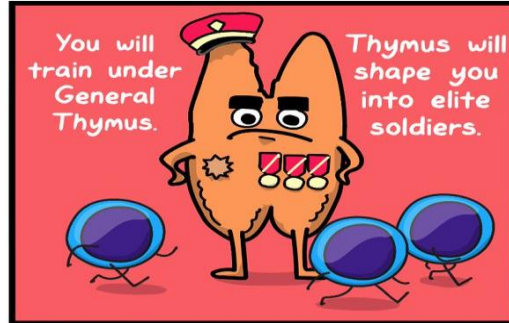
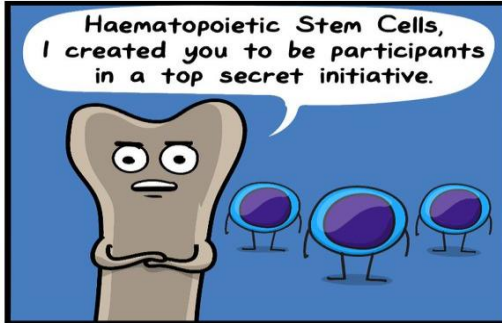
1. Benign or encapsulated thymoma: cytologically & biologically benign
2. Malignant thymoma

**Type I:** cytologically benign but infiltrative & locally aggressive

**Type II:** (thymic carcinoma): cytologically & biologically malignant

# THYMUS – Thymomas

- Thymomas are rare, most occur in middle-aged adults.
- 30% asymptomatic; 30-40% produced local manifestations (cough, dyspnea, and superior vena cava syndrome).
- The remainder were associated with a systemic disease, most commonly **myasthenia gravis (MG)**.
- Thymoma is discovered in 15-20% of patients with MG, & removal of the tumor **often leads to improvement**.
- Thymomas may be associated with several other paraneoplastic syndromes; include (in rough order of frequency) pure red cell aplasia, hypogammaglobulinemia, and multiorgan autoimmunity.



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Thank You