Mediastinum Tumors

General

Region located between the lungs, sternum, spine, thoracic inlet, and diaphragm.

About half of tumors are asymptomatic→ identified on imaging.
Symptoms often result from compression/invasion of structures→ cough, pain, dyspnea.
May block superior vena cava→ "**SVC syndrome**"→ face swelling, distended neck veins, distended collaterals→ often malignant→ Adults: think lung cancer or lymphoma; Kids: Leukemia/lymphoma.

Differential Diagnosis by Location:

Anterior	Superior	Middle	Posterior
Thymic tumors Germ cell tumors Thyroid tumors Parathyroid tumors Lymphoma Paraganglioma Hemangioma Lipoma	Thymic tumors Thyroid tumors Lymphoma Parathyroid tumors	Pericardial cyst Bronchial cyst Lymphoma	Neurogenic tumors Schwannoma Neurofibroma Ganglioneuroma MPNST Paraganglioma Neuroblastoma Gastrointestinal cyst Bronchogenic cyst

The Classic 5 "T's" of Anterior Mediastinal Masses

Thymus
Thyroid
Teratoma
***T**errible* lymphoma
Thoracic Aorta

Developmental Cysts

Congenital anomalies that develop during embryogenesis.

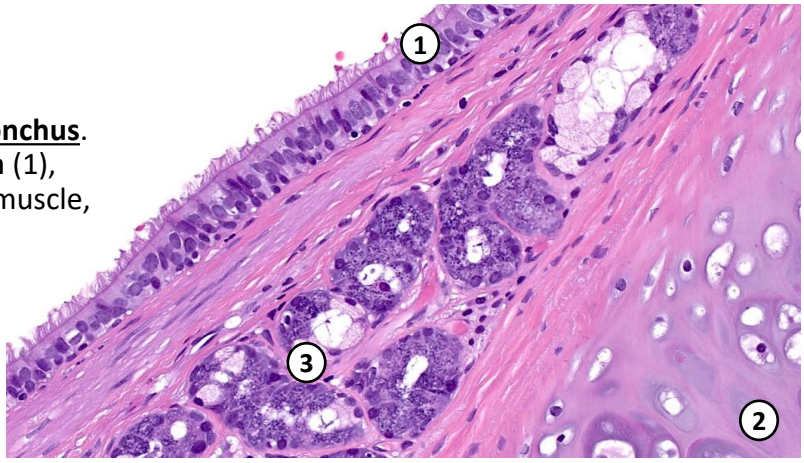
Bronchogenic Cyst

Abnormal tracheobronchial tree branching.

Often **well-formed structures <u>resembling bronchus</u>**. Contain a combination of: **Ciliated epithelium** (1), **cartilage** (2), submucosal glands (3), smooth muscle, and/or degenerative changes. Unilocular.

Cured by excision. Can get infected.

Can be hard to distinguish from esophageal duplication cysts if ciliated and no cartilage, can say simply *"Foregut cyst"*

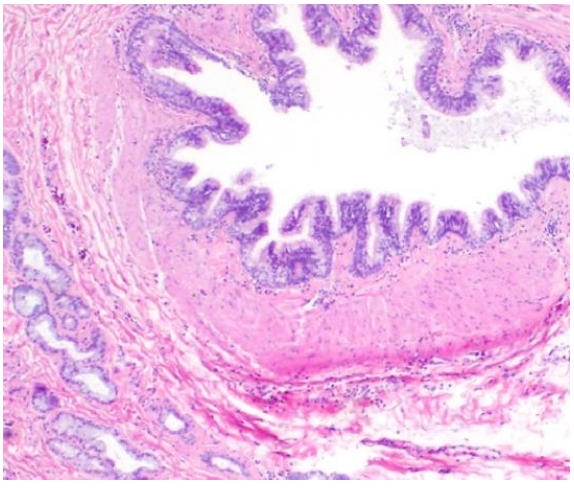


Gastrointestinal Duplication Cysts

Attached to the GI tract (but lumens not contiguous, unlike a diverticulum), with epithelium that resembles some part of the GI tract, and a **well-developed double layer of smooth muscle** (resembling normal bowel layers). **<u>NO</u> Cartilage.**

<u>Esophageal Duplication Cyst:</u> Columnar (ciliated or non-ciliated), squamous, or mixed epithelium. Can contain heterotopic lung or thyroid.

<u>Enteric Duplication Cyst:</u> Variable epithelium, usually gastric or duodenal.



Thymic Tumors

Thymoma

Thymic epithelial neoplasms with a ***variety*** **of histologic patterns**.
Overall rare, but most common mediastinal tumor in adults.

Multiple subclassifications (see below), **but stage is much more important prognostically!**
(*All* subtypes can behave aggressively or indolently, mostly important to aid in recognition and DDX)

Frequent association with **paraneoplastic syndromes**:
Most common = **Myasthenia gravis** (autoantibodies block acetylcholine receptors between muscle & nerves → weakness)
Other syndromes: Collagen and autoimmune disorders (e.g., lupus), immunodeficiencies, endocrine disorders, dermatologic disorders, enterocolitis, etc..

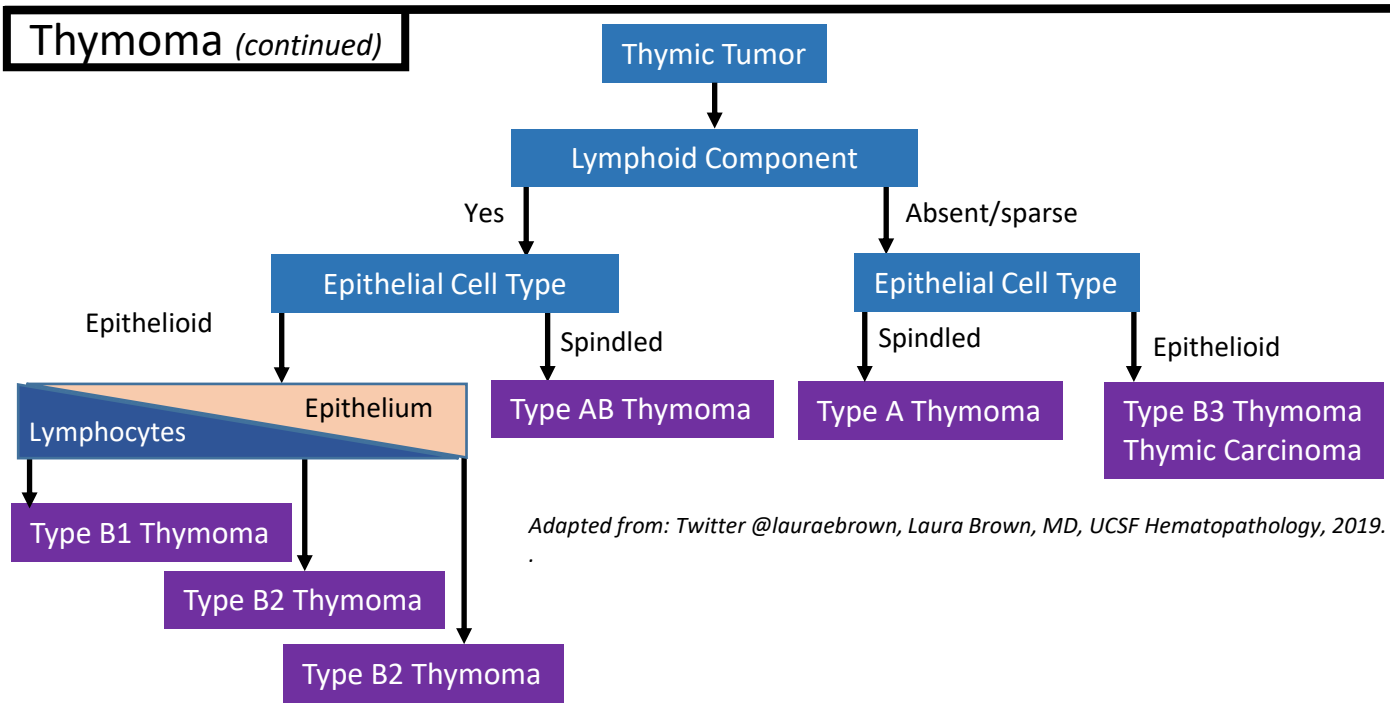
Type	Composition	Proportion Epithelium	Proportion Lymphocytes	Prognosis
Type A	Bland spindled to ovoid cells, few or no admixed lymphocytes	Predominant, spindled/oval	Few/none	Excellent
Type AB	Both lymphocyte poor (type A) and lymphocyte-rich (type B) components, with a significant proportion of immature T cells	Significant	Significant	Very good
Type B1	Predominantly lymphocytes with dispersed epithelial cells (that do not form clusters)	Low, no clusters, polygonal	Predominant	Very good
Type B2	Predominantly lymphocytes, with small clusters of epithelial cells	Low, small clusters	Significant	Fair
Type B3	Predominantly atypical polygonal epithelial cells in sheets.	Predominant, epithelioid	Few	Fair, often high stage
Micronodular with lymphoid stroma	Multiple small tumors with bland spindled cells surrounded by lymphoid stroma	Significant, spindled	Significant. B & T cells, without epithelial cells	Excellent
Metaplastic	Biphasic tumor consists of solid polygonal epithelial cells in a background of bland spindled cells	Predominant, epithelioid and spindled	Few/none	Very good

Subtyping:
Some thymomas are heterogeneous and show multiple patterns of growth. In these cases, list the different patterns quantified by %. Also, be careful definitely subtyping a thymoma on a limited sampling (likely best to just Dx as "Thymoma" and give the pattern(s) present in the biopsy).

Note: Type AB thymomas are inherently heterogeneous.

Immunohistochemistry:
Most do not require IHC for subtyping. Often used to differentiate from Non-thymomas.
Thymic epithelial cells → AE1/AE3, p63, PAX8.
T-Cells in thymus → CD5, CD3, TdT (immature thymic T-cells)

Thymoma *(continued)*



Adapted from: Twitter @lauraebrown, Laura Brown, MD, UCSF Hematopathology, 2019.

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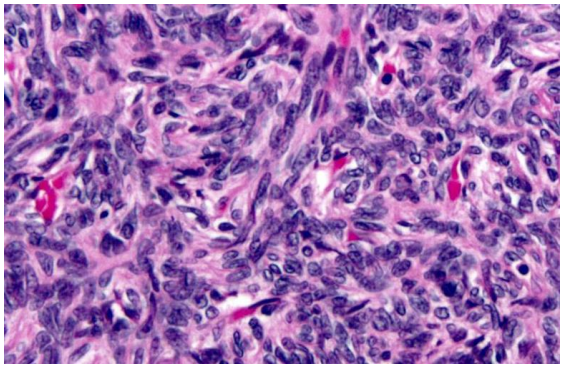
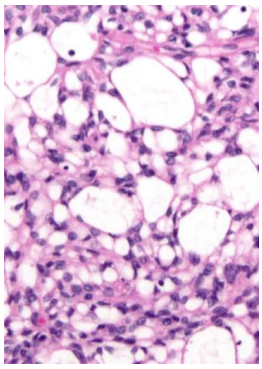
Type A Thymoma

Spindled/oval cells with <u>few or no admixed immature lymphocytes</u>. Bland nuclei with powdery chromatin. Can have a microcystic appearance.

Usually low stage. Often lobulated and **circumscribed**/encapsulated.

Excellent prognosis.



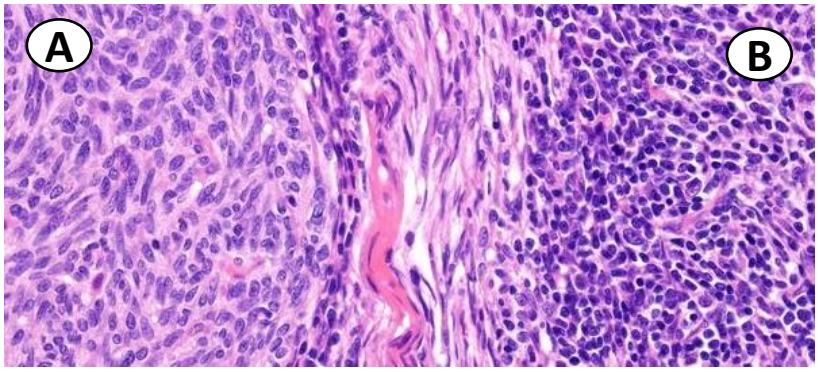


Type AB Thymoma

2 components: A) lymphocyte-poor spindle cell component **<u>and</u>** B) lymphocyte-rich component

<u>Varying proportions</u>, but > 10% of tumor with moderate infiltrate of immature TdT+ T-cells.

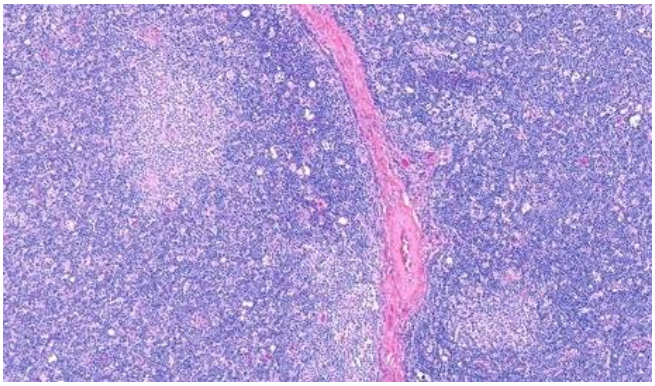
Usually low stage, lobulated, and very good prognosis.



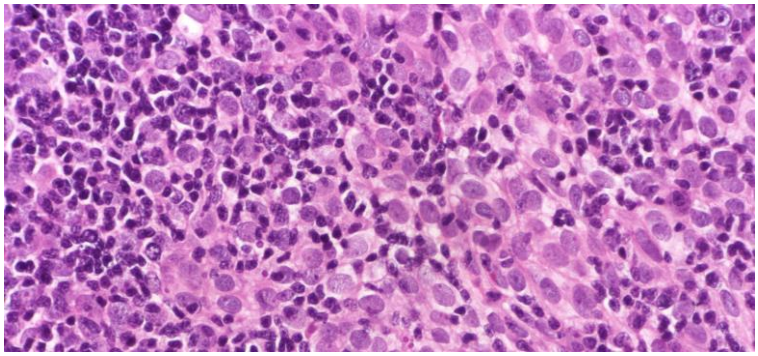
Type B1 Thymoma

<u>Closely resembles normal thymus</u>: Dispersed epithelial cells that do <u>*not*</u> form clusters and are set in a **<u>dense background of immature T cells</u>** mimicking thymic cortex. Also has areas of medullary differentiation (nodular pale areas ± Hassall's corpuscles; mostly TdT- T cells with a substantial B-cell population).

Usually nodular with a very good prognosis.



Type B2 Thymoma

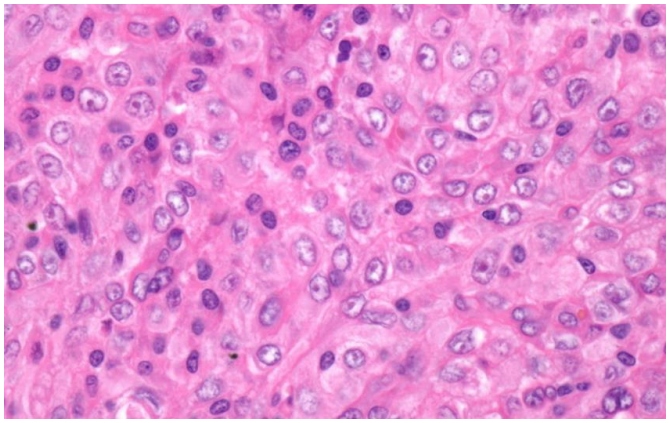


Polygonal neoplastic epithelial cells set in a background of numerous immature T cells.

Epithelial cells denser than in B1 and are usually clustered with round vesicular nuclei.

Often encapsulated with a fair to good prognosis.

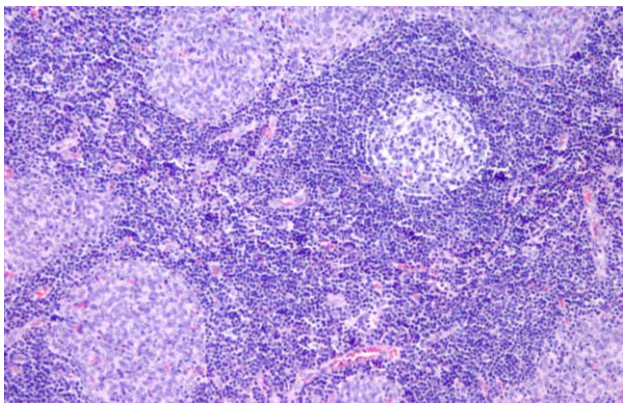
Type B3 Thymoma



Mild or moderately **atypical polygonal pink epithelial cells with lobules of sheet-like or solid growth with fibrous septae**. Often few intermingled immature T-cells.

Usually **poorly circumscribed**→ extensions into mediastinal fat/organs→ most patients have local **symptoms** (e.g., chest pain or SVC syndrome)→ fair prognosis overall, frequent recurrences.

Micronodular Thymoma with Lymphoid Stroma

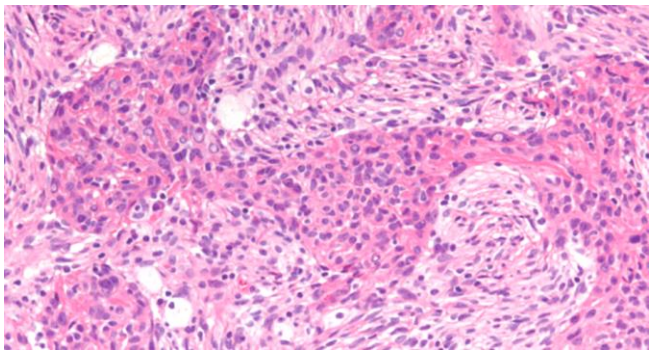


Multiple epithelial nodules surrounded by prominent lymphoid stroma containing mature B and T cells and devoid of epithelial cells.

May contain germinal centers and/or plasma cells.

Excellent prognosis

Metaplastic Thymoma



Biphasic: Composed of alternating areas of solid epithelial cells and bland slender spindle cells. Absent to few lymphocytes.

Very rare. No paraneoplastic syndrome.

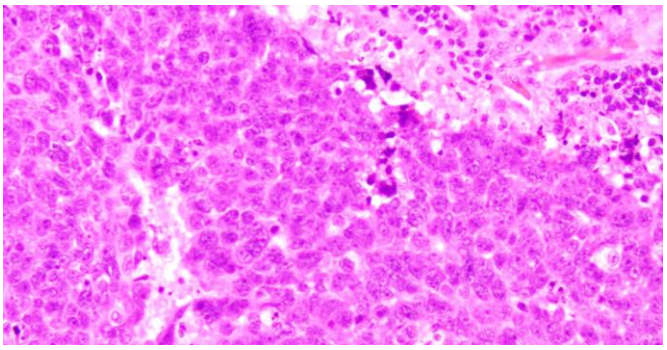
YAP1-MAML2 gene fusions

Microscopic Thymoma: Multifocal thymic epithelial proliferations, < 1mm, composed of bland spindled to polygonal cells in well-circumscribed nodules embedded in the medulla or cortex. Very rare.

Sclerosing Thymoma: Abundant collagen-rich stroma in an otherwise conventional thymoma. Very rare.

Lipofibroadenoma: Benign thymic tumor that resembles a fibroadenoma of the breast. Very rare.

Thymic Carcinomas



Thymic epithelial tumor with **malignant cytologic features** that lacks thymic organization.
Resembles conventional carcinomas in other organs.
Often unequivocal cytologic atypia.
Often *un*encapsulated and *no* fibrous septae.
Variable T cell infiltrate

IHC: (+) **CK AE1/AE3, p63, PAX8, CD5, CD117,** GLUT1, MUC1. Focal Synaptophysin often.

Types of Thymic Carcinoma

Squamous Cell Carcinoma: Most common type of thymic carcinoma. Resembles SCC elsewhere. Lacks normal thymic architecture (e.g., lobulation, lymphocytes, etc…). Frankly invasive into nearby structures and often present with symptoms. Often eosinophilic cytoplasm and abundant stroma.

Basaloid Carcinoma: High N:C basaloid appearance with cystic and papillary architecture and peripheral palisading. Lots of mitoses and necrosis. Very aggressive.

Mucoepidermoid Carcinoma: Like in other organs (Squamoid cells, mucus-producing cells, and intermediate cells). MAML2 translocations.

Lymphoepithelioma-like Carcinoma: poorly-differentiated squamous cell carcinoma with an associated rich lymphoplasmacytic infiltrate (resembles nasopharyngeal carcinoma). Often EBV-positive.

Clear Cell Carcinoma: Composed predominantly of cells with vacuolated clear cytoplasm.

Sarcomatoid Carcinoma: consists completely or partly of spindled cells.
If heterologous elements→ Carcinosarcoma.

NUT Carcinoma: Like elsewhere, NUT gene rearrangement. Monomorphic round cells with characteristic abrupt keratinization. Often stain with squamous markers. NUT IHC +. Extremely aggressive.

Adenocarcinomas: Heterogeneous group showing glandular and/or mucin production.

Undifferentiated Carcinoma

Thymic Neuroendocrine Tumors

IHC Markers of Neuroendocrine Differentiation:
Synaptophysin, Chromogranin, INSM1. Less so CD56.
Cytokeratins often show perinuclear "dot-like" staining.

Rare. Classified using same criteria as in lung.
No smoking association. Can see with MEN1.
(See Lung Tumor Notes for more info)

	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell carcinoma
Mitoses/2mm^2	0-1	2-10	>10 (median 70!)	>10 (median 80!)
Necrosis	No	Focal, if any	Yes	Yes, extensive
Morphology	Organoid or trabecular growth, uniform polygonal cells, finely granular "salt and pepper" chromatin		Large cell size, vesicular to coarse chromatin, frequent prominent nucleoli, and abundant cytoplasm	Small fusiform to round cells, scant cytoplasm, finely granular chromatin, Lots of mitoses
Ki-67	Up to 5%	Up to 20%	40-80%	Almost 100%
Combined with non-small cell component	No	No	Sometimes	Sometimes

Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015.

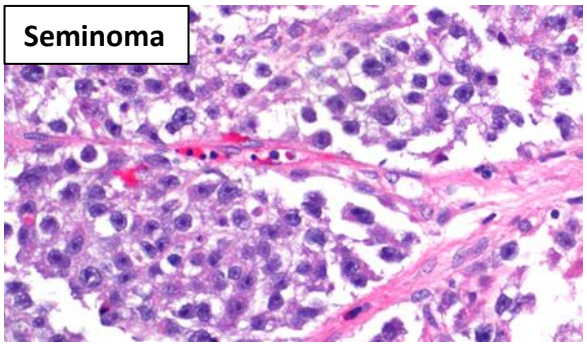
Germ Cell Tumors

Note: For more info, refer to the Testicle and Ovary guides

Morphologically identical to gonadal counterparts!
Associated with Klinefelter syndrome (XXY)
- Prepubertal→ Mostly teratomas or Yolk Sac
- Women→ Mostly teratomas
- Men→ Teratomas, Seminoma, YST, and mixed

Seminoma

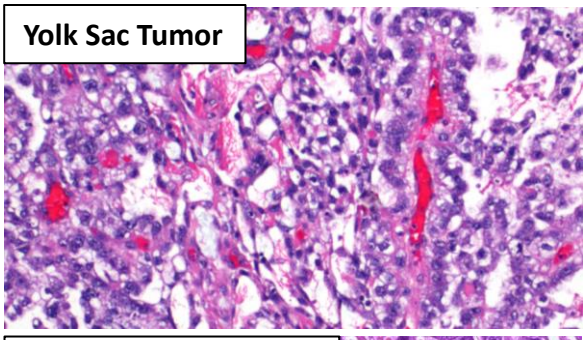
Large polygonal cells with clear to eosinophilic cytoplasm, distinct cell membranes, vesicular chromatin, and prominent nucleoli. Fibrous septae and **nested architecture**
Lymphocytic infiltrate; Sometimes granulomas



Yolk Sac Tumor

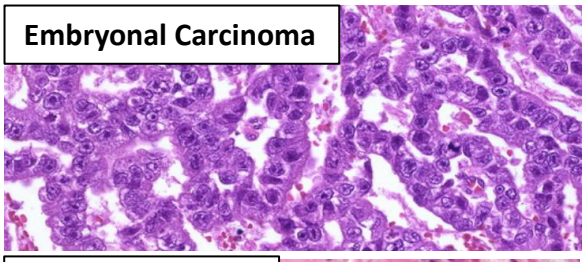
Many patterns/architecture. Often hypocellular myxoid areas
- Most common = reticular/microcystic
- Can also be solid, papillary, etc…

Classic: **Schiller-Duval Bodies**
Hyaline globules. **Elevated Serum AFP**



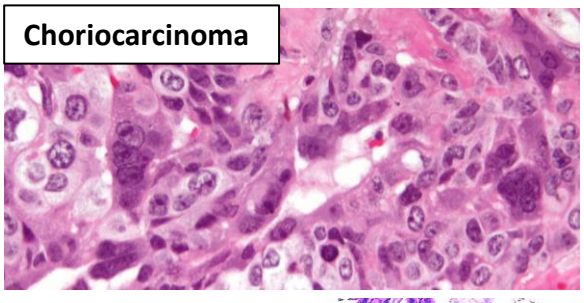
Embryonal Carcinoma

Large "Primitive" cells
Vesicular nuclei with prominent nucleoli
Coarse, basophilic chromatin. Amphophilic cytoplasm
Variable architecture (nests, sheets, glands)



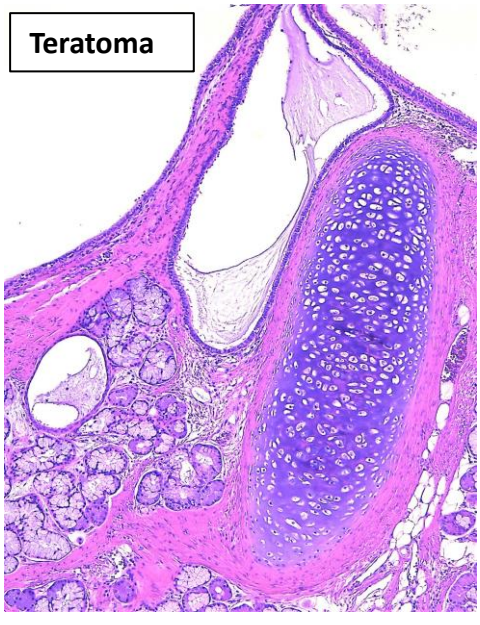
Choriocarcinoma

Malignant cytotrophoblasts (mononuclear) *and* syncytiotrophoblasts (multinucleated)
Abundant **Hemorrhage**



Teratoma

Composed of tissues from 2-3 germ layers.
Common elements: Skin (with adnexal structures), Cartilage, GI, Brain, etc… Very good to excellent prognosis.
Mature→ exclusively mature (adult-type) tissues
Immature→ has immature fetal/embryonic tissue

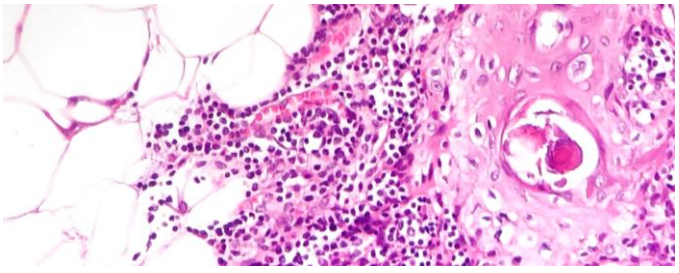


Germ Cell Tumor Immunohistochemistry:

IHC Stain	Seminoma	Embryonal Carcinoma	Yolk Sac Tumor	ChorioCA
SALL4	+	+	+	+
OCT 3/4	+	+	-	-
D2-40	+	+/-	-	-
CD117	+	-	-	-
CD30	-	+	-/+	-
Glypican 3	-	-	+	+/-

Soft Tissue Tumors

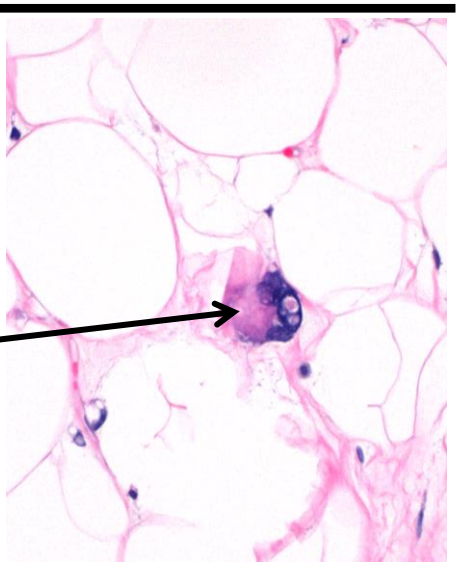
Thymolipoma



Encapsulated tumor with mature adipose tissue and interspersed normal thymic tissue.
Benign→ cured with excision. Rare.

Lipoma: mature adipose tissue only (like elsewhere). Rare in mediastinum.

Liposarcoma



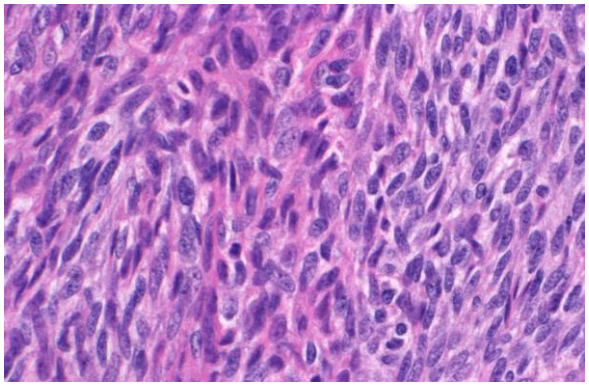
Similar to liposarcomas in soft tissue.
Most common sarcomas of mediastinum, often well-differentiated liposarcomas or dedifferentiated liposarcomas→ both have giant marker and ring chromosomes that contain amplified regions of 12q including MDM2 and CDK4 (detect with **MDM2 FISH**)

Well-differentiated liposarcoma: Range of appearances. Variable lipoblasts and hyperchromatic atypical cells in a background of adipocytes and fibrous tissue.

Dedifferentiated liposarcoma: Contain an WDL component, with an abrupt transition to another component, which is usually an undifferentiated pleomorphic sarcoma

Often poor prognosis.

Synovial Sarcoma



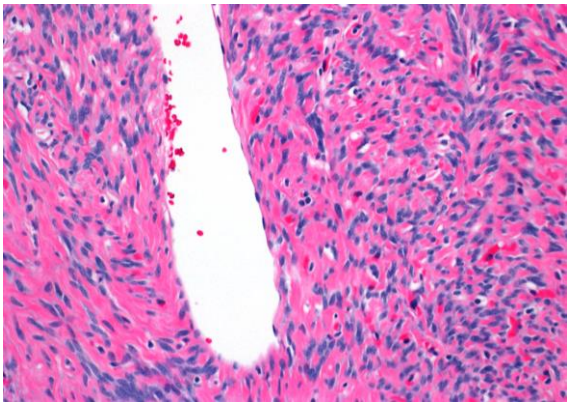
Malignant spindle cell neoplasm of uncertain histogenesis. Poor prognosis.

Like in soft tissue, monophasic or biphasic proliferation of spindled cells with stubby nuclei and frequent Stag-horn vessels.

IHC: Patchy EMA and CK (particularly strong in epithelial areas). Usu. CD99 (+). TLE-1 (+)

Molecular: SS18-SSX gene fusions t(X;18)

Solitary Fibrous Tumor



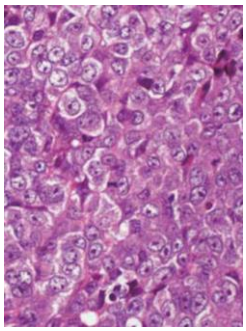
Usually benign.

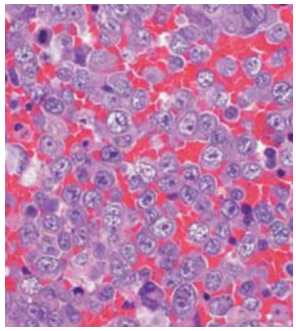
"**Patternless pattern**" of varying cellularity of bland spindled cells with varying amounts of collagenized stroma.
Prominent "**Staghorn vessels**" (dilated, thin-walled, branching vessels).
Can be hyalinized or myxoid.

IHC: **STAT6 (+).** Also, CD34, CD99 (+, but variable).

Molecular: **NAB2/STAT6 gene fusion**

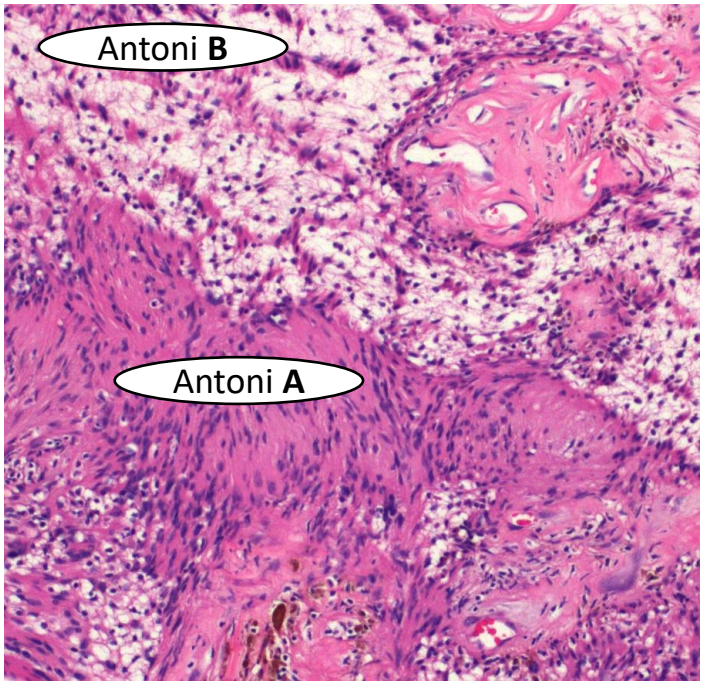
SMARCA4-deficient Thoracic Sarcomas





Malignant. Centered in thorax. **Very aggressive**.
Diffuse sheets of mildly discohesive, relatively monotonous, and undifferentiated epithelioid cells with prominent nucleoli.
IHC: **(+) CD34**, SALL4, (+/-)CK
Molecular: **SMARCA4 mutations** (part of SWI/SNF chromatin remodeling complex, like INI-1)

Schwannoma

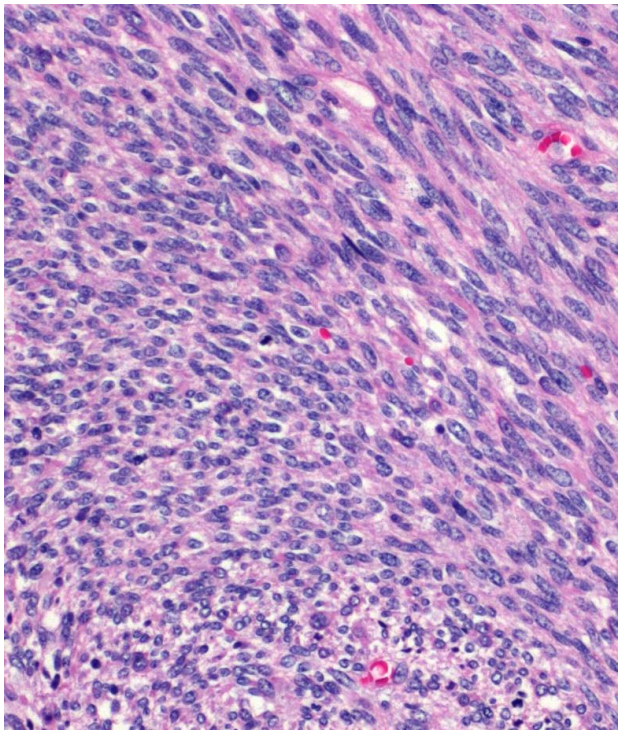


Benign. Often associated with nerve. Usu. adults.
Composed entirely of well-differentiated Schwann cells. Very low risk of transformation.
Usually solitary and sporadic in posterior mediastinum.

Typically encapsulated.
Alternating compact spindle cells (Antoni A) and hypocellular less orderly areas (Antoni B)
Rows of nuclear palisading → Verocay bodies.
Axons not present in lesion→ pushed to periphery.
Hyalinized blood vessels and lymphoid aggregates common.

IHC: Strong, diffuse S100, scattered CD34, moderate calretinin. Neurofilament highlights displaced axons at periphery.

Malignant Peripheral Nerve Sheath Tumor (MPNST)



Malignant. Adults. Frequently in setting of **NF1**.
Often poor prognosis.

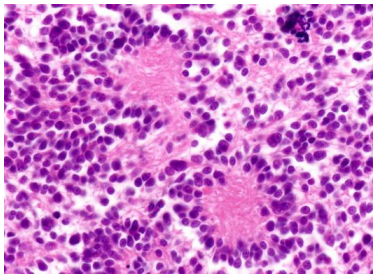
Must arise from a peripheral nerve or pre-existing peripheral nerve sheath tumor or display histologic/IHC evidence of nerve sheath differentiation.

Spindled cells arranged in sweeping fascicles.
Densely cellular areas alternate with less cellular areas giving a "marble-like" effect.
Can have herringbone architecture.
Wavy, buckled nuclei.
Geographic necrosis and/or mitotic activity (often greater than 10/10 HPFs).

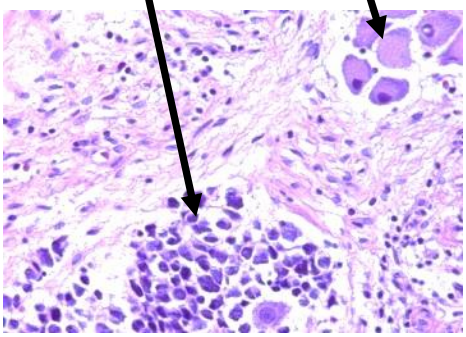
IHC: **Patchy S100 and SOX10.**
Loss of H3K27me3 expression (associated with worse prognosis. Not entirely specific—see with SUZ12 and EED gene inactivation)

Neuroblastoma → Maturing → Ganglioneuroblastoma → Maturing → Ganglioneuroma

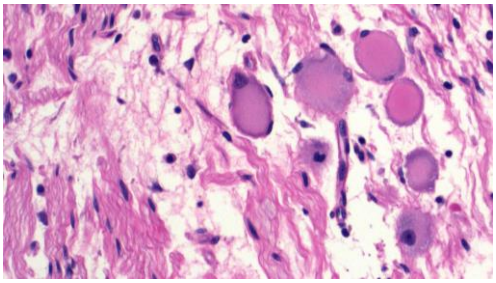
Most **primitive**/aggressive **Malignant**. Vast majority **<5 years** SRBCT +/- rosettes, neurofibrillary matrix



Intermediate differentiation. Malignant. Neuroblastoma + Ganglion cells



Most mature; Benign Ganglion cells set in fibrillary stroma **NO** neuroblastoma



Peripheral neuroblastic tumors derive from the sympathetic nervous system (therefore develop anywhere along the distribution of the sympathoadrenal neuroendocrine system), often in posterior mediastinum.

Stains: Schwann cells (+) S100, Ganglion cells (+) Synaptophysin, neurofilament

Ganglioneuroma: Although some likely represent matured neuroblastoma, it is thought that most are *de novo*. Multiple/diffuse and/or syndrome-related (MEN 2b, Cowden, and NF1) → Ganglioneuromatosis

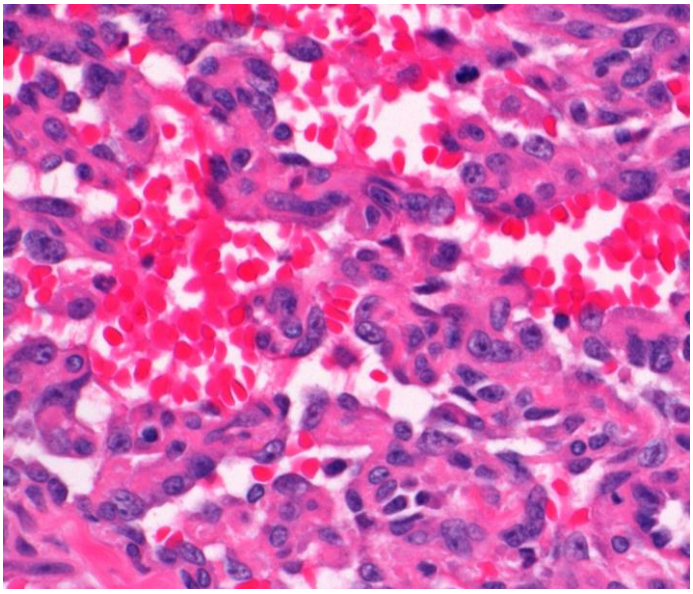
Angiosarcoma

Malignant. Very aggressive. Typically elderly.

Variable degrees of vascular differentiation.
Some areas show well-formed anastomosing vessels, while other areas may show solid sheets of high-grade cells. Can be epithelioid or spindled.
Often extensive hemorrhage.

Unlike benign lesions: significant cytologic atypia, necrosis, endothelial cells piling up, and mitotic figures (although mitoses can be seen in some benign tumors)

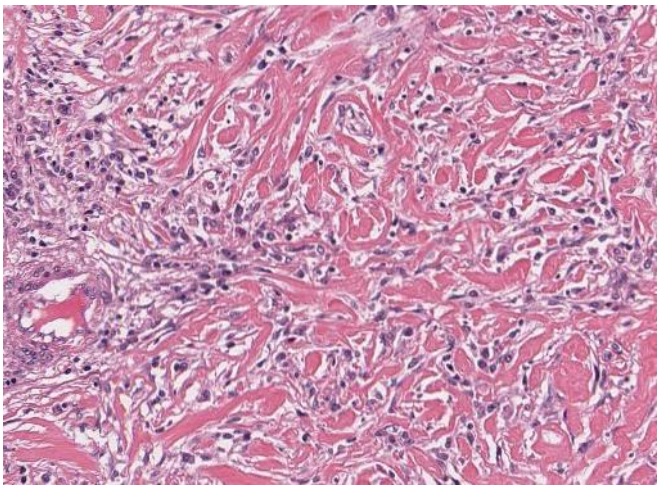
IHC: CD31, ERG, FLI1, often CD34



Sclerosing (fibrosing) Mediastinitis

***Non*-neoplastic fibrosis** of mediastinum compressing and infiltrating normal structures.

Bland spindled cells with lymphoplasmacytic infiltrate
Sometimes dense (keloid-like) collagen.
May see dystrophic calcifications.



May be caused by:
- prior infection/response to **Histoplasma** or TB
- **IgG4-related disease**
- Autoimmune diseases
- Radiation

Thyroid & Parathyroid Tumors

Thyroid Tumors:

Often arise in an *extension* of the thyroid from the neck (as opposed to ectopic thyroid).
Identical appearance, IHC, and behavior to thyroid tumors in the neck (see separate guide).
General IHC:
Tumors derived from follicular epithelium (PTC, follicular carcinoma): (+) TTF1, PAX8, Thyroglobulin, CK
Medullary thyroid carcinoma: (+) TTF1, Synaptophysin, Calcitonin, CK, (-) Thyroglobulin, (+/-) PAX8

Parathyroid Tumors:

Ectopic. Up to 20% of all parathyroid neoplasms are located in the mediastinum (often near/in thymus as share a common origin in 3rd branchial pouch). Often present with hyperparathyroidism and resulting hypercalcemia (kidney stones, bone pain, etc..). Identical appearance, IHC, and behavior (see separate guide). IHC: (+) CK, Synaptophysin, Chromogranin, GATA-3, PTH. (-) TTF1, Thyroglobulin, Calcitonin; (+/-) PAX8

Lymphomas

Classical Hodgkin Lymphoma:
Most common type of primary mediastinal lymphoma! Peak incidence in late adolescence/young adult.
Reed-Sternberg cells (classically large binucleated cells with abundant cytoplasm and prominent nucleoli with perinucleolar clearing) in a background of inflammatory cells. Lacunar RS cells are smaller with hyperlobated nuclei. Often lots of eosinophils.
RS cell IHC: (+) CD30, CD15, MUM1. Characteristic weak PAX5. (-)CD20, CD45
Most common variant: Nodular Sclerosis Classical Hodgkin Lymphoma—cellular nodules separated by dense fibrous bands. Often has lacunar RS cells.

Primary Mediastinal Large B-cell Lymphoma:
Aggressive large B-cell lymphoma arising in the mediastinum. Most often in young adults.
Presents with localized mass in thymic area and minimal associated distant lymphadenopathy.
Diffuse growth of large cells with abundant, often clear, cytoplasm.
IHC: (+) CD19, CD20, CD79a, PAX5.
Requires clinical exclusion of widespread extrathoracic disease as morphology and IHC identical to DLBCL.

T lymphoblastic leukemia/lymphoma:
Use lymphoma term when confined to a mass lesion, Leukemia when there is extensive peripheral blood and bone marrow involvement. Most common in late childhood to early adulthood.
Typically present acutely with symptoms related to a large mediastinal mass such as airway compromise.
Mediastinal disease often centered around thymus, involving nearby lymph nodes too.
Medium-sized cells with scant cytoplasm and fine chromatin. Lots of mitoses.
IHC/Flow: (+)TdT, CD34, CD1a, CD99, CD3,

Germ Cell Tumors with associated Hematologic Malignancy:
Coexisting clonally related mediastinal germ cell tumor and a hematologic malignancy, which can be systemic or localized. Can be any type of heme malignancy, often acute leukemia. Very poor prognosis.

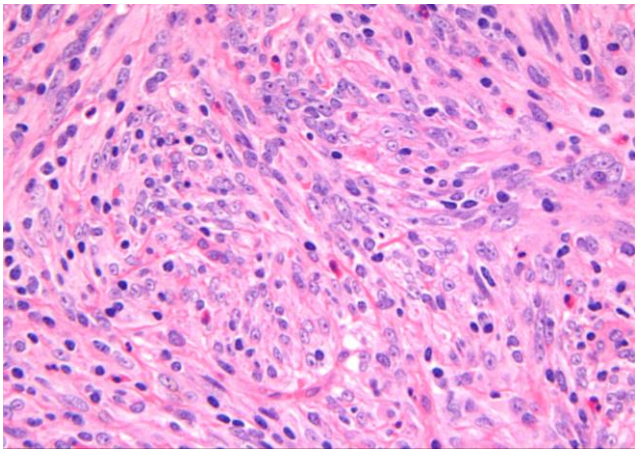
Metastases

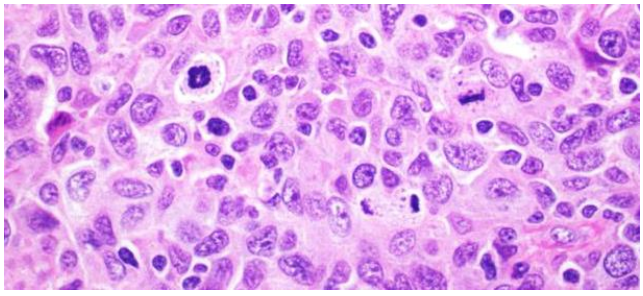
Always a consideration!!

Most common = Lung.
Also consider: Breast, Esophageal, Stomach, etc…

Histiocytic and Dendritic Cell Neoplasms

Follicular Dendritic Cell Sarcoma



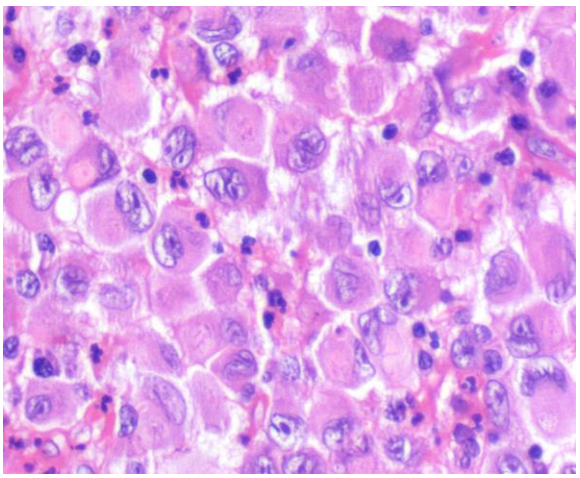


Intermediate-grade malignancy of follicular dendritic cells.
Spindled tumor cells with **indistinct cell borders**, lightly eosinophilic cytoplasm, and associated **lymphocytes**.
Oval vesicular nuclei with small nucleoli.
Variable architecture. Usually only mild pleomorphism.
IHC: **(+) CD21, CD23, D2-40.** Variable, weak CD68 & S100.
Usually localized at time of Dx. Usually **Adults**. **Rare**.
May arise from hyaline-vascular Castleman's disease.
Subset of patients have recurrences or metastases.

Interdigitating dendritic cell sarcoma: Rare. Very similar to FDCS (above), but derived from interdigitating dendritic cells. Plumper cells. IHC: (+) S100, (-)SOX10, CD1a, CD21, CD23, (+/-) CD68, CD45

Fibroblastic reticular cell tumor: Also similar to FDCS (above). IHC: (+) Vimentin, (-) S100, CD21, CD23. (+/-) CK, CD68

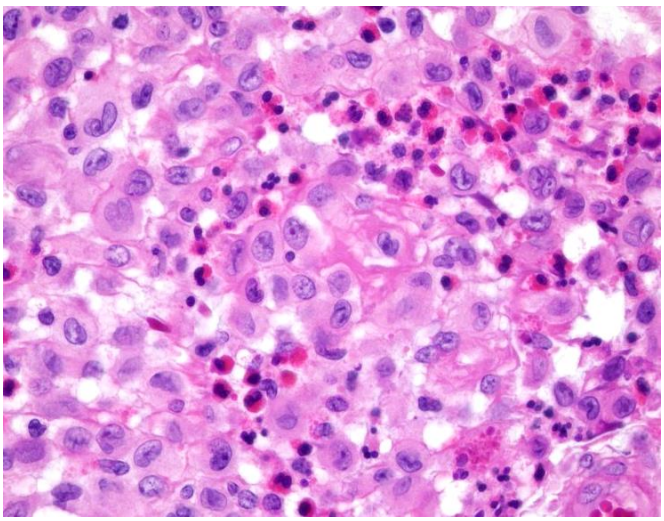
Histiocytic Sarcoma



Rare. Wide age range.
Malignant proliferation of cells with histiocytic differentiation (*excluding* acute monocytic leukemia associated cases).
Large, round, discohesive cells with abundant eosinophilic cytoplasm. Often pleomorphic. Nuclei often eccentric and vesicular.

IHC: **Must express at least one histiocytic marker** (e.g., CD68, CD163, or lysozyme). (-)Langerhans cell, myeloid, and follicular dendritic cell markers (in addition to epithelial and melanocytic)

Langerhans Cell Histiocytosis



Neoplastic proliferation of Langerhans cells.
Discohesive cells with **grooved/contorted nuclei**, fine chromatin, and eosinophilic cytoplasm.
Often admixed **eosinophils** and multinucleated giant cells.

IHC: **(+)S100, CD1a, Langerin** (CD207)
Molecular: Frequent **BRAF V600E**
Electron Microscopy: Birbeck granules

Overtly malignant cytology→ **Langerhans cell *Sarcoma***