

AMSER Rad Path Case of the Month:

22-year-old with chest pain and mediastinal mass

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Patient Presentation

- **HPI:**
 - 22-year-old male with history of dural venous thrombosis currently on chronic coumadin therapy.
 - Presents to PCP for chronic pain management, reports a 3-day history of chest pain & tachycardic in 140s.
 - Sharp chest pain with radiation down left arm, worse with inspiration/when supine.
 - Associated palpitations.
 - Denies: SOB, N/V, diaphoresis, LE edema/pain, abdominal pain, changes in bowel/bladder habits.
- **PMHx:**
 - Atypical hemolytic uremic syndrome with positive MCP/CD46 mutation.
 - Dural venous sinus thrombosis, intracranial hemorrhage, seizures.
 - SLE
 - Secondary HTN
- **Medications:**
 - Warfarin, gabapentin, hydroxychloroquine, levetiracetam, mycophenolate mofetil.

Pertinent VS, PE and Labs

VS: BP 174/122 HR 137 RR 24 O2 97%. temp 37 C

PE:

- Gen: no acute distress, AOX4
- HEENT: nl
- CV: no murmurs, nl perfusion, no edema, regular rhythm, tachycardic
- Pulm: CTAB, non-labored respirations, equal and clear breath sounds
- Chest wall: no tenderness
- MSK: no swelling or deformities, tender to palpation over L shoulder

Labs:

- CRP 10.8 (H), repeat 10 (H)
- Cr 1.3 (pt's baseline)
- Troponin 5.78 (H), repeat 5.7 (H)
- WBC 12, plt 280

Other pertinent history:

- last check for Coumadin was therapeutic at 2
- Renal function at baseline
- No history of PE or DVTs

What Imaging Should We Order?

**American College of Radiology
ACR Appropriateness Criteria®
Acute Nonspecific Chest Pain-Low Probability of Coronary Artery Disease**

Variant 1: Acute nonspecific chest pain; low probability of coronary artery disease. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☼
CTA coronary arteries with IV contrast	Usually Appropriate	☼☼☼☼
US echocardiography transthoracic resting	May Be Appropriate (Disagreement)	○
Radiography ribs and thoracic spine	May Be Appropriate	☼☼
CT chest with IV contrast	May Be Appropriate	☼☼☼☼
CT chest without and with IV contrast	May Be Appropriate	☼☼☼☼
CT chest without IV contrast	May Be Appropriate	☼☼☼☼
CTA chest with IV contrast	May Be Appropriate	☼☼☼☼
V/Q scan lung	May Be Appropriate	☼☼☼☼
US echocardiography transesophageal	Usually Not Appropriate	○
US echocardiography transthoracic stress	Usually Not Appropriate	○
Arteriography coronary	Usually Not Appropriate	☼☼☼☼
Fluoroscopy barium swallow and upper GI series	Usually Not Appropriate	☼☼☼☼
MRA chest without and with IV contrast	Usually Not Appropriate	○
MRA chest without IV contrast	Usually Not Appropriate	○
MRA coronary arteries without and with IV contrast	Usually Not Appropriate	○
MRA coronary arteries without IV contrast	Usually Not Appropriate	○
MRI heart function and morphology without and with IV contrast	Usually Not Appropriate	○
MRI heart function and morphology without IV contrast	Usually Not Appropriate	○
MRI heart with function and inotropic stress without and with IV contrast	Usually Not Appropriate	○
MRI heart with function and inotropic stress without IV contrast	Usually Not Appropriate	○
MRI heart with function and vasodilator stress perfusion without and with IV contrast	Usually Not Appropriate	○
Nuclear medicine scan gallbladder	Usually Not Appropriate	☼☼
CT heart function and morphology with IV contrast	Usually Not Appropriate	☼☼☼☼☼
SPECT or SPECT/CT MPI rest and stress	Usually Not Appropriate	☼☼☼☼☼

← Chest XR PA + lateral xray performed day 1

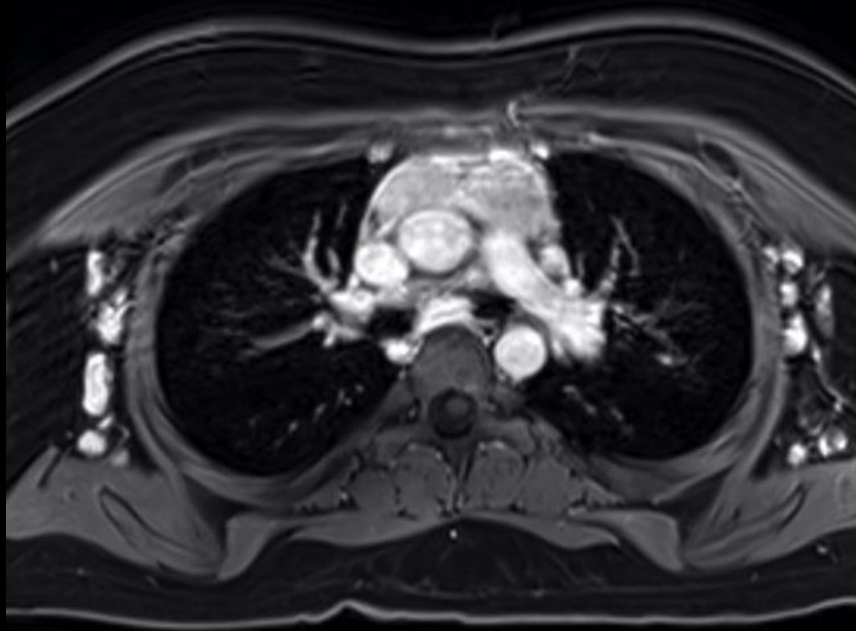
← CT chest w/ contrast performed day 4

← Cardiac MRI w/o & w/ contrast performed day 2

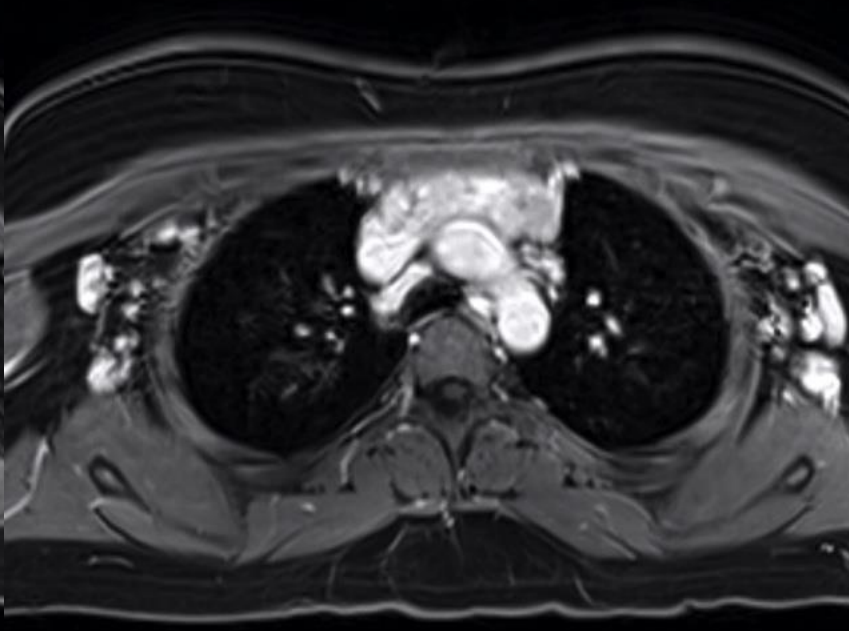


Cardiac MRI Findings: Unlabeled

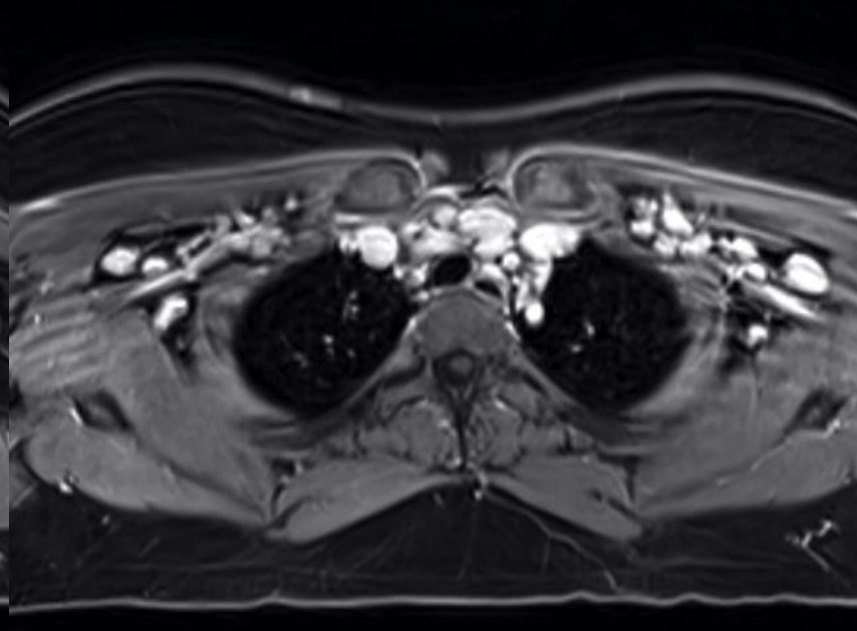
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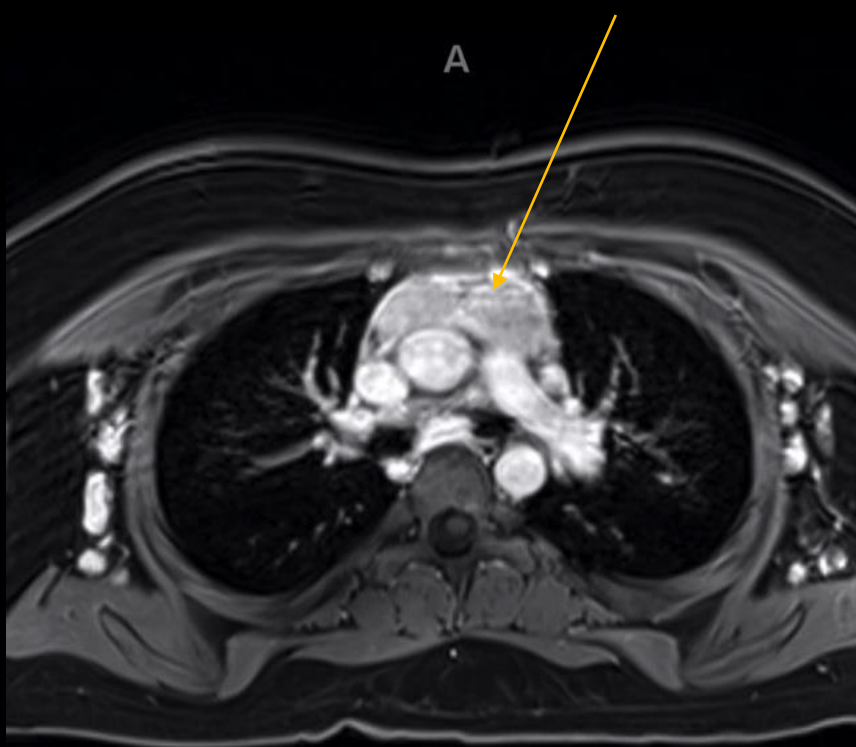
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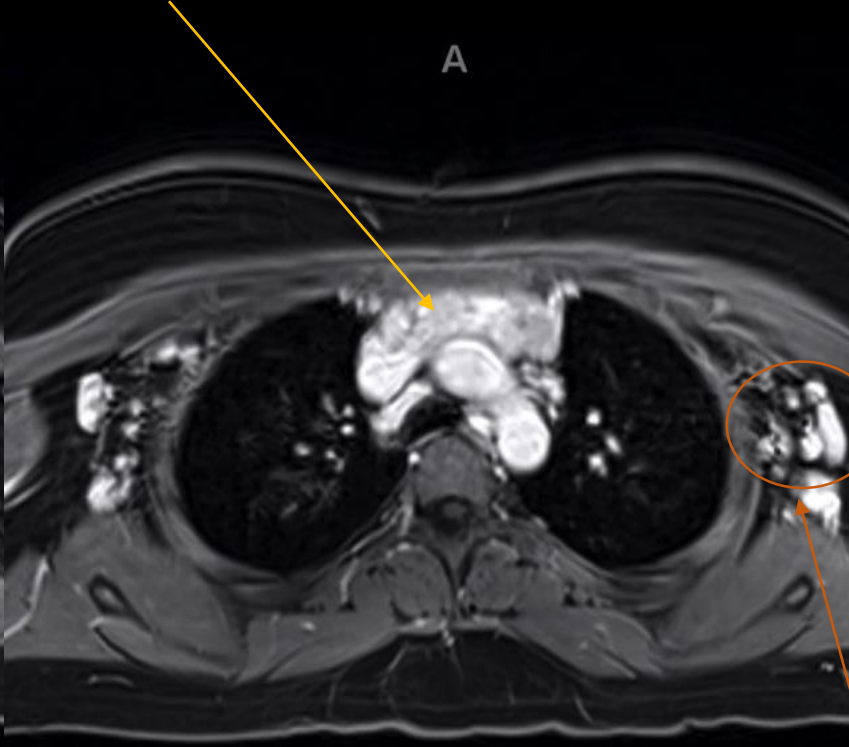
Cardiac MRI Findings: Labeled

Suspected anterior mediastinal mass demonstrating diffuse and patchy enhancement

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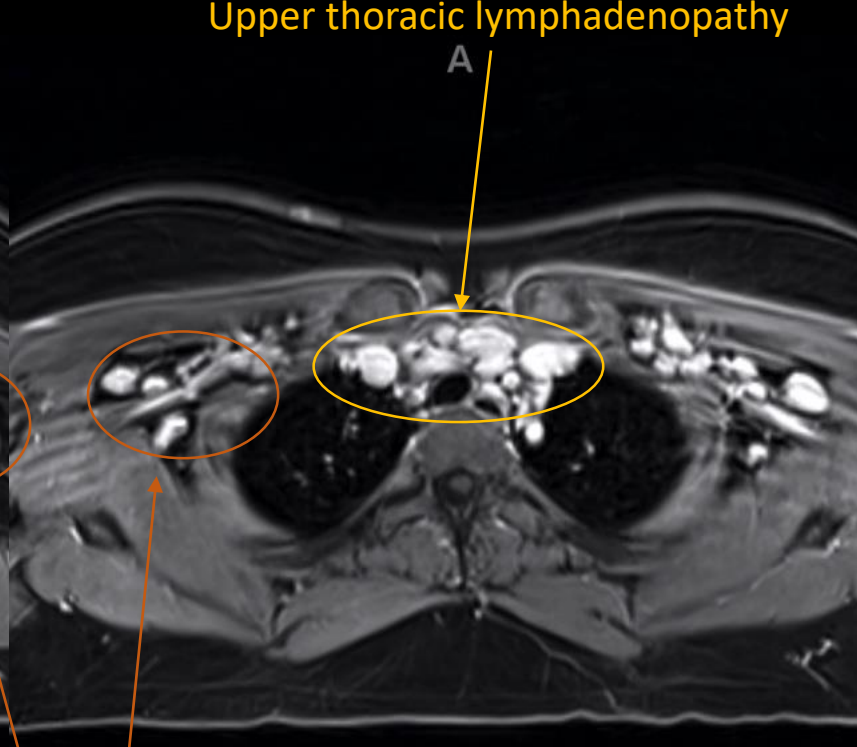


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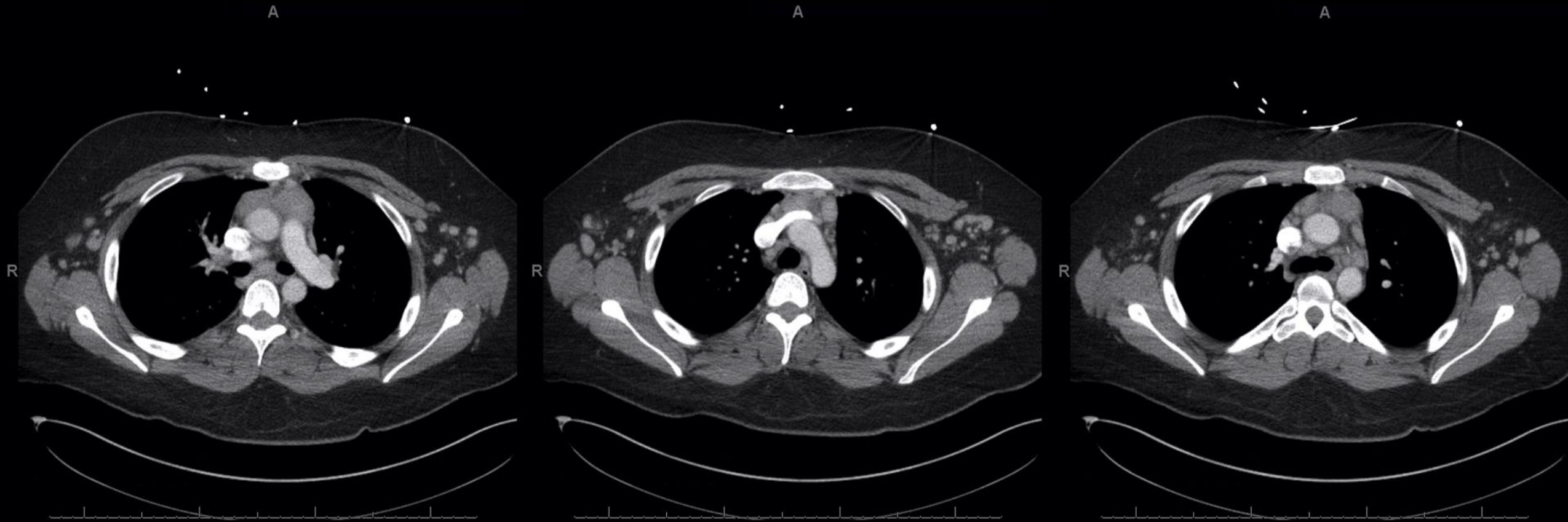
Upper thoracic lymphadenopathy

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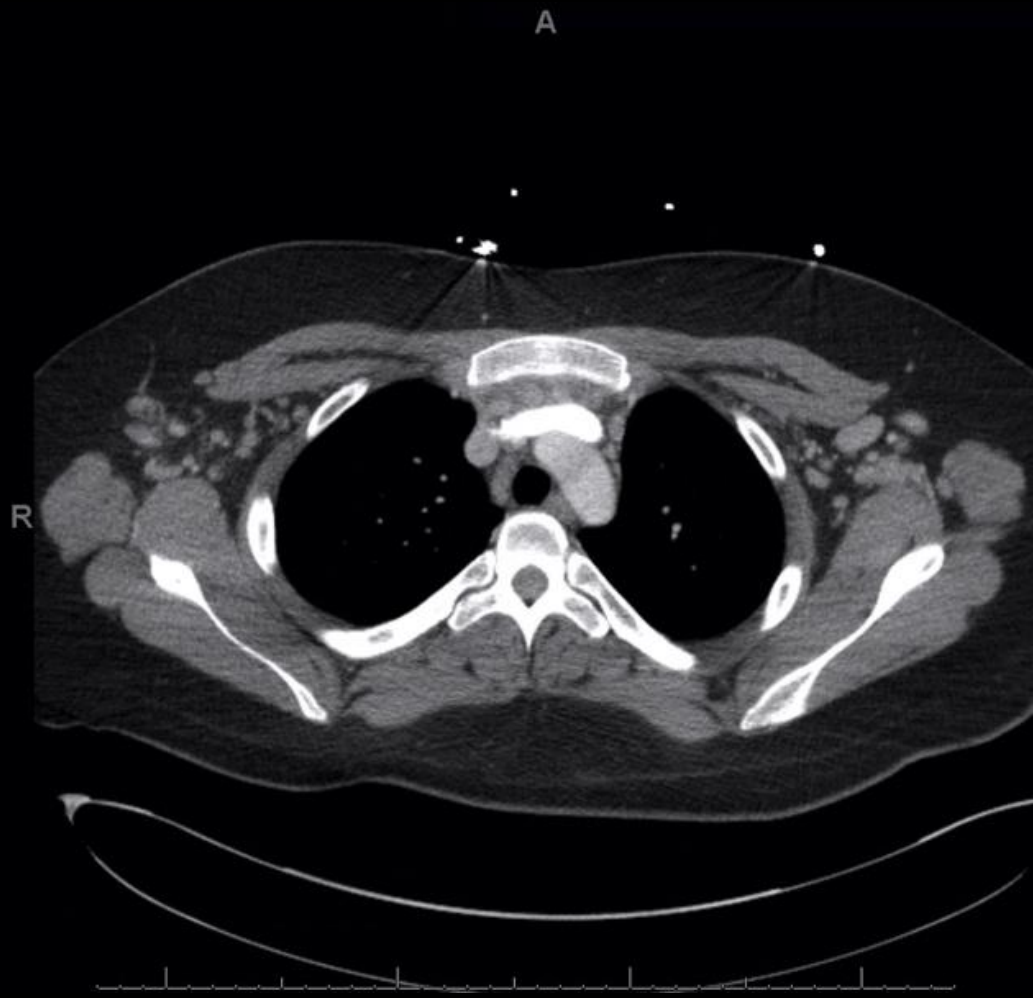


Axillary lymphadenopathy

CT Chest Findings part 1: Unlabeled

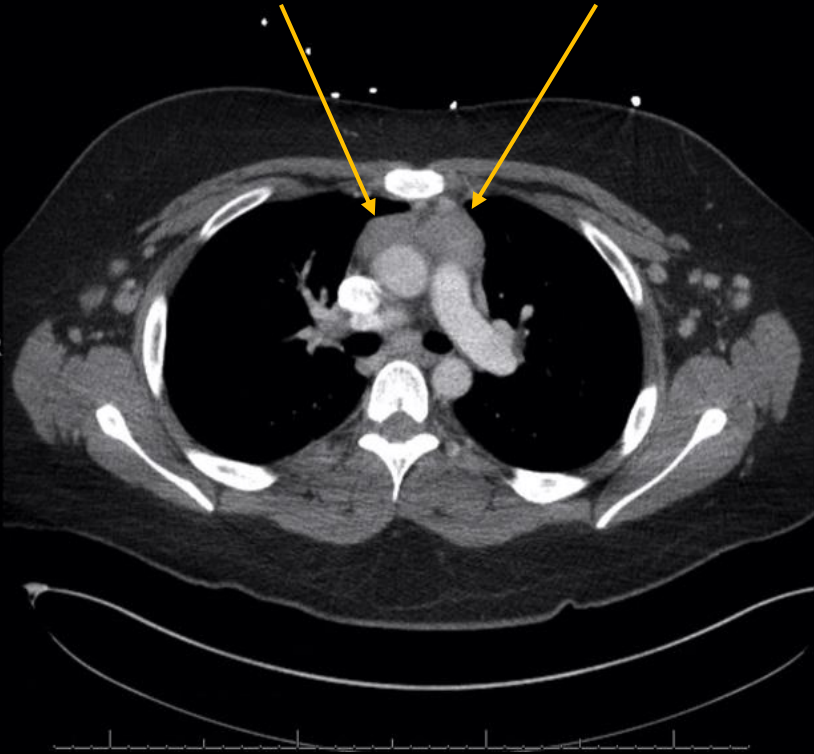


CT Chest Findings part 2: Unlabeled

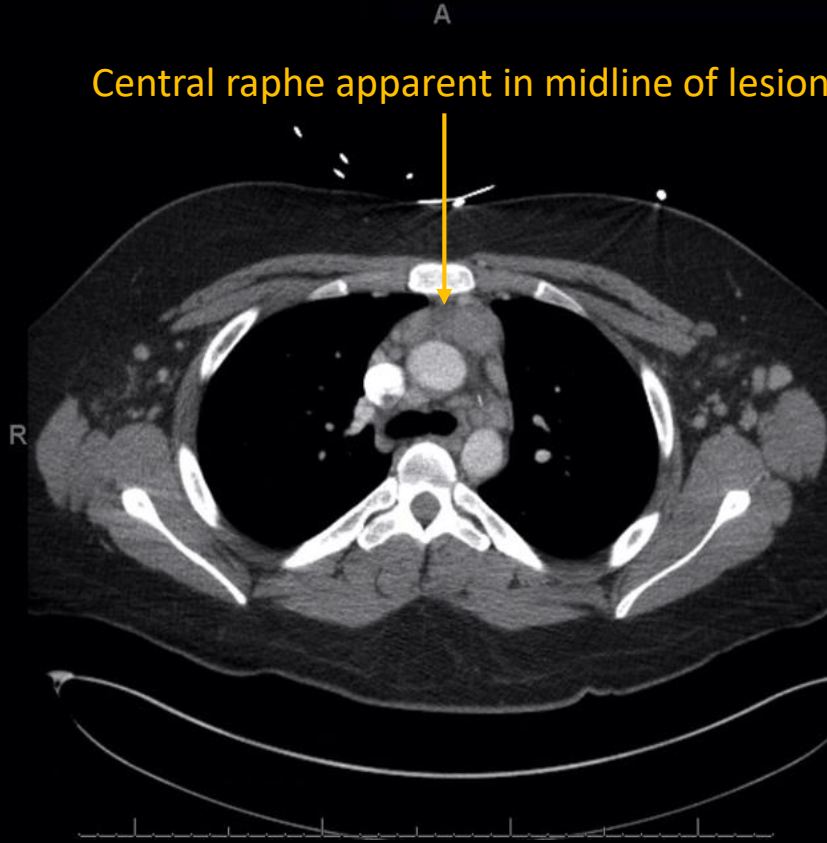


CT Chest part 1: Labeled

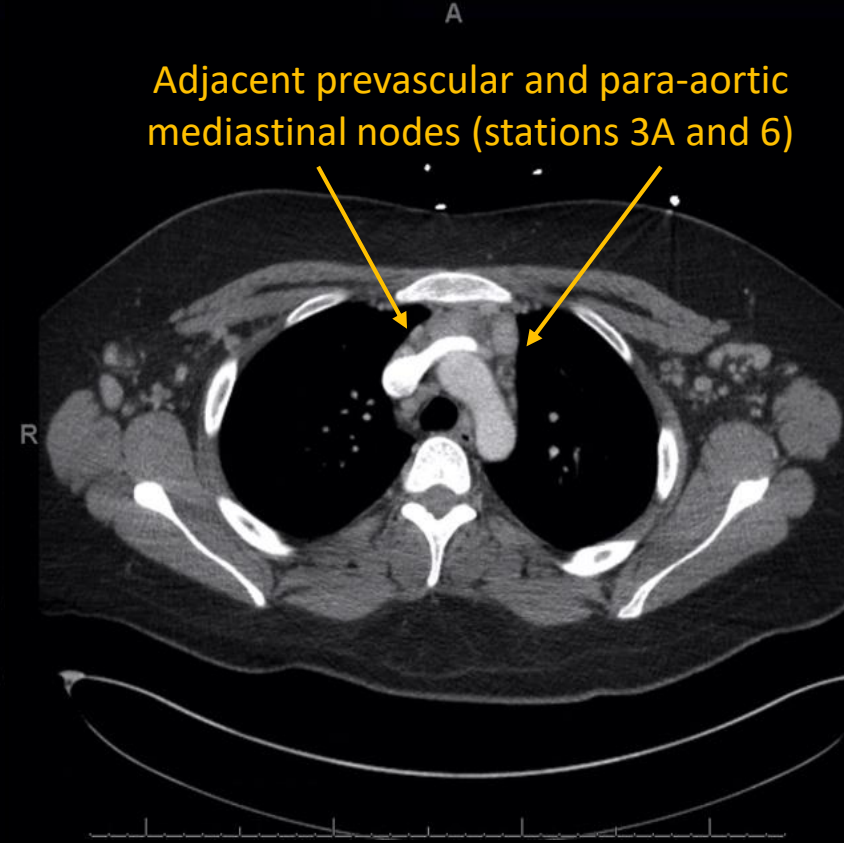
Bilobed enhancing soft tissue lesion in superior mediastinum



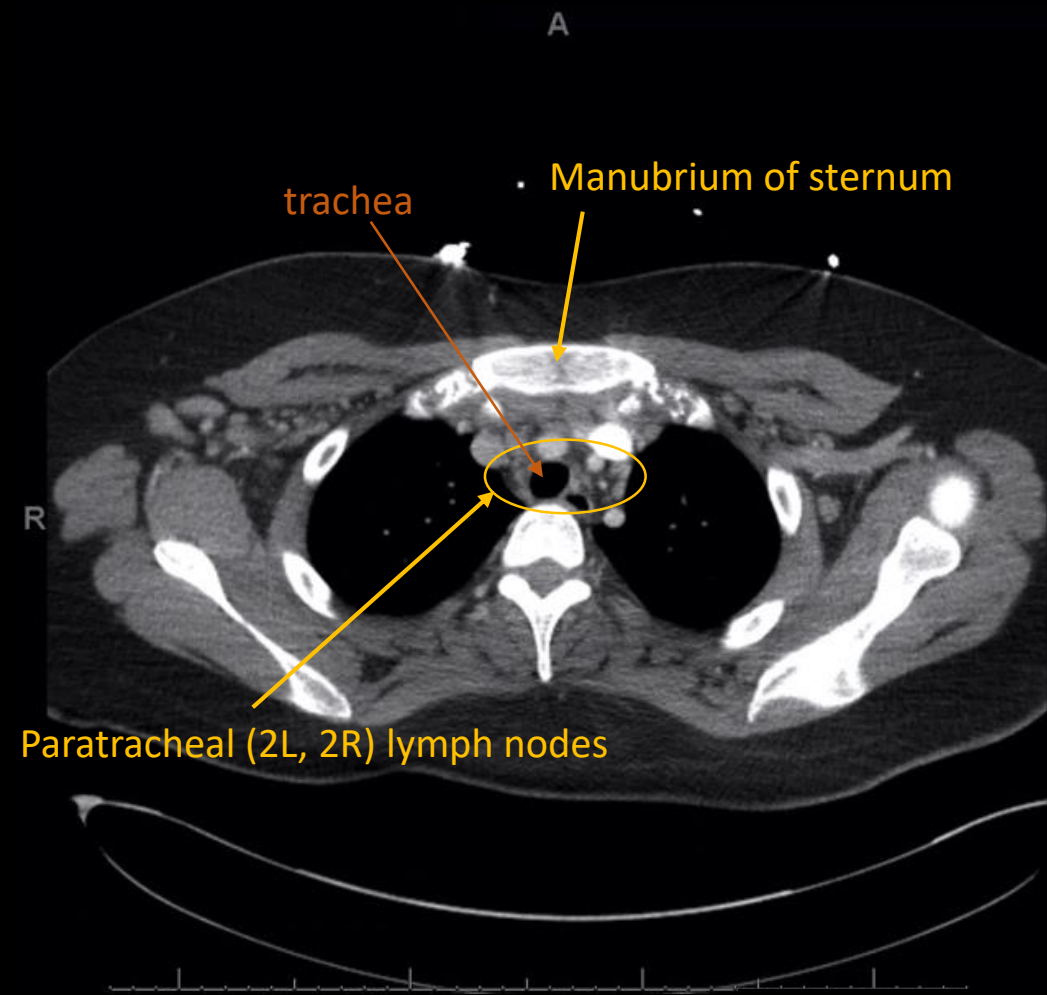
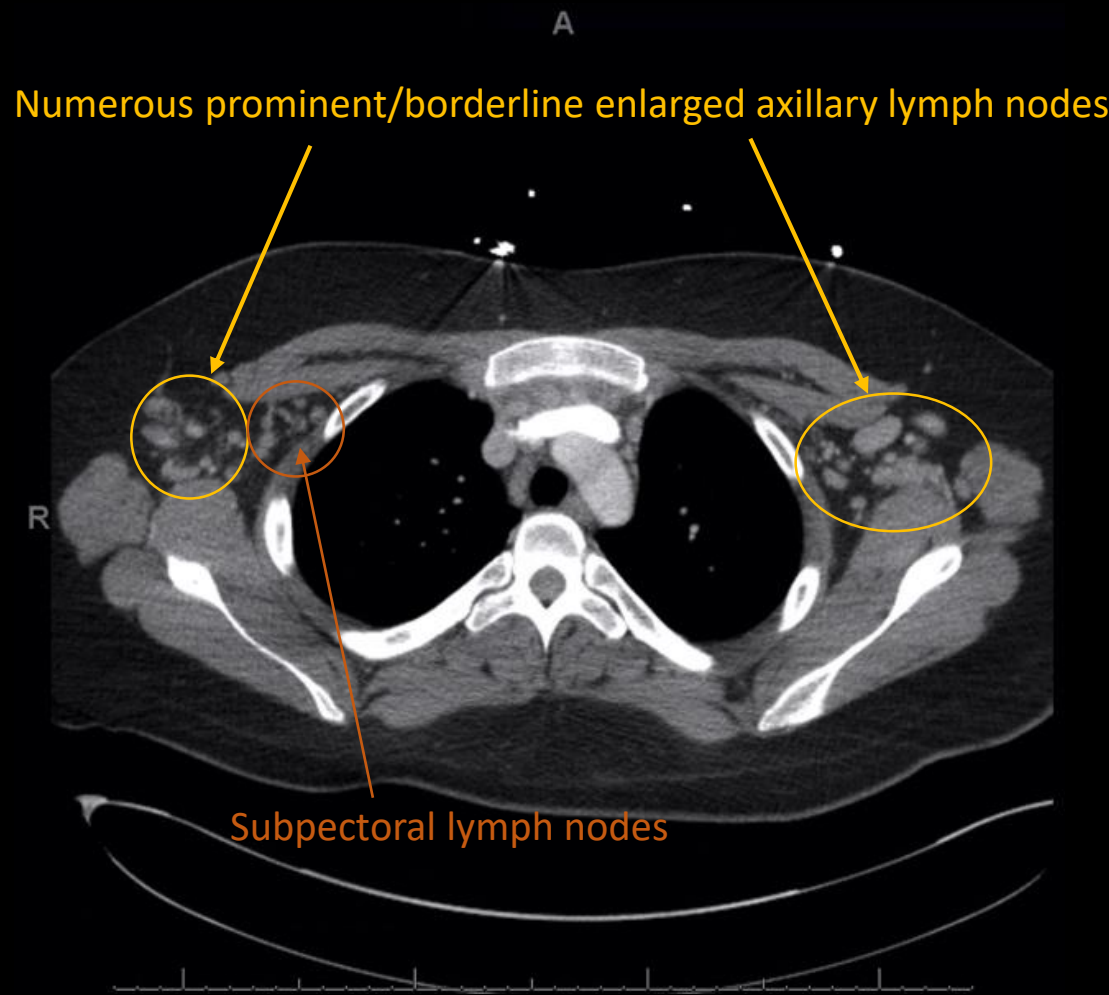
Central raphe apparent in midline of lesion



Adjacent prevascular and para-aortic mediastinal nodes (stations 3A and 6)



CT Chest Findings part 2: Labeled



*Patient subsequently underwent left video-assisted thoracoscopic surgery (VATS) with biopsy of mediastinal mass.

DDX

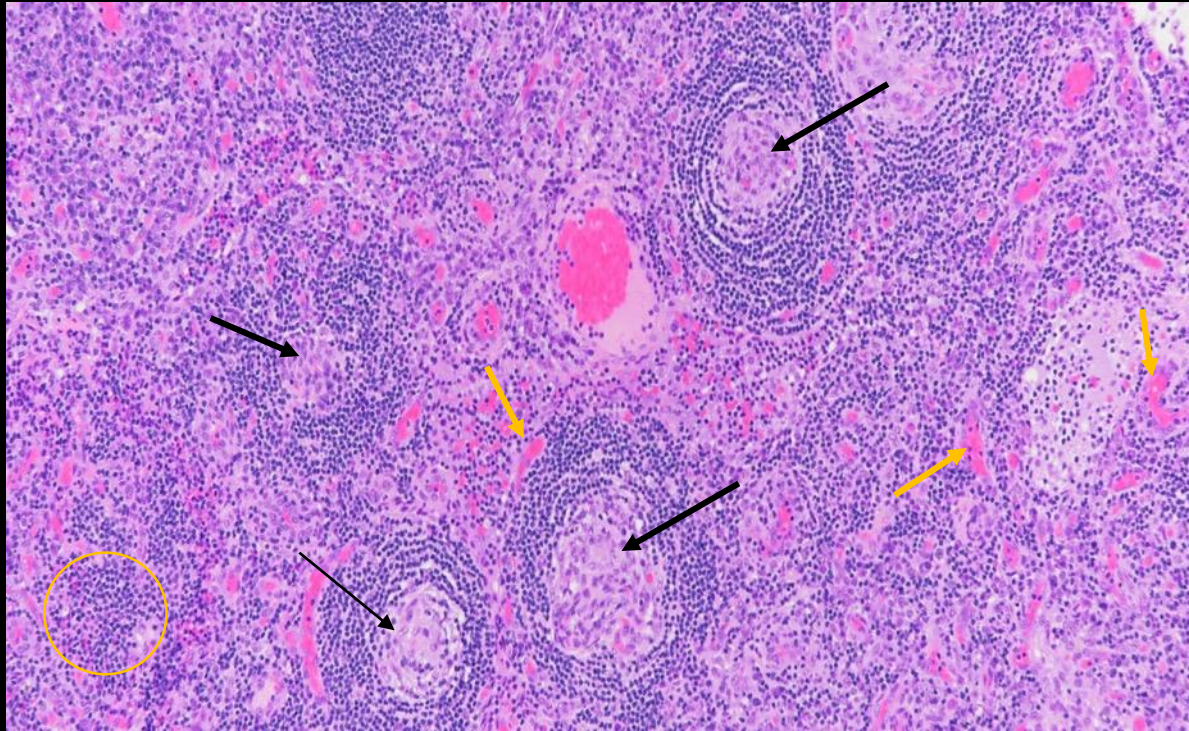
Mediastinal mass:

- Prominent thymus
- Thymic hyperplasia
- Other thymic-based lesions

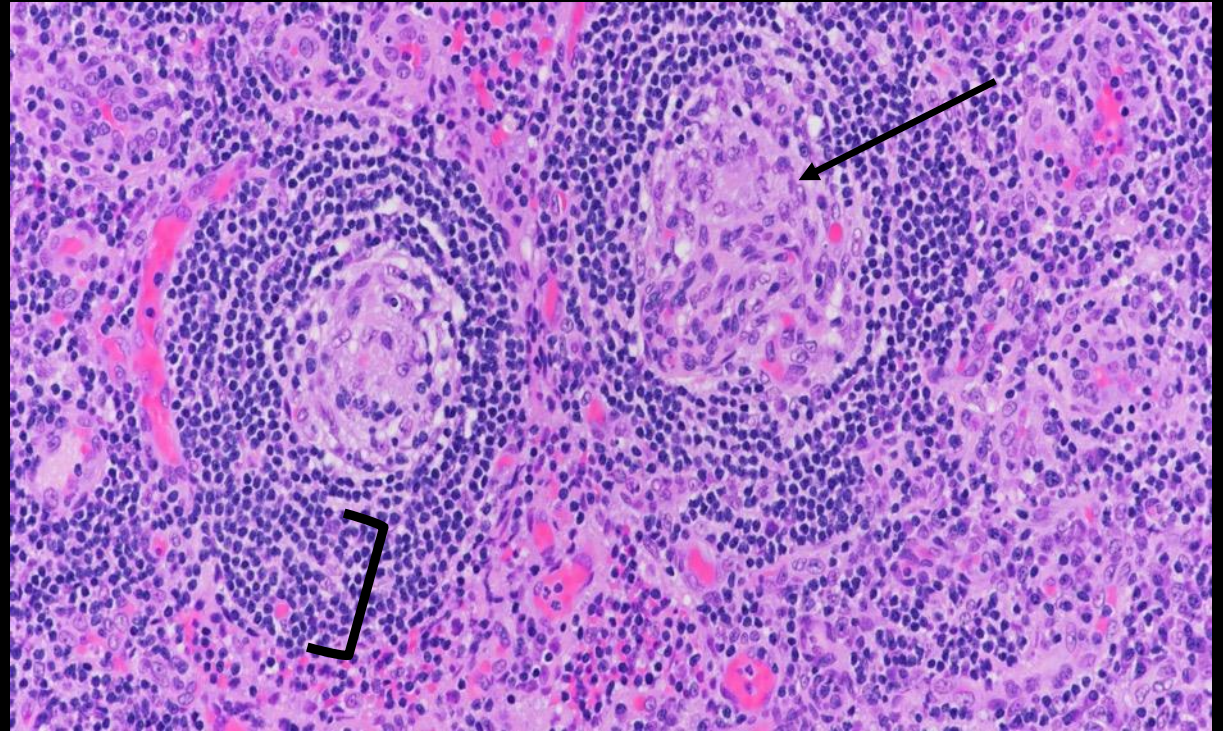
Diffuse lymphadenopathy:

- Reactive lymphadenopathy
- Connective tissue disorder
- Lymphoma
- Infection such as HIV

Histopathology H&E

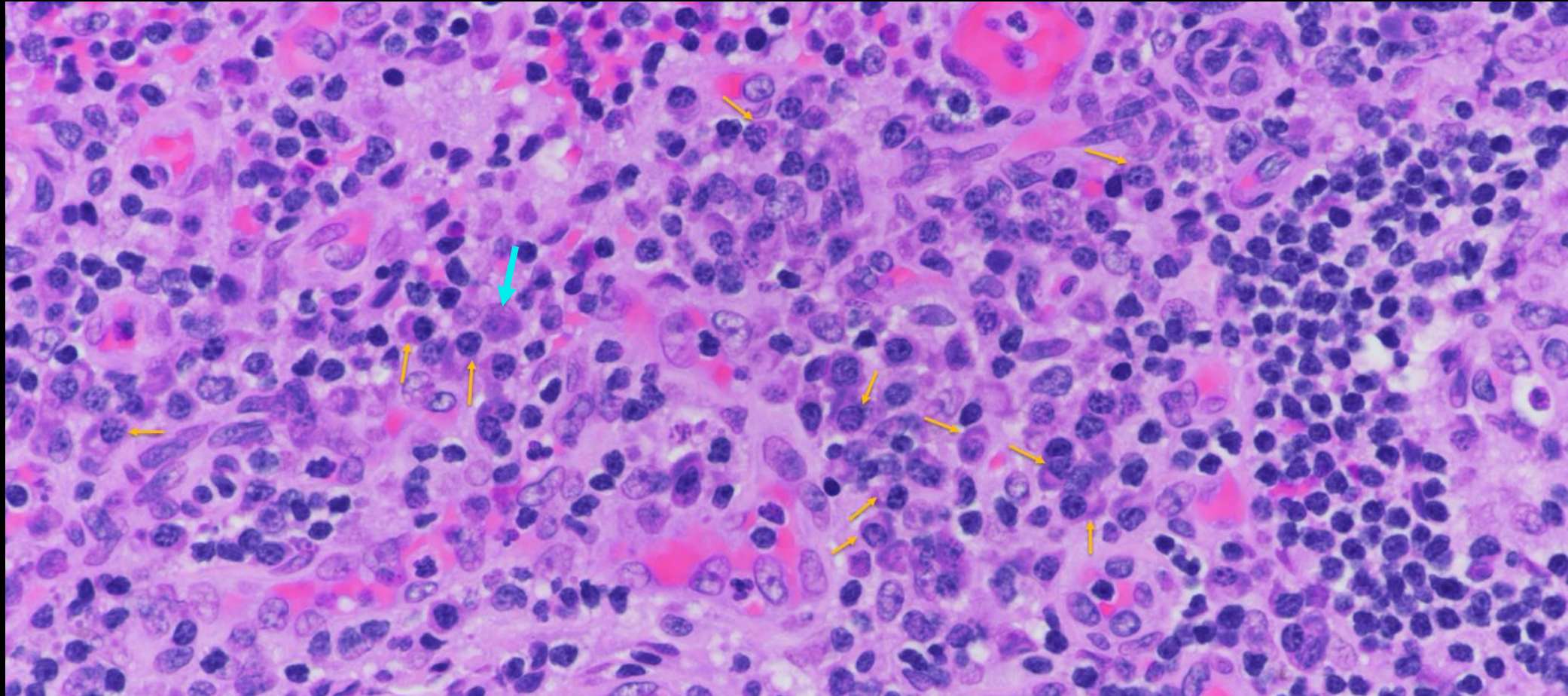


Enlarged lymph nodes with **numerous follicles** (black arrows) throughout the cortex and medulla. Expansion of interfollicular areas with **sheets of plasma cells** (yellow circle) and **proliferation of blood vessels** (yellow arrows).



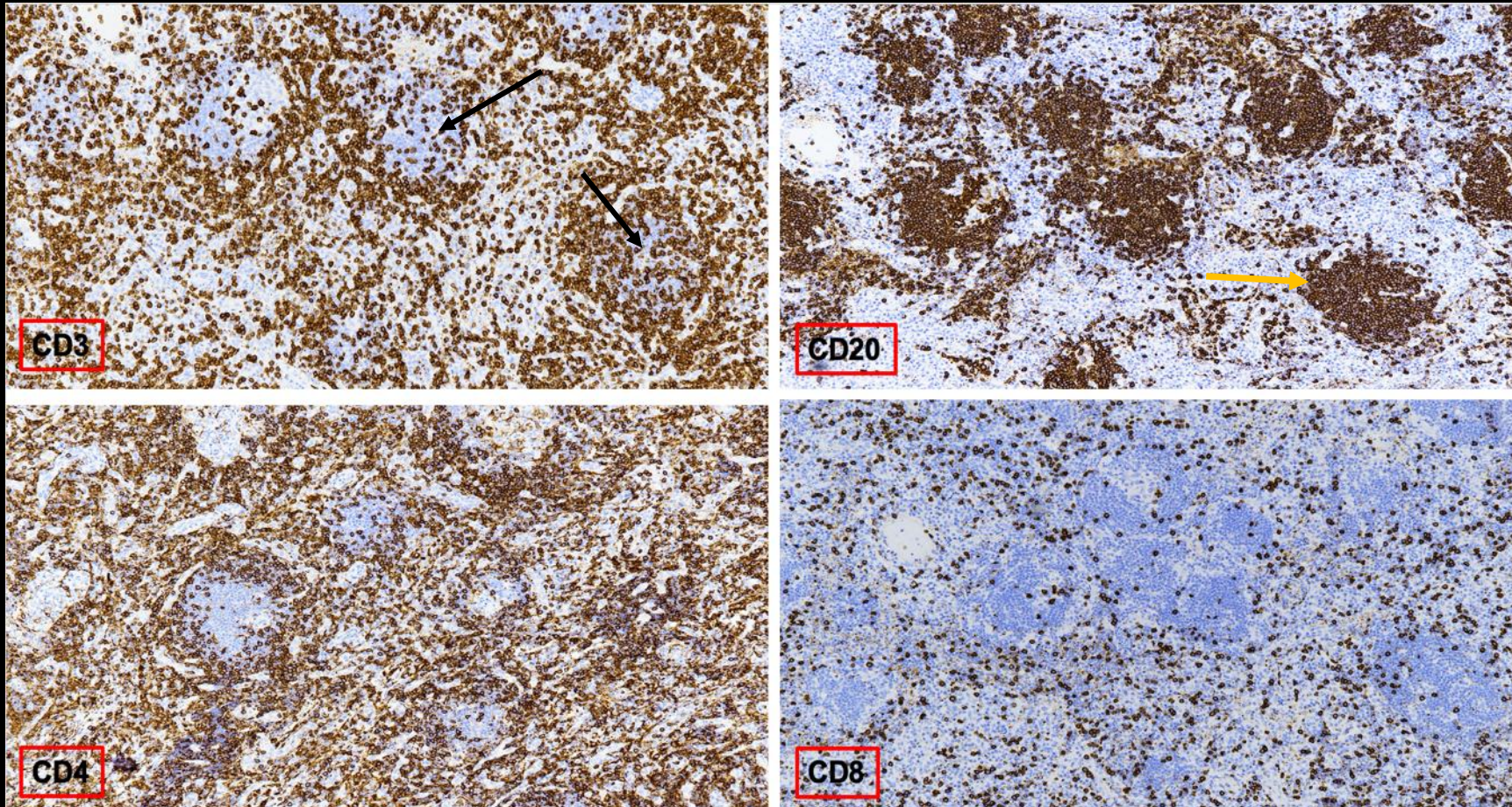
High power view of reactive-appearing follicle (black arrow). Mantle zone comprised of **concentric rings** (bracket) of **small lymphocytes** ("onion skin")

Histopathology cont. H&E



Interfollicular areas/medulla occupied by numerous mature plasma cells with eccentric nuclei and prominent Golgi (yellow arrows) with occasional binucleate forms (blue arrow).

Immunostaining



- Brown-black color in cell membranes indicative of positive staining (immunoperoxidase reaction positive).
- Light blue is Hematoxylin counterstain (immunoperoxidase reaction negative).

CD3: T-cells present around and between atrophic follicles (black arrows)

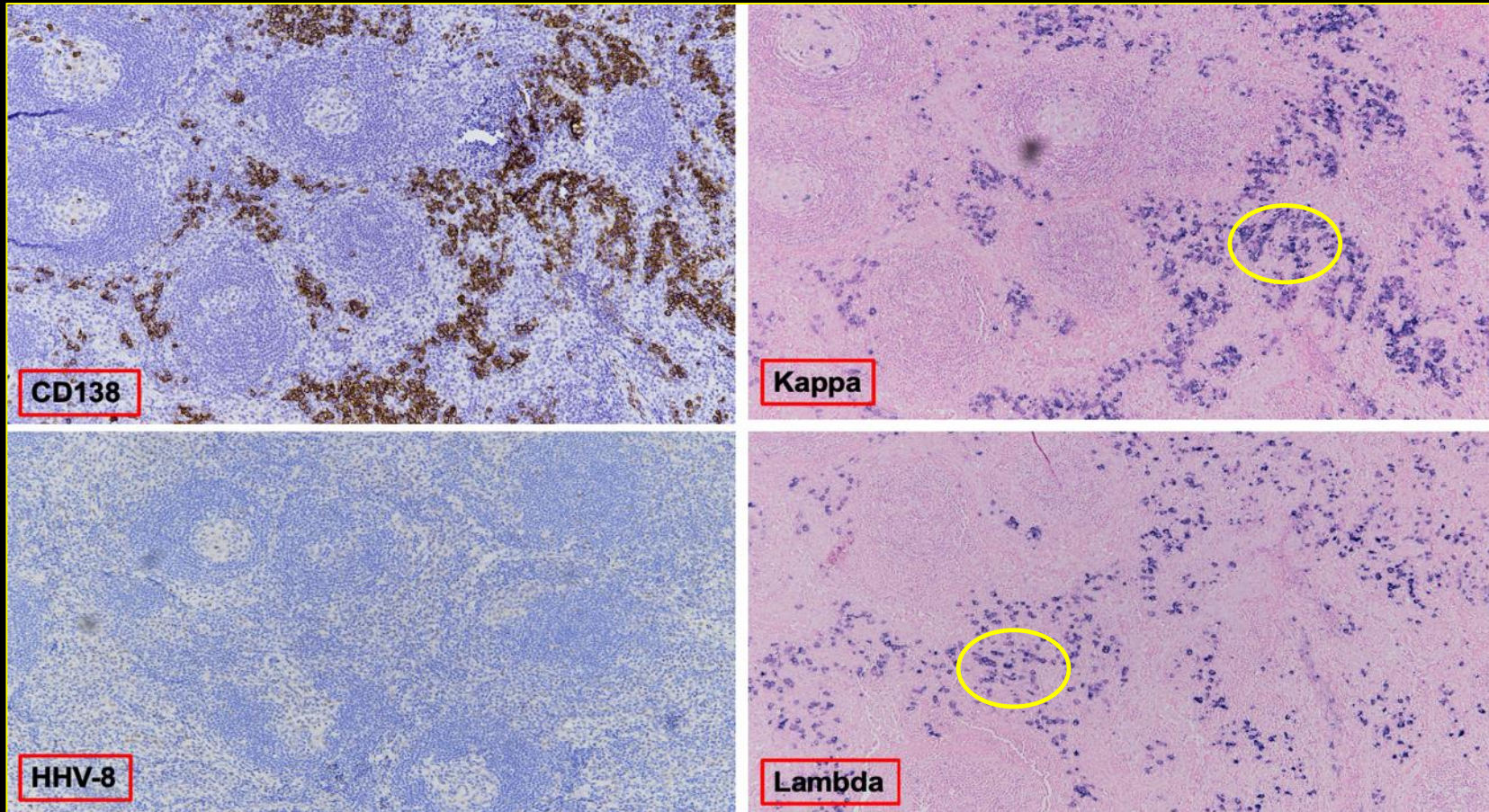
CD4: Helper T-cells*

CD20: atrophic B-cell follicles (yellow arrow)

CD8: Suppressor/cytotoxic T-cells*

*brown immunostaining denotes positivity for these elements)

Immunostaining cont.



- Plasma cells are polyclonal (normal kappa/lambda ratio with about 2x as many kappa+ plasma cells compared to lambda+ plasma cells).

CD138: stain showing plasma cells*
HHV-8: negative

Kappa/lambda light chains (yellow circles) by in situ hybridization (purple staining positive)

*brown immunostaining denotes positivity for these elements

Final diagnosis:

Castleman disease: HHV-8 positive plasma cell variant

Case Discussion: Castleman disease

- What is it?
 - A nonclonal lymphoproliferative disorder and cause of nonneoplastic lymphadenopathy.
- Disease manifestation:
 - Diverse and able to affect any body region (neck, chest, abdomen, pelvis).
 - Can mimic malignant or benign pathologies.
- Variants:
 - Hyaline vascular type (classic) – more likely to be unicentric disease (UCD) & commonly found in mediastinum (**enhancing mass** that displaces surrounding structures).
 - **Plasma cell variant** (less common) – more likely to be multicentric, a systemic disease that manifests as enhancing diffuse lymphadenopathy.
 - **Castleman's associated with HHV-8** – often multicentric disease (MCD).

Case Discussion cont.

- Pathophysiology:
 - MCD likely attributed to deregulation of inflammatory mediators, particularly IL-6 (driven by HHV-8 in some cases)
 - Resulting in systemic manifestation of disease due to lymphovascular proliferation
 - IL-6 is a cytokine produced by T/B-cells, monocytes, endothelial cells and fibroblasts.
 - HHV-8/Kaposi's sarcoma-associated herpesvirus (KSHV) is a lymphotropic virus, and nearly all HIV-associated CD are HHV-8 positive.
 - KSHV encodes for proteins implicated in cell cycle regulation, apoptosis and cytokine signaling.

Case Discussion cont.

Proposed model of CD pathophysiology with the involvement of different mechanisms.

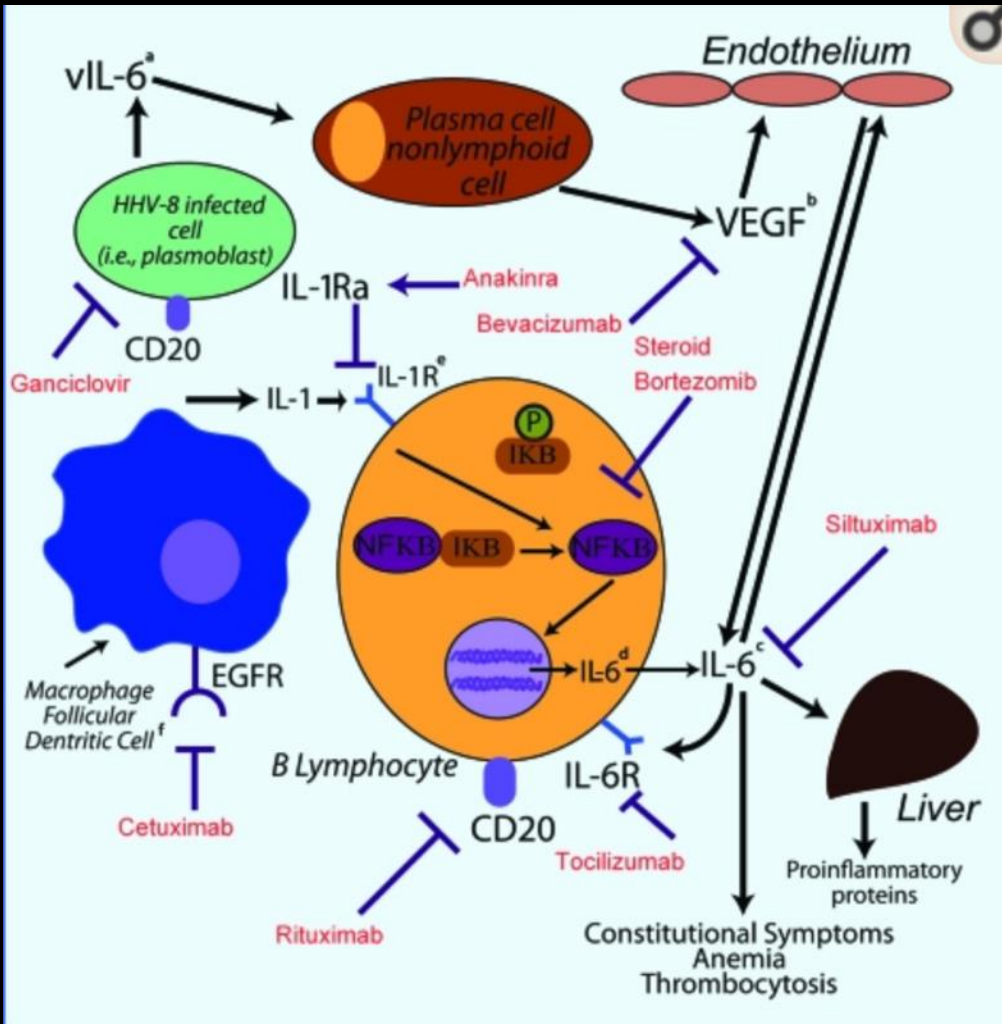


Figure referenced from: El-Osta HE, Kurzrock R. Castleman's disease: from basic mechanisms to molecular therapeutics. *Oncologist*. 2011;16(4):497-511.

HHV-8 infected cells secrete IL-6
 ↓
 Production of VEGF by nonlymphoid or plasma cell
 ↓
 VEGF-induced lymphoid and vascular proliferation

Case Discussion: Castleman disease

Treatment:

- Standard for UCD is surgical resection (excellent prognosis with complete excision).
- Radiation therapy good secondary option.
- **Primary for MCD HHV-8+ is Rituximab.**

Clinical Features

- Dependent on uni vs. multicentric, subtype (hyaline vascular vs. plasma cell), coexisting infx (HHV-8 and/or HIV), other associated disorders.
- Common: systemic sx's (fever, weight loss), **lymphadenopathy, organomegaly, renal dysfunction, pulmonary edema.**

Entity	Primary Treatment	Additional Treatment Options	Additional Considerations
UCD	Surgical excision (13,93)	Radiation if patient is not surgical candidate (94) Neoadjuvant rituximab if lesion too large at time of diagnosis (54,95)	Preoperative embolization of large feeding vessels may be performed before surgery (96)
MCD (HHV8 positive)	Rituximab (monoclonal antibody that binds to CD20 antigen and decreases exogenous production of IL-6 by HHV8 virus) (97-101)	Antiherpesvirus medications (zidovudine, valacyclovir) (102-104) Single-agent chemotherapy (etoposide) (104) Interferon- α (105) Multiagent chemotherapy (ie, CHOP or CVP) often used in cases of rapid progression (11)	Rituximab can exacerbate Kaposi sarcoma (92) Coexistent HIV infection should be adequately managed (100,105) Rituximab leads to 11-fold decrease in lymphoma development in this population (106)
MCD (HHV8 negative)	Siltuximab (monoclonal antibody that binds endogenous IL-6, which drives lesion growth in this population) (54,107-109)	Thalidomide (54,110) Steroids (dexamethasone, prednisolone) (54,111) Bortezomib (proteasome inhibitor that decreases VEGF and IL-6 levels) (112,113) Tocilizumab (IL-6 receptor antagonist) (111) Rituximab (11,97,107) Multiagent chemotherapy (113)	Siltuximab is only FDA-approved immunomodulator for treatment of MCD (108) Rituximab less effective in this population since it is predominantly effective against exogenous IL-6 created by HHV8 virus
MCD (POEMS syndrome)	High-dose immunosuppressive agents and steroids (114)	Autologous peripheral blood stem cell transplantation (54) Bortezomib (115) Thalidomide (114) Lenalidomide (54CkyMschka11)	...

References

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