Cross Canada Rounds

March 17, 2016

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Alberta Children's Hospital

- Consent was obtained from the family for case presentation
- There are no disclosures relevant to this presentation

Case Presentation

- 8 year old female
  - Immigrated from Eastern Europe 2 months prior to presentation
- Referred to ACH Emergency for assessment of clubbing and cyanosis

History

- 4 year history of progressive SOB with exertion
  - Exercise limitation relative to peers
  - Breaks after 10-20 min of activity
  - Peripheral and central cyanosis with activity
  - Would stop activity and "squat" during activity
- Less energy than peers since 4 yrs of age
- Hepatomegaly noted since 5 yrs of age

Past Medical History

- Term infant, normal perinatal course
- Admitted at 2 yrs transient synovitis
- Pneumonia at 2 yrs of age → PICU (Europe)
  - No intubation
- Treated for latent TB
- Poor concentration and headache
  - No improvement with stimulant

- Nasal surgery for "excess tissue"

- No regular medications
- No known allergies
- Completed primary immunization series (Europe)
  - BCG vaccine at birth and 5 yrs
- FmHx:
  - Father with joint pain with activity
  - Maternal GM Thyroid dysfunction, arthritis

Pertinent Findings on ROS

- Complaints of vague abdominal pain
- No cough, URTI, wheeze
  - URTI ~ 2x/yr
- Occasional epistaxis
- No fevers, weight loss, night sweats
- No animal exposures
- No TB exposures

Physical Exam

- RR: 18, Oxygen Saturations 86-88% on RA
  - Increase to 90-92% on 3L/min via nasal prongs
- Anthropometrics: 97th centile for ht and wt
- Friable Little's area
- Clear, equal breath sounds bilaterally, no adventitial sounds, no increased WOB
- Normal S1/S2, no murm. Pulse strong. CR < 2s
- Significant clubbing, perioral cyanosis
- Abdo and Neuro: Benign, uncooperative, immature

What is your differential?

What is your differential?

- Low inspired Partial pressure of Oxygen
- Hypoventilation
- Shunt
  - Arteriovenous malformation
  - Cardiac (right to left shunt)
- V/Q mismatch
  - Congenital malformations
  - Swyer-James Syndrome
- Diffusion
  - Fibrosis
  - Interstitial lung disease
  - Hemoglobinopathy

Ali S, *Kendig's*, 2012
Ochs, *Kendig's*, 2012

What investigations would you like?

Previous Investigations

- Positive TST x 2 (4 and 6 yrs of age)
  - CXR not consistent with TB disease
  - Rx with Isoniazid x 6 months

- CBC
  - Hgb 162
  - Plt 168
  - WBC 9.5

Previous Imaging

- Echo
  - No congenital cardiac malformation
  - Normal LV, RV, Atria
  - Mild Tricuspid atresia

- CT angiography
  - Normal thoracic aorta, normal aortic arch
  - Normal pulmonary arteries and veins
  - SVC normal
  - Parenchymal normal

Does this change your differential?

What investigations would your do next?

Bloodwork

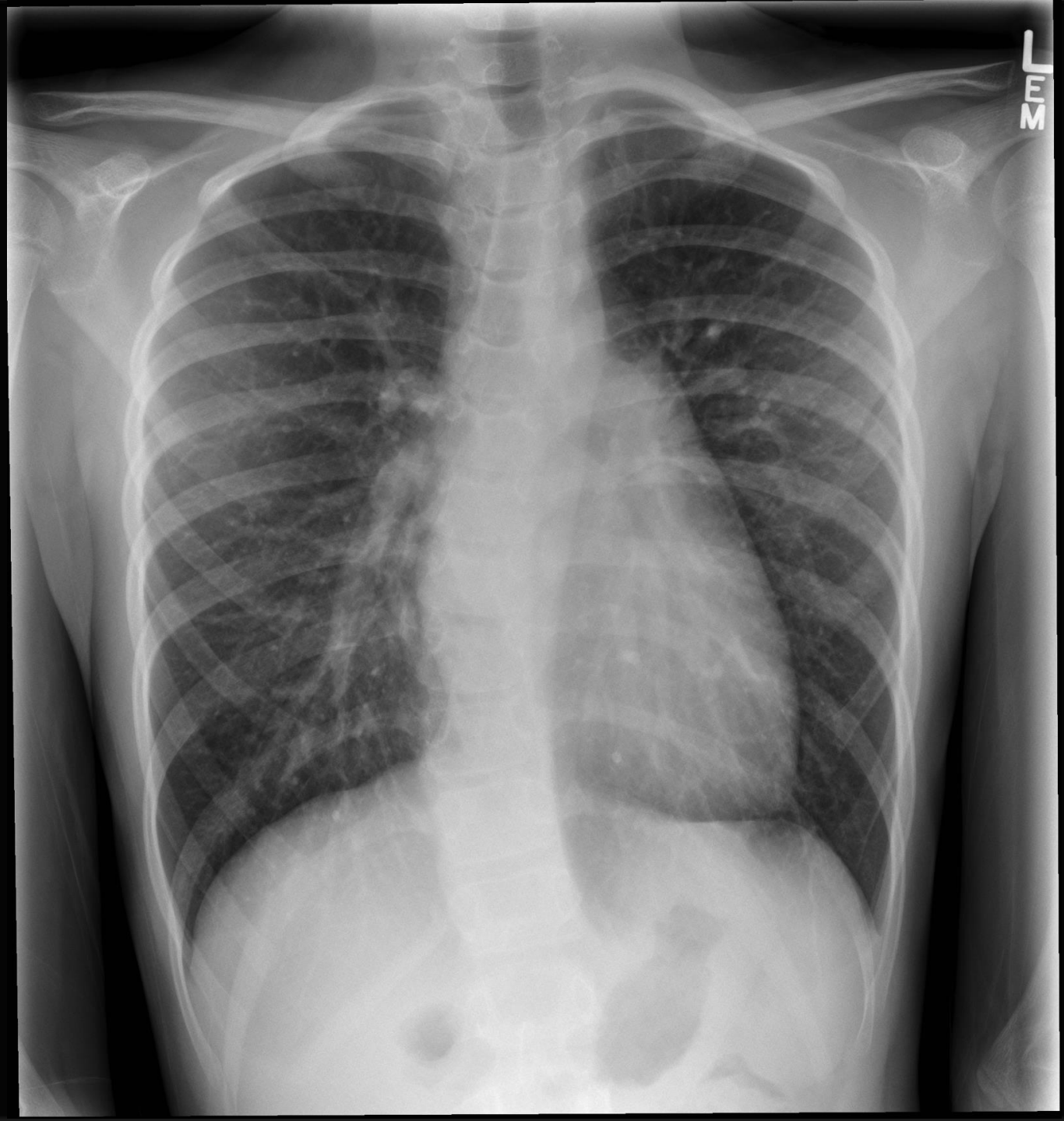
- CBC:
  - Hgb 167 (110-157)
  - Hct 0.51 (0.34-0.46)
  - WBC 7.2
  - Plt 165
- CRP < 1.0, ESR 1
- Lytes, Cr, Urea: Normal
- ABG: 7.44/35/41/24 (room air)
- Quantiferon – Gold: Negative

Liver Panel

- Liver enzymes (ALT, AST, GGT, Alk Phos): Normal
- Bili: 10 (direct 2)
- Ammonia: 115 (12-47)
- INR: 1.5, PTT 39.2
- Albumin: 35
- Protein: 62

PFTs

- Poor study
  - Exhaled for 1 sec, variable effort, complaints of dyspnea
- SpO2 80% on (room air)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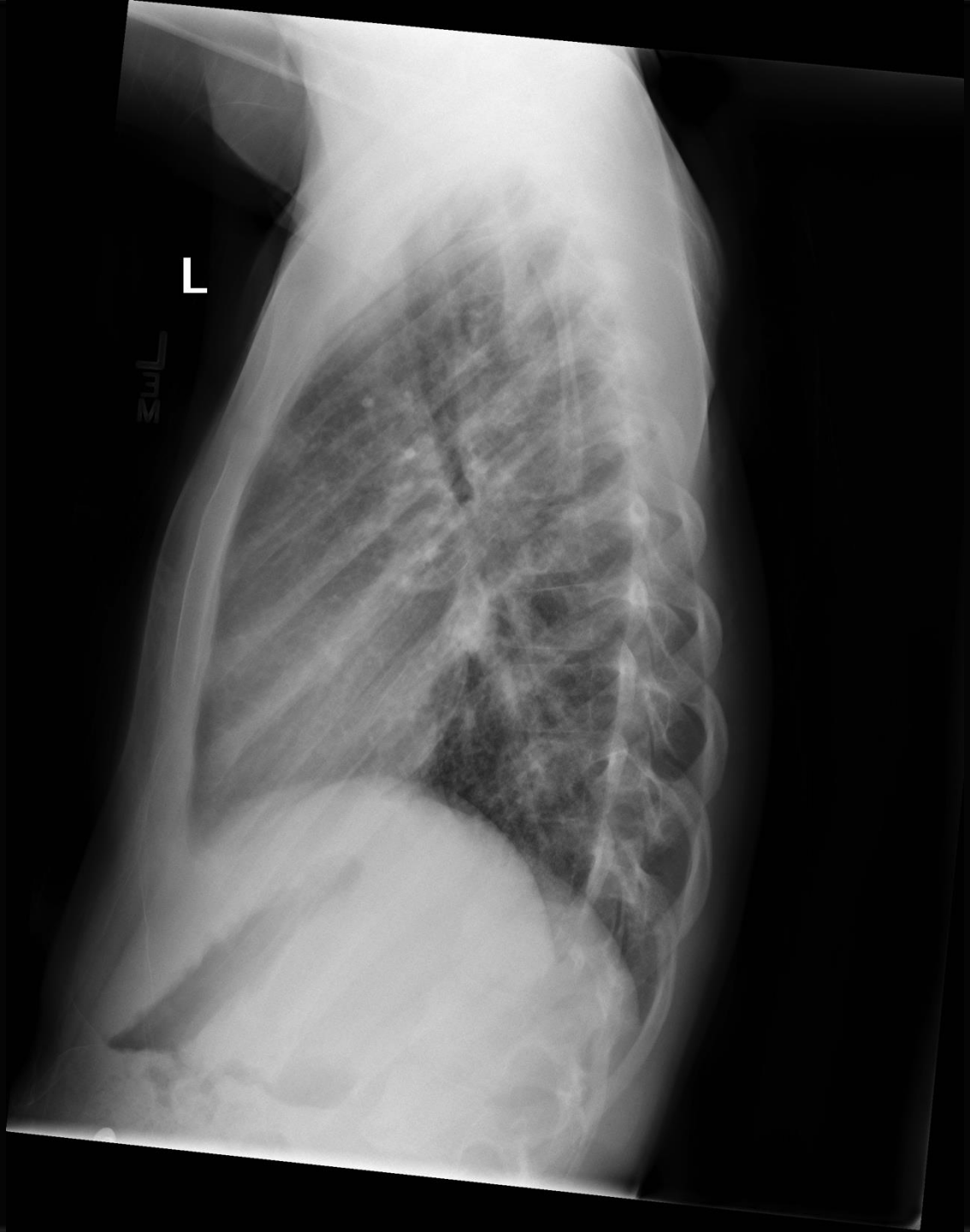
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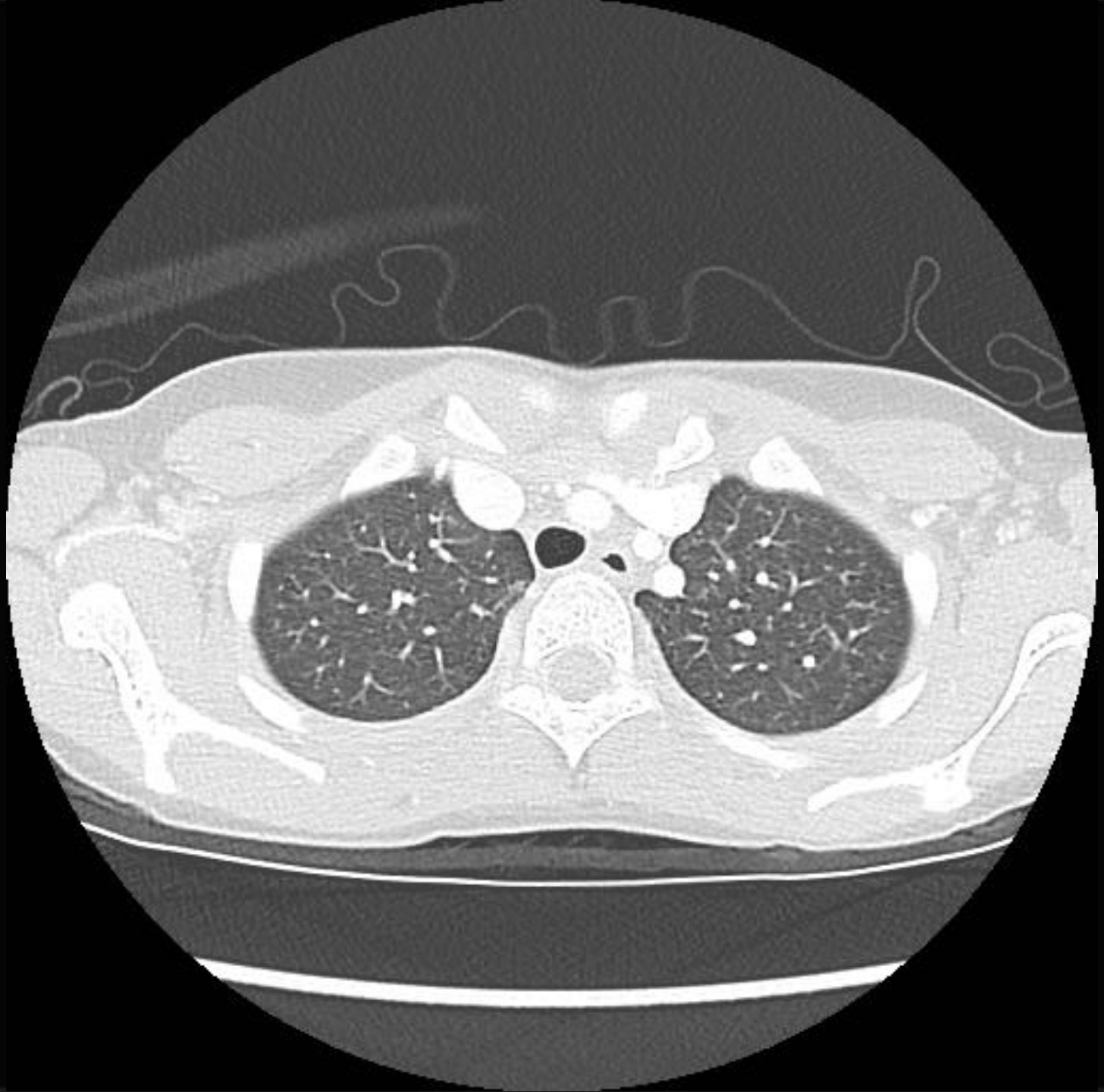
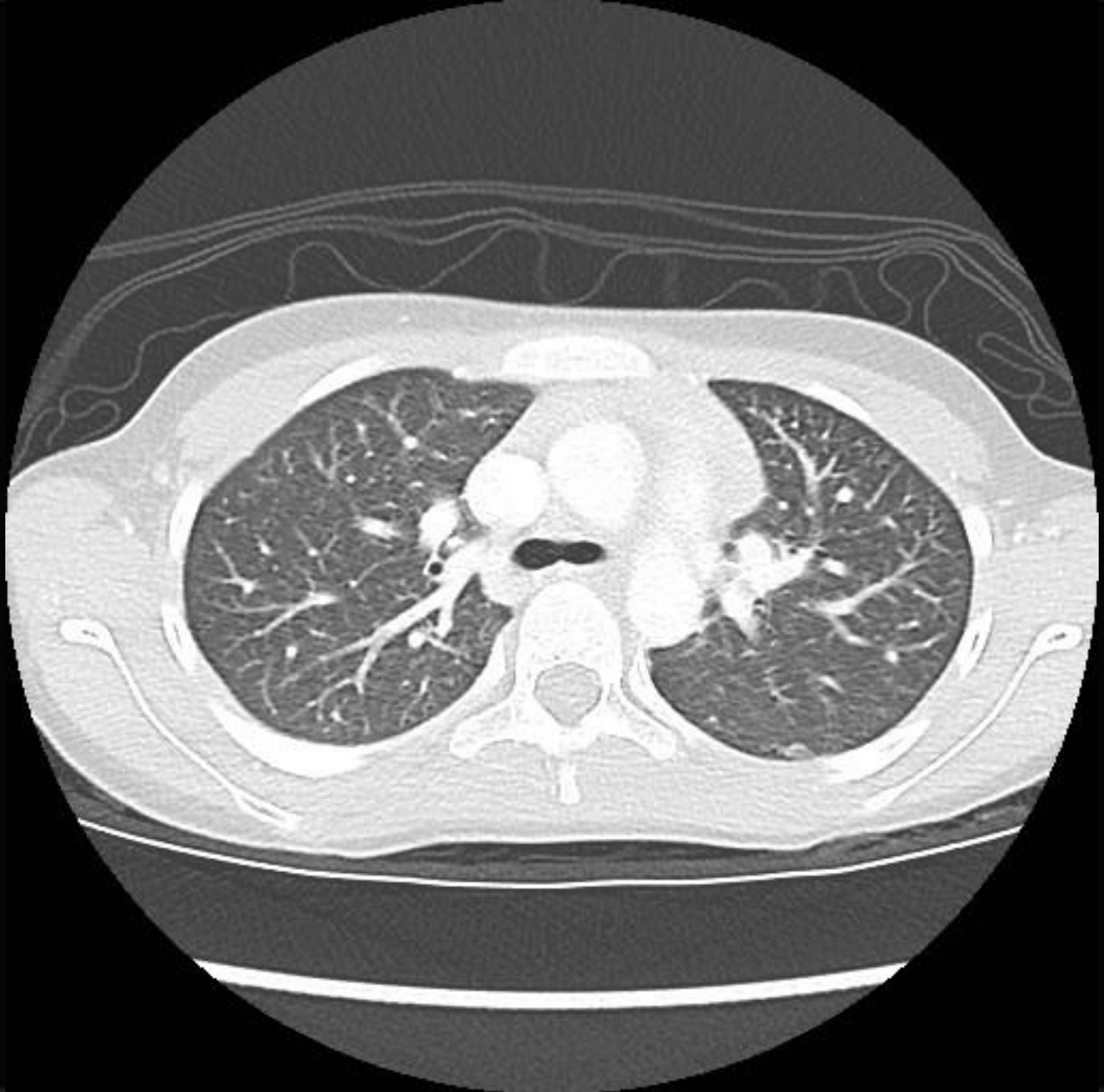
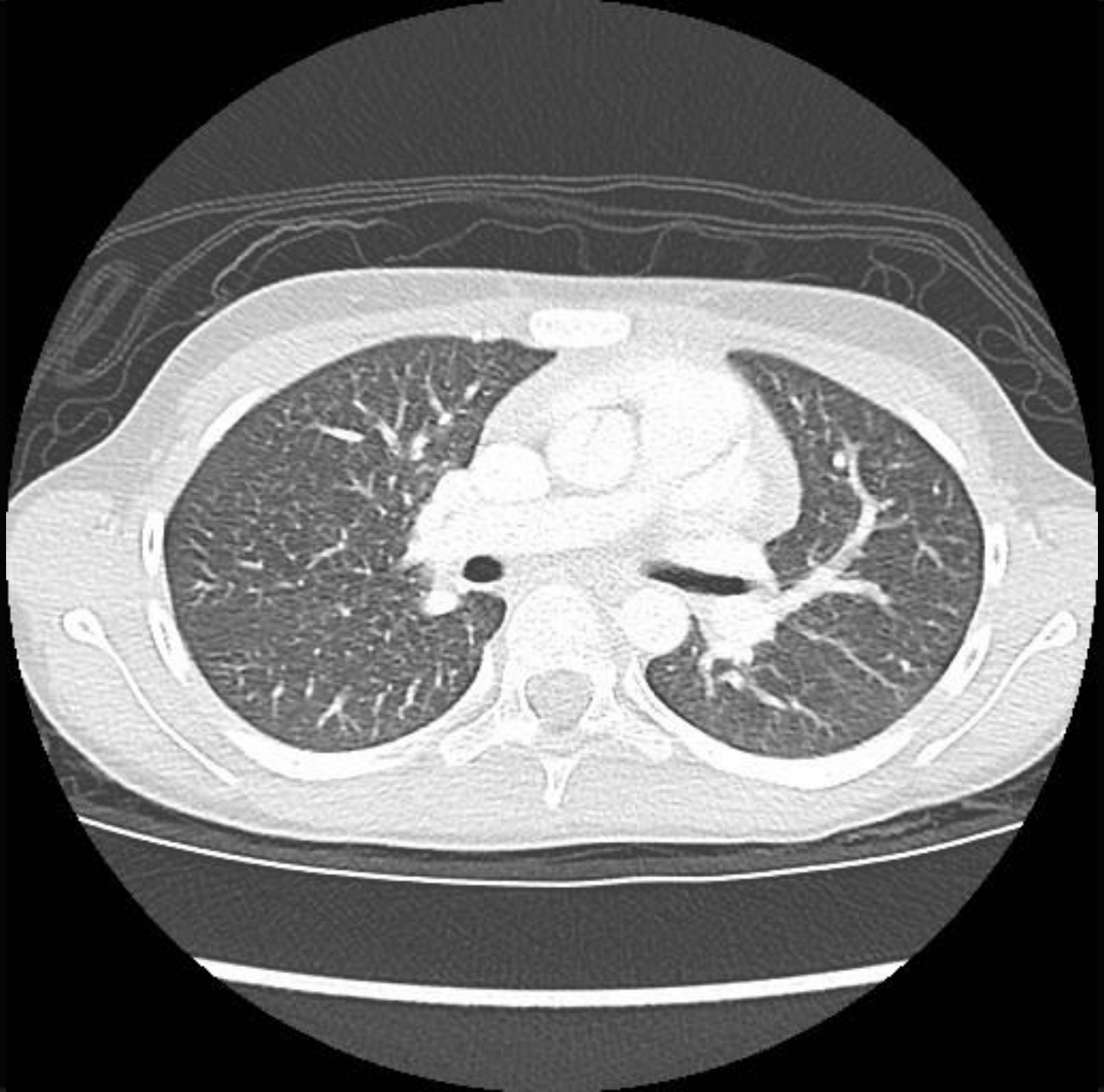
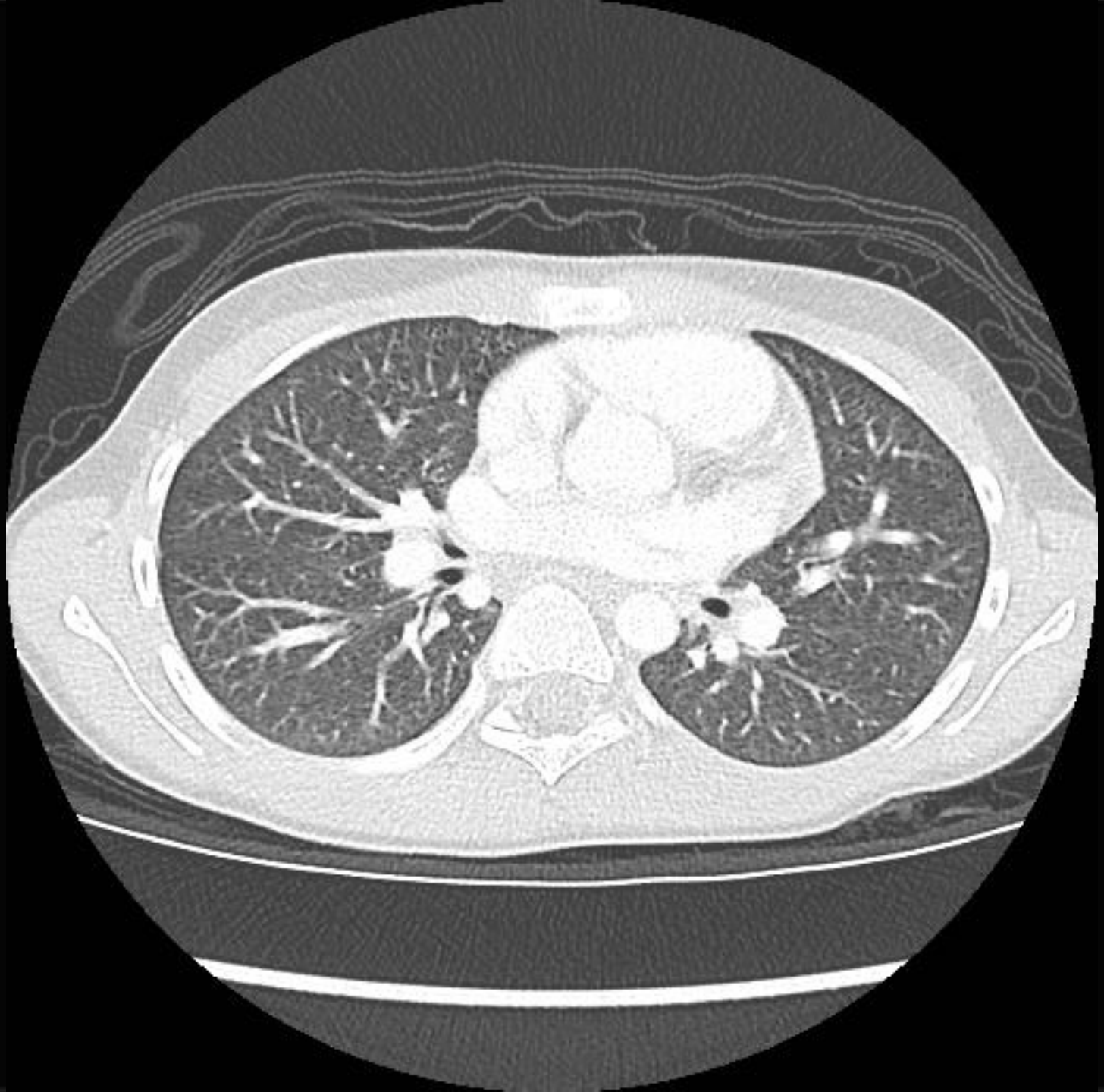
Echocardiogram

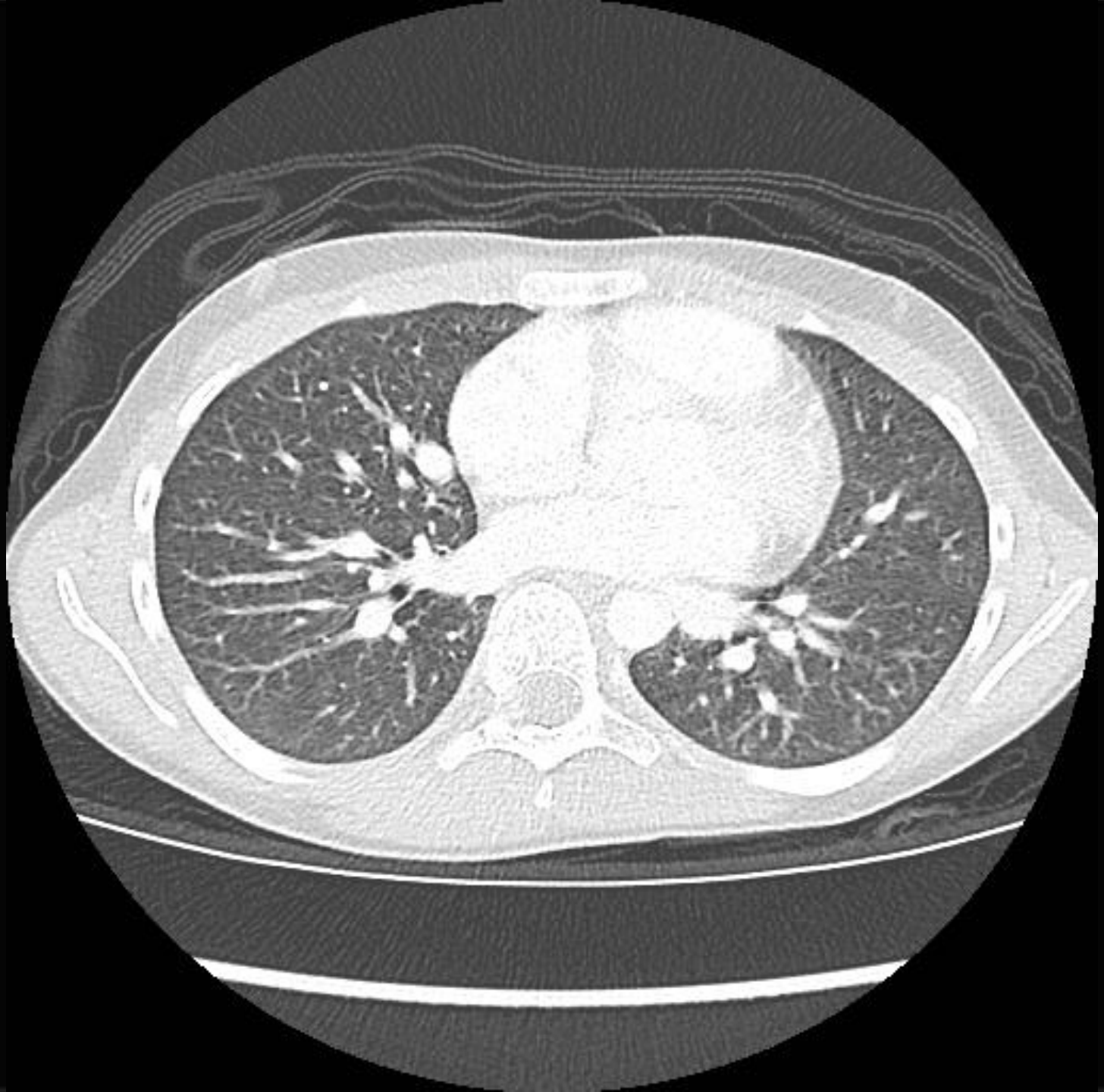
- Structurally normal heart
- Good biventricular function
- Normal septal curvature
- No shunts seen

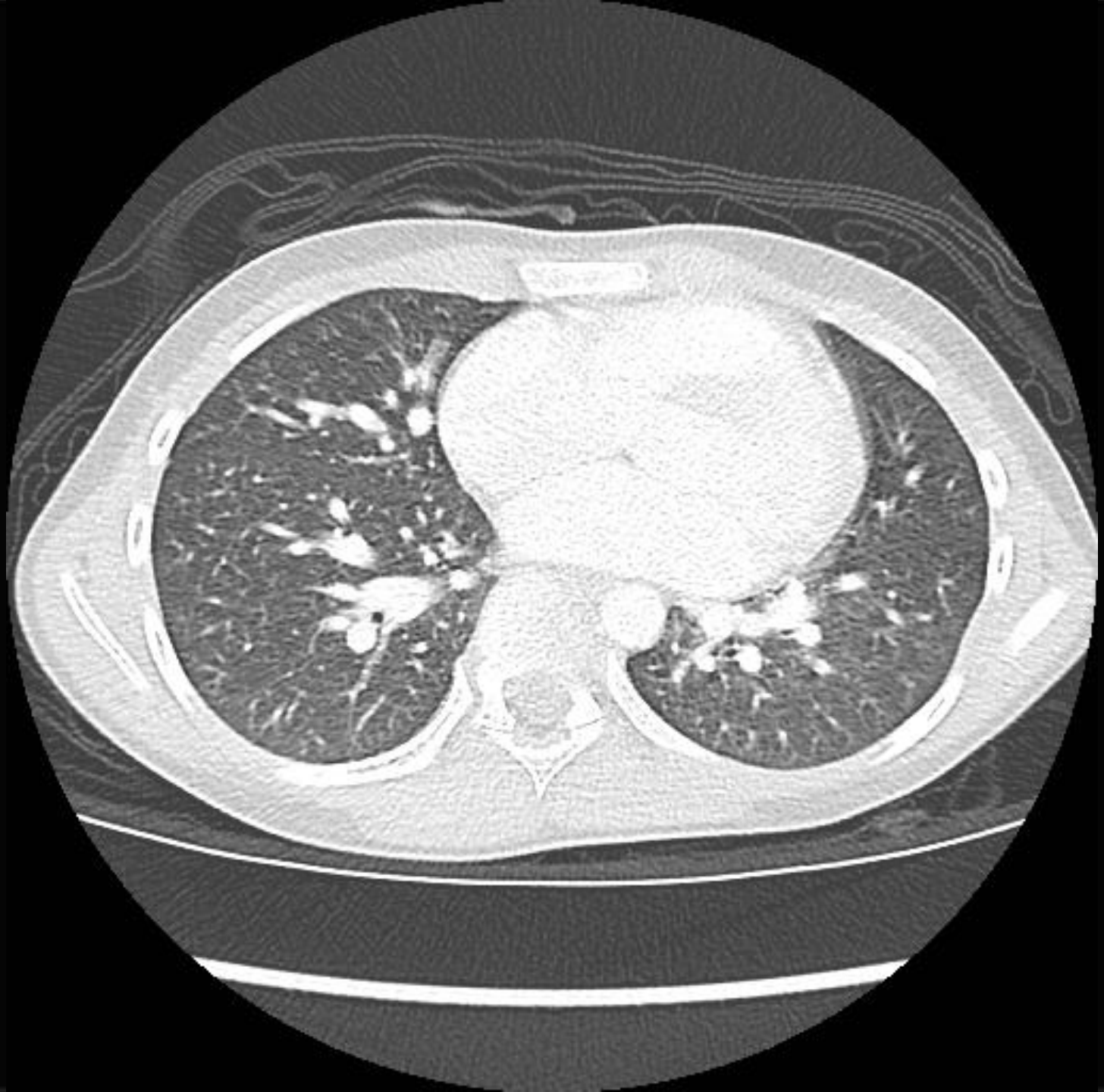


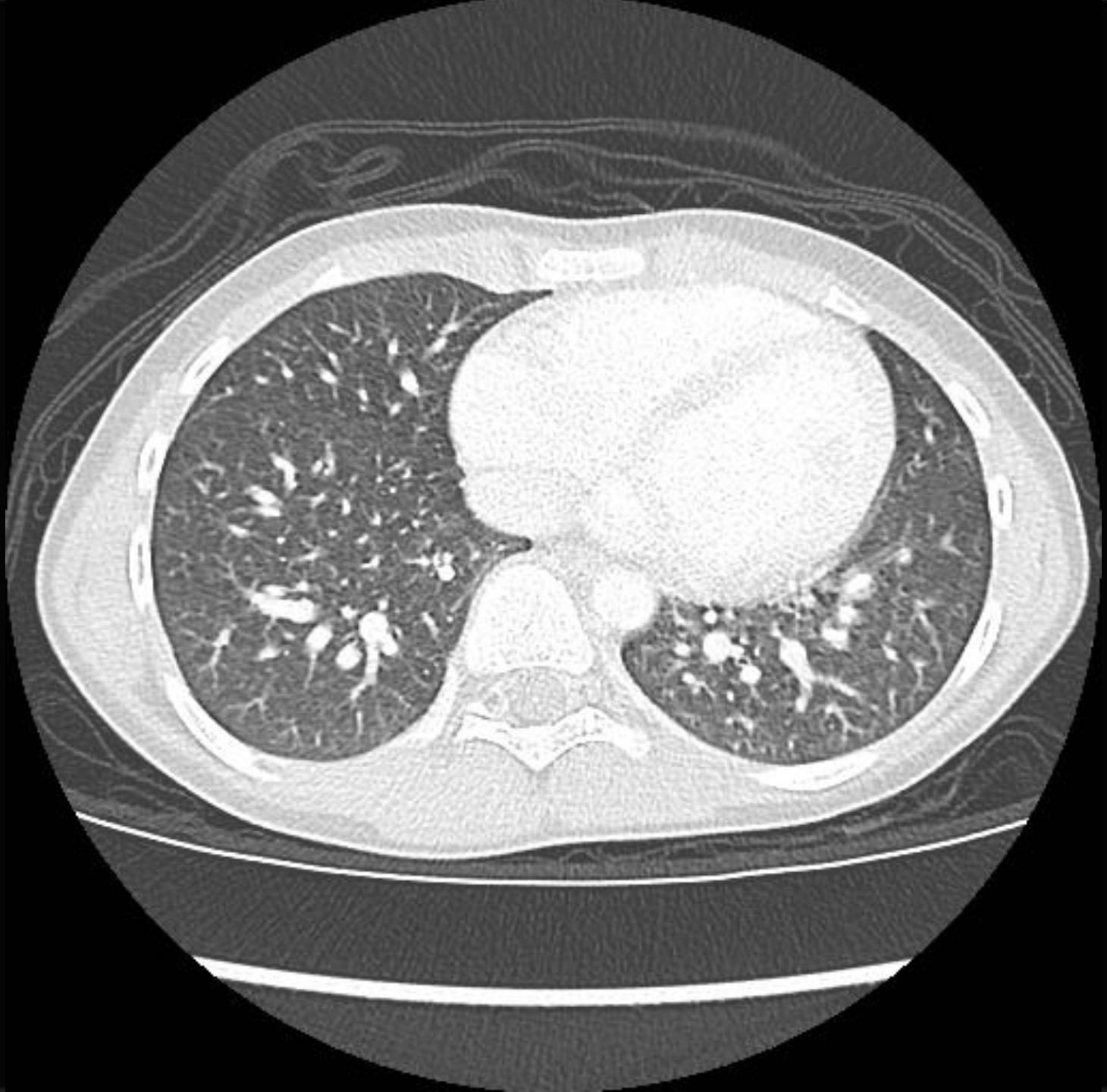


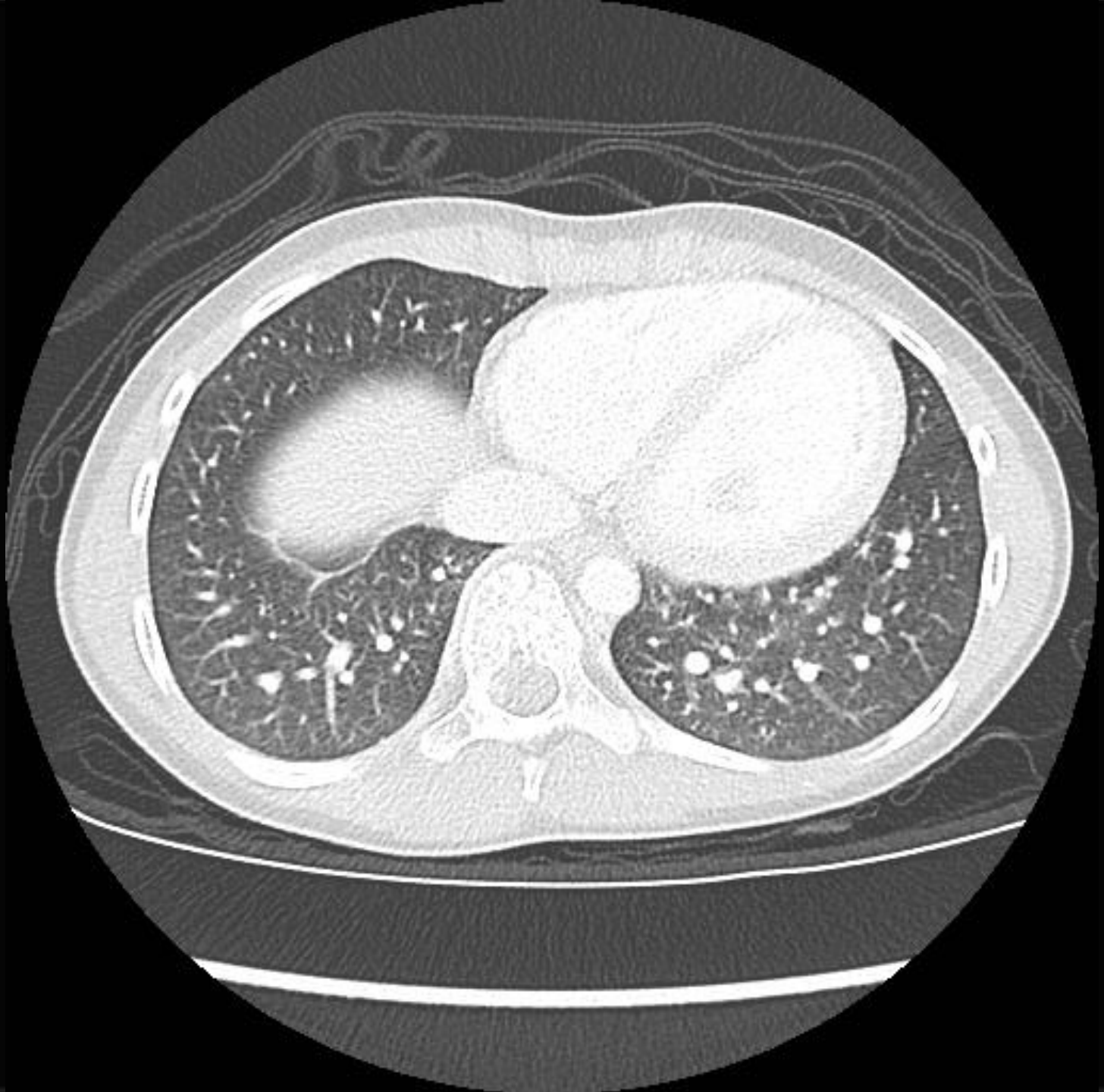


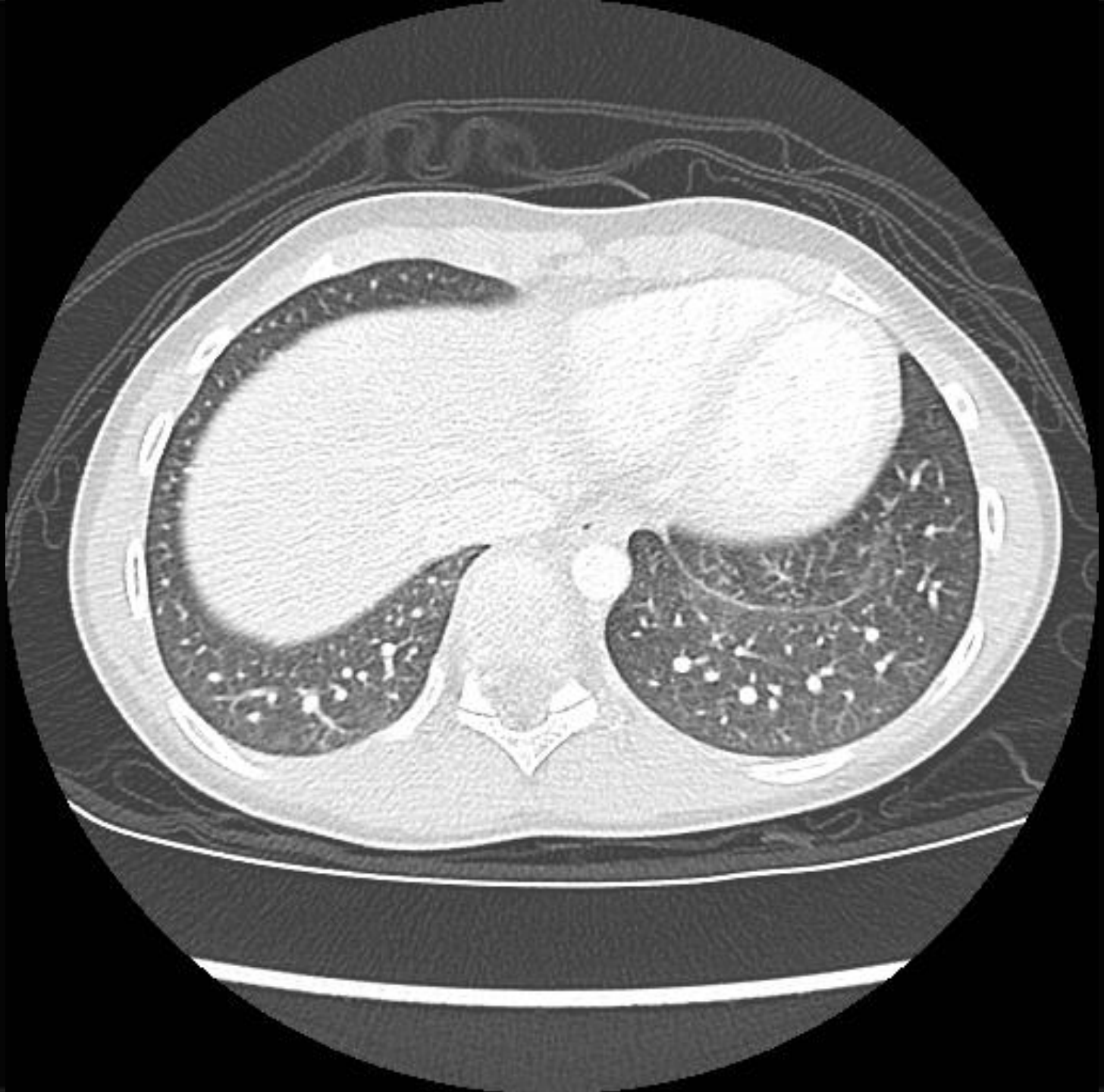












CT

- Chest:
  - Clear lungs, no reticular nodular shadowing
  - No AVM
  - No gas trapping
  - Prominent vascularity

- Abdo (seen on inferior slices of chest CT)
  - Non-enhancing focal lesion seen in the liver
  - Portal vein not visualized

Ultrasound

- Gall bladder, biliary tree, spleen, kidneys normal
- Left hepatic lobe focal lesion
- Unable to visualize portal vein

MRI

- MRI:
  - Congenital absence of main portal vein, with drainage of splenic and mesenteric veins into the prominent IVC
  - Scattered liver lesions, likely regenerative nodular hyperplasia

Working Diagnosis

Abernethy Malformation with presumed Hepatopulmonary syndrome

Hepatopulmonary Syndrome (HPS)

With specific attention on Congenital Portosystemic Shunt (CPSS)

Objectives

- Definition HPS
- Anatomy of CPSS
- Pathophysiology of HPS
- Diagnostic criteria for HPS
- Clinical presentation – Clues for Respirologist
- Work up and investigations
- Treatment and prognosis

Definition - HPS

- Clinical condition "characterized by a defect in arterial oxygenation induced by pulmonary vascular dilation in the setting of liver disease"

- Typically consists of 3 aspects:
  - Liver disease (or associated anomaly)
  - Pulmonary vasodilation
  - Oxygenation defect

Rodriguez-Roisin R, *NEJM*, 2008

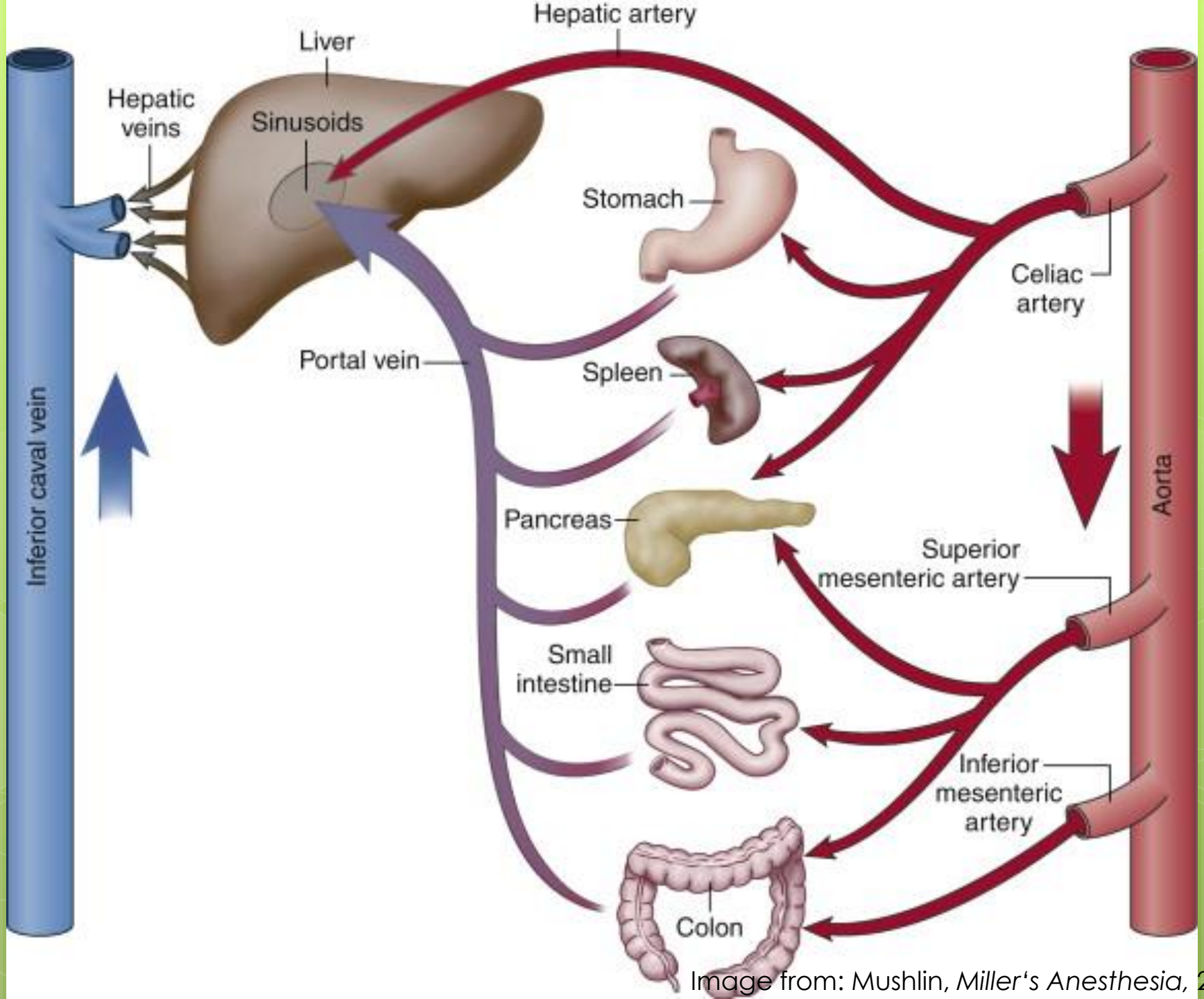
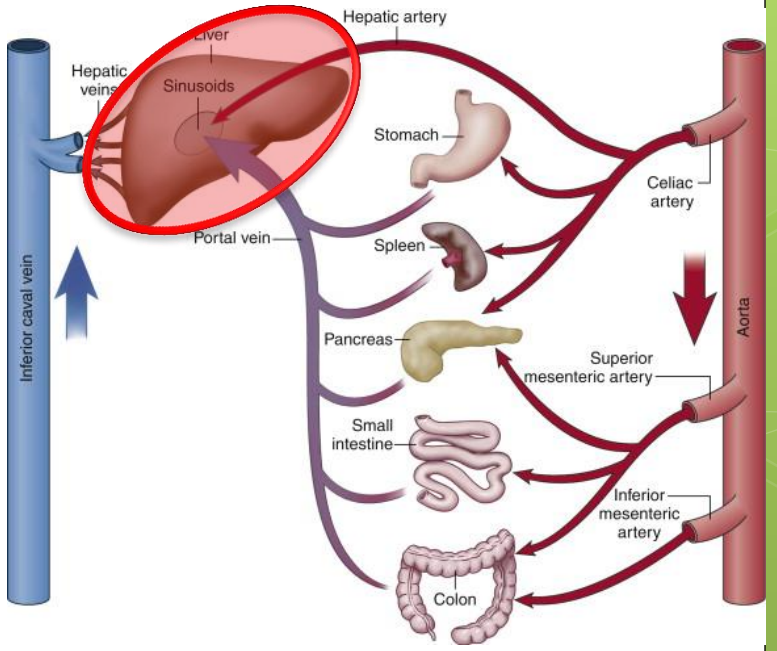


Image from: Mushlin, *Miller's Anesthesia,* 2015

Liver Disease

- Viral hepatitis
- Autoimmune
- Primary Sclerosing Cholangitis
- NAFLD
- Biliary Atresia
- Portal vein thrombosis
- Metabolic liver disease
- Wilson disease



Noli K, *Pediatrics*, 2008

Image from: Mushlin, *Miller's Anesthesia*, 2015

Abnormal Hepatic Blood Flow

- Congenital Portosystemic Shunt
  - Intrahepatic
    - Types 1-5
  - Extrahepatic
    - Type 1 (Abernethy)
    - Type 2

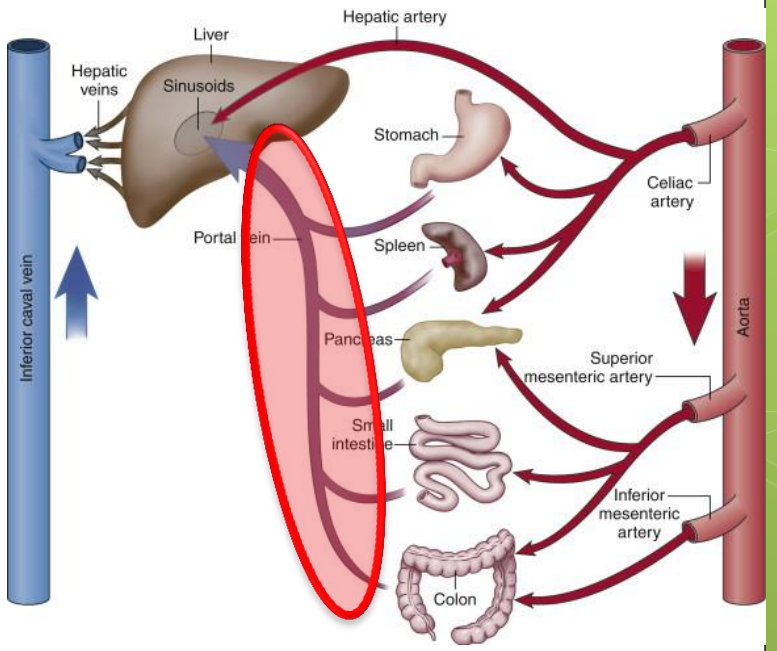


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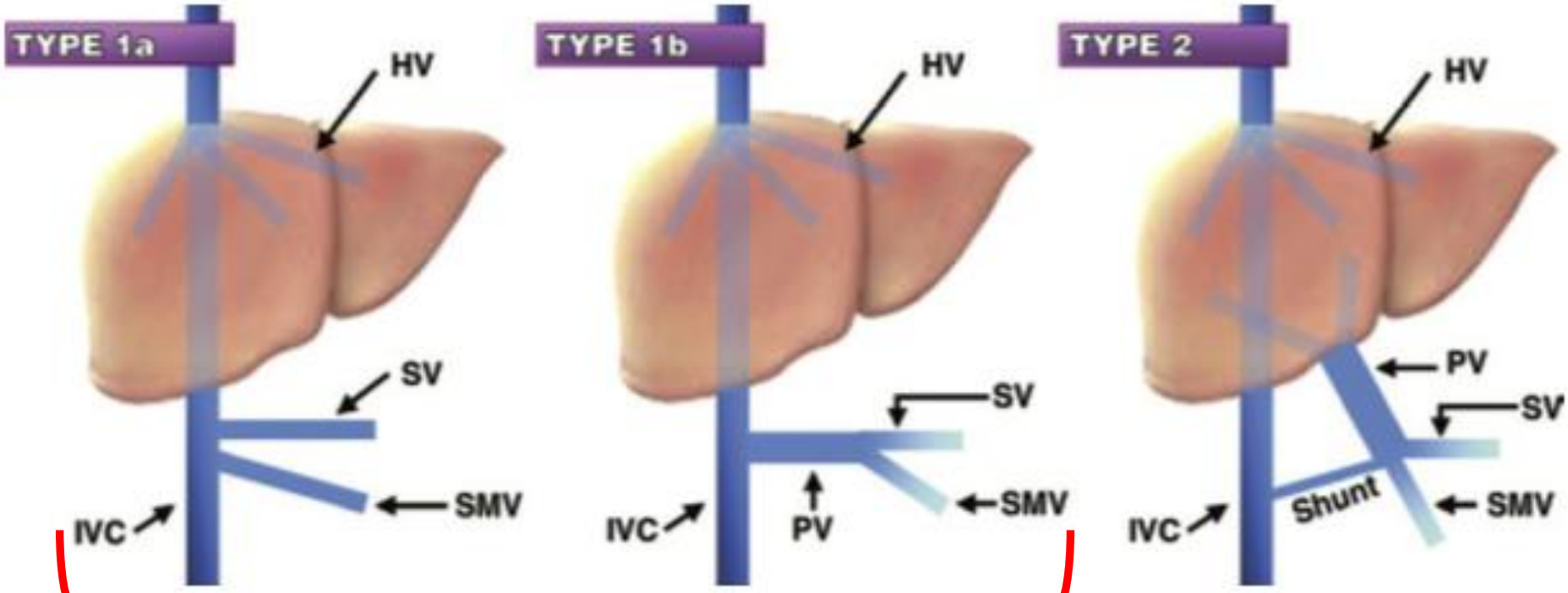
Image from: Mushlin, *Miller's Anesthesia*, 2015

Anatomy – Extrahepatic CPSS



Abernethy Malformation

Alonso-Gamarra, Radiographics, 2011

Clinical Associations - CPSS

- Congenital Heart Disease (31%)
  - ASD, PFO, VSD, PDA, TOF
  - Dextrocardia, Aortic valve stenosis
- Gastrointestinal
  - Nodular liver lesions (22 - 50%)
  - Heterotaxy, Biliary Atresia , Polysplenia, malrotation, duodenal atresia, annular pancreas
- Skeletal (8%)
- Renal Tract (7%)
- CNS
  - Brain abscess

Murray CP, Pediatr Radiol, 2003
Sokollik C, J Pediatr Gastroenterol Nutr, 2013

Pathophysiology - HPS

- Marked dilation of pulmonary capillary vessels
- Angiogenesis, with pulmonary arteriovenous communications
- Reduced vascular tone and compensatory vasoconstriction in response to hypoxemia

Pathologic Mechanisms

1. Nitric Oxide
   - Increased pulmonary production of nitric oxide
   - Multiple presumed mechanisms play a role
     - Nitric Oxide Synthase (endogenous and induced)
     - Endothelin-1 and Endothelin-B receptors
     - Bacterial translocation leading to macrophage derived NO
       - TNF-a
     - cGMP pathways

Raevens S, *Liver Int,* 2015
Rolla G, *Hepatology*, 1997
Rodriguez-Roisin R, *NEJM*, 2008

Pathologic Mechanisms

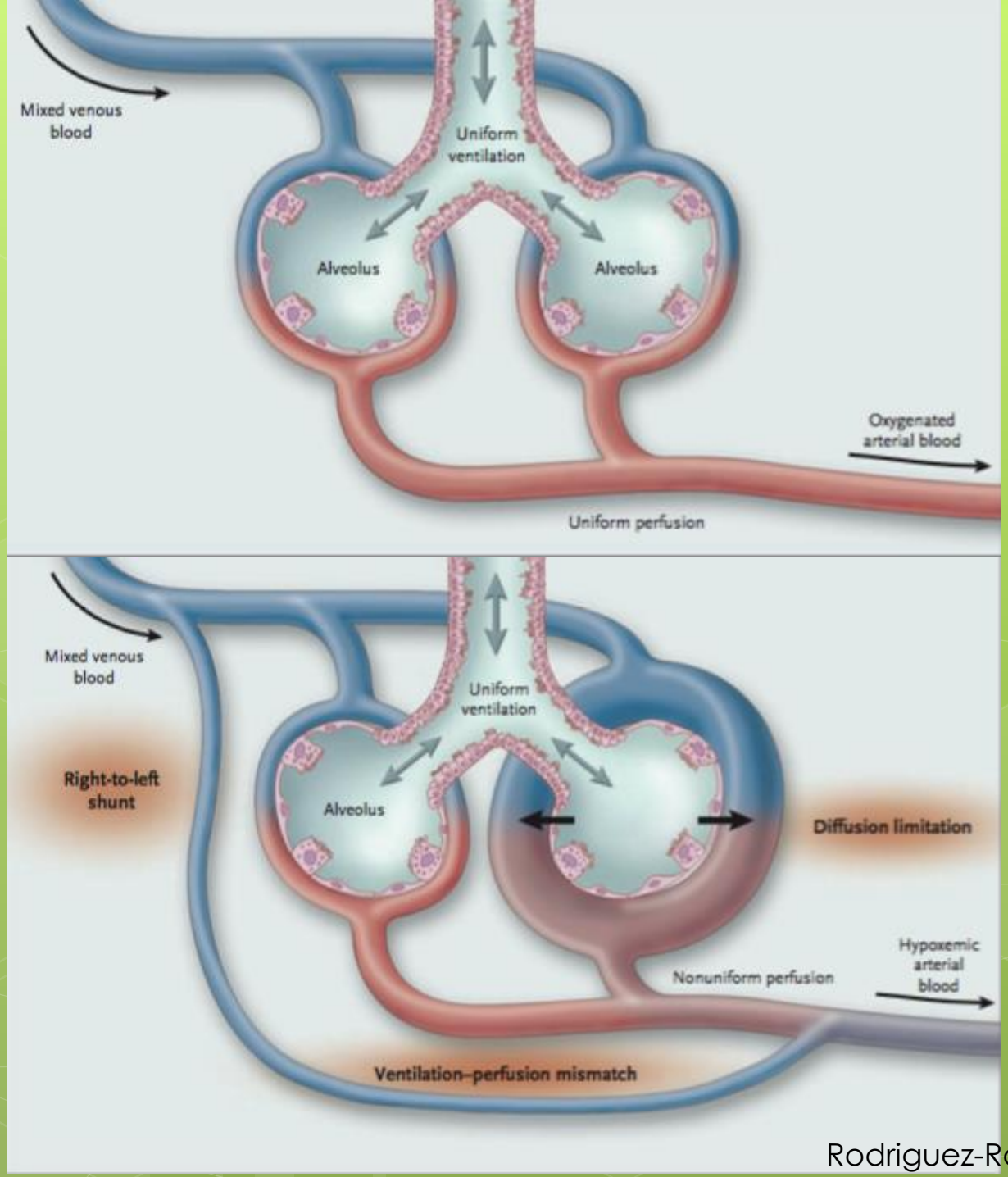
2. Presumed role of Carbon monoxide

3. Angiogenesis
   - Pulmonary accumulation of macrophages leading to increased VEGF
     - Bacterial translocation and TNF-a
   - VEGF also involved in NO production via NOS

Arguedas MR, *Gastroenterology*, 2005
Raevens S, *Liver Int*, 2015
Rodriguez-Roisin R, *NEJM*, 2008

Normal

HPS



Rodriguez-Roisin R, *NEJM*, 2008

Prevalence of HPS

- Poorly established in pediatrics
  - Estimated at 9-29% in patients with chronic liver disease
  - Some literature suggests increased prevalence (40%) in patients with cirrhosis and portal hypertension

Noli K, *Pediatrics*, 2008
Borkar VV, *Liver Int*, 2015

Clinical Manifestations

- Highly variable
  - Asymptomatic, to severe disease with multi-organ involvement
- Non-specific
  - Historic and physical findings often overlap significantly with other respiratory illnesses

Clues on History – For the Respirologist

- Pulmonary:
  - Dyspnea (exertional and at rest)*
    - Often relieved with supine (Platypnea)
- CNS
  - Changes to mentation, developmental delay, learning difficulties
- Hepatic
  - Jaundice, abdominal pain/distention, mass, bleeding, pruritis
  - Weight gain/loss

Borkar VV, *Liver Int*, 2015
Raevens S, *Liver Int*, 2015
Alonso-Gamarra E, *Radiographics*, 2011
Sokollik C, *J Pediatr Gastroenterol Nutr*, 2013

Clues on Exam – For the Respirologist

- CNS
  - Behaviour change (irritable, somnolent)
  - Confusion, difficulty concentrating
- Pulmonary
  - Decreased oxygen saturations, tachypnea
    - Orthodeoxia
- MSK:
  - Spider nevi, digital clubbing*, cyanosis*
- Abdomen:
  - HSM, ascites

Borkar VV, *Liver Int*, 2015
Raevens S, *Liver Int*, 2015
Alonso-Gamarra E, *Radiographics*, 2011
Sokollik C, *J Pediatr Gastroenterol Nutr*, 2013

Diagnostic Criteria

- Oxygenation defect
- Pulmonary Vascular dilation
- Liver Disease

Rodriguez-Roisin R, *NEJM*, 2008

Diagnostic Criteria

- Oxygenation defect
  - $PaO_2 < 80mmHg$, OR
  - AaO_2 gradient ≥ 15 mmHg
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Rodriguez-Roisin R, *NEJM*, 2008

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Rodriguez-Roisin R, *NEJM*, 2008

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- Liver Disease
  - Portal HTN, cirrhosis, CPSS

Rodriguez-Roisin R, *NEJM*, 2008

Severity - HPS

- Mild
  - PaO2 ≥ 80 mmHg
- Moderate
  - PaO2 ≥ 60 to < 80 mmHg
- Severe
  - PaO2 ≥ 50 to < 60 mmHg
- Very Severe
  - PaO2 < 50 mmHg
  - PaO2 < 300 mmHg while on 100% Oxygen

Rodriguez-Roisin R, *NEJM*, 2008

Pulmonary Vascular Dilation

- Contrast enhanced transthoracic echocardiogram
  - Most practical method for detection of pulmonary vasodilation
  - Opacification of left atrium occurs 3-6 cardiac cycles after right atrium
- Trans-esophageal contrast echocardiogram
  - Better able to differentiate borderline cases

Raevens S, *Liver Int*, 2015
Rodriguez-Roisin R, *NEJM*, 2008
Alonso-Gamarra E, *Radiographics*, 2011

Pulmonary Vascular Dilation

- Peripherally administered Technetium-99 labeled aggregated albumin
  - Monitor with lung and body uptake to quantitatively demonstrate shunt
  - Uptake > 6% outside of the lungs confirms vasodilation

Raevens S, *Liver Int*, 2015
Rodriguez-Roisin R, *NEJM*, 2008

Abdominal Imaging

- Ultrasound
  - Initial screen for abnormal vascular communication, or abnormal development
  - Use of doppler to demonstrate flow direction
- CT/MRI +/- angiography
  - Useful for documentation of vasculature
  - Characterizes liver nodules

Alonso-Gamarra E, *Radiographics*, 2011

Bloodwork – Liver Disease

- Chemistry
  - +/- Elevated levels of Ammonia, Galactose
  - +/- Elevated transaminases & bilirubin

Sokollik C, *J Pediatr Gastroenterol Nutr*, 2013

Other Investigations?

- High Resolution Chest CT
  - Can be helpful to show complex AVMs
- Pulmonary angiography
  - Typically not useful in HPS, as dilation is diffuse
  - Can be useful if coiling an AVM

Raevens S, *Liver Int*, 2015
Sokollik C, J Pediatr Gastroenterol Nutr, 2013

Treatment

- Patients with intrahepatic CPSS (Type 2) may close spontaneously within the first year of life
  - If shunts persist, closure should be considered
    - Surgical vs interventional radiology
  - Believed to improve encephalopathy, pulmonary disease, liver masses, hyperammonemia, hypoxemia

Sokollik C, J Pediatr Gastroenterol Nutr, 2013

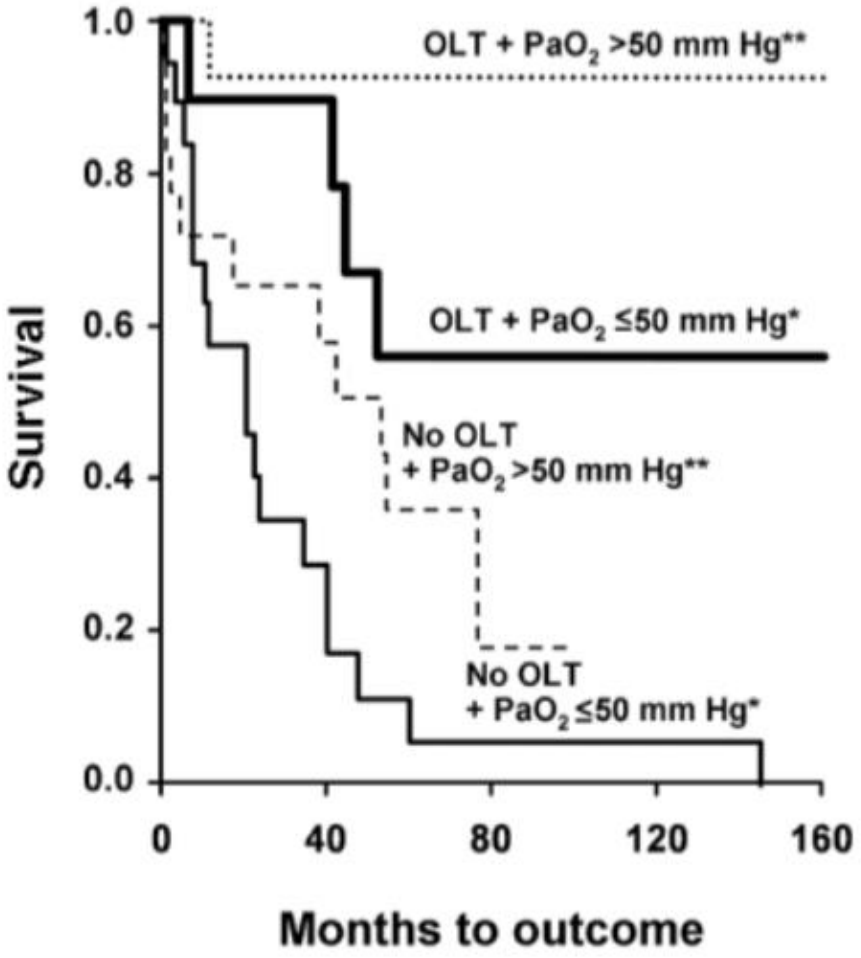
Treatment

- For all other causes of HPS, liver transplant is only definitive therapy
  - Improves hypoxemia and pulmonary dilation in all patients
  - > 85% of patients have improvement within 1 year
- No effective medical therapies exist

Raevens S, *Liver Int*, 2015
Rodriguez-Roisin R, *NEJM*, 2008
Porres-Aguilar M, *Eur Respir Rev*, 2012

Prognosis

- Survival directly related to severity of HPS
  - Higher mortality in those with lower PaO2
  - PaO2 < 50 at increased risk



Arguedas MR, *Hepatology*, 2003
Swanson KL, *Hepatology*, 2005

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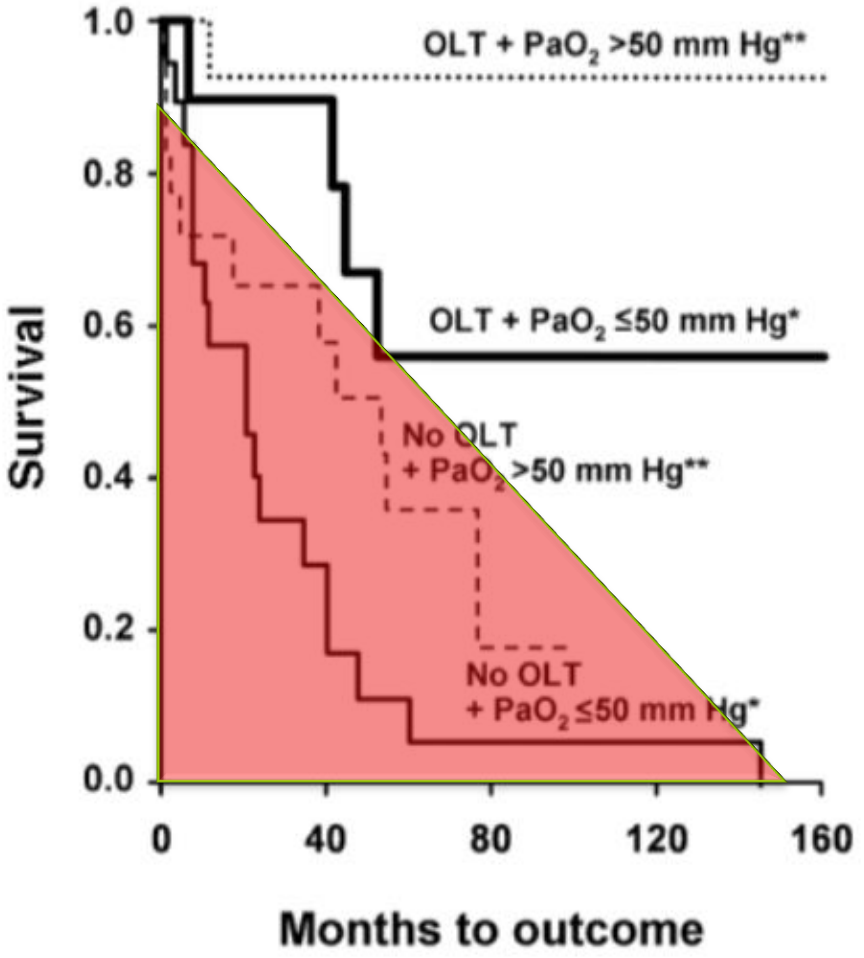

Arguedas MR, *Hepatology*, 2003
Swanson KL, *Hepatology*, 2005

Prognosis

- Prognosis post transplant seems to be better in children
  - One year survival rate of 93%
  - Overall mortality remains at ~28% while accounting for pre-transplant death

Al-Hussaini A, Pediatr Transplant, 2010
Rodriguez-Roisin R, *NEJM*, 2008

Back to our patient…

- Bubble Echo
  - Following injection, contrast appear in left heart 5 beats later
    - Supports presence of pulmonary vascular dilation

Back to our patient…

- Our patient had:
  - Hypoxemia (PaO_2: 41, AaO_2 Gradient: 45)
  - Vascular dilation (as identified on contrast echo)
  - Congenital absence of the portal vein
- Indicative of severe Hepatopulmonary Syndrome
- Gastroenterology was consulted for assessment of liver transplant, and she currently is awaiting assessment

Thank you for your time

Questions?

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Liver Nodules in CPSS

- Commonly associated with CPSS (up to 50%)
  - Focal Nodular Hypoplasia
  - Nodular Regenerative Hyperplasia
  - Adenomatous Hyperplasia
  - Hepatoblastoma
  - Hepatocellular Carcinoma

Alonso-Gamarra E, *Radiographics*, 2011

Liver Nodules in CPSS

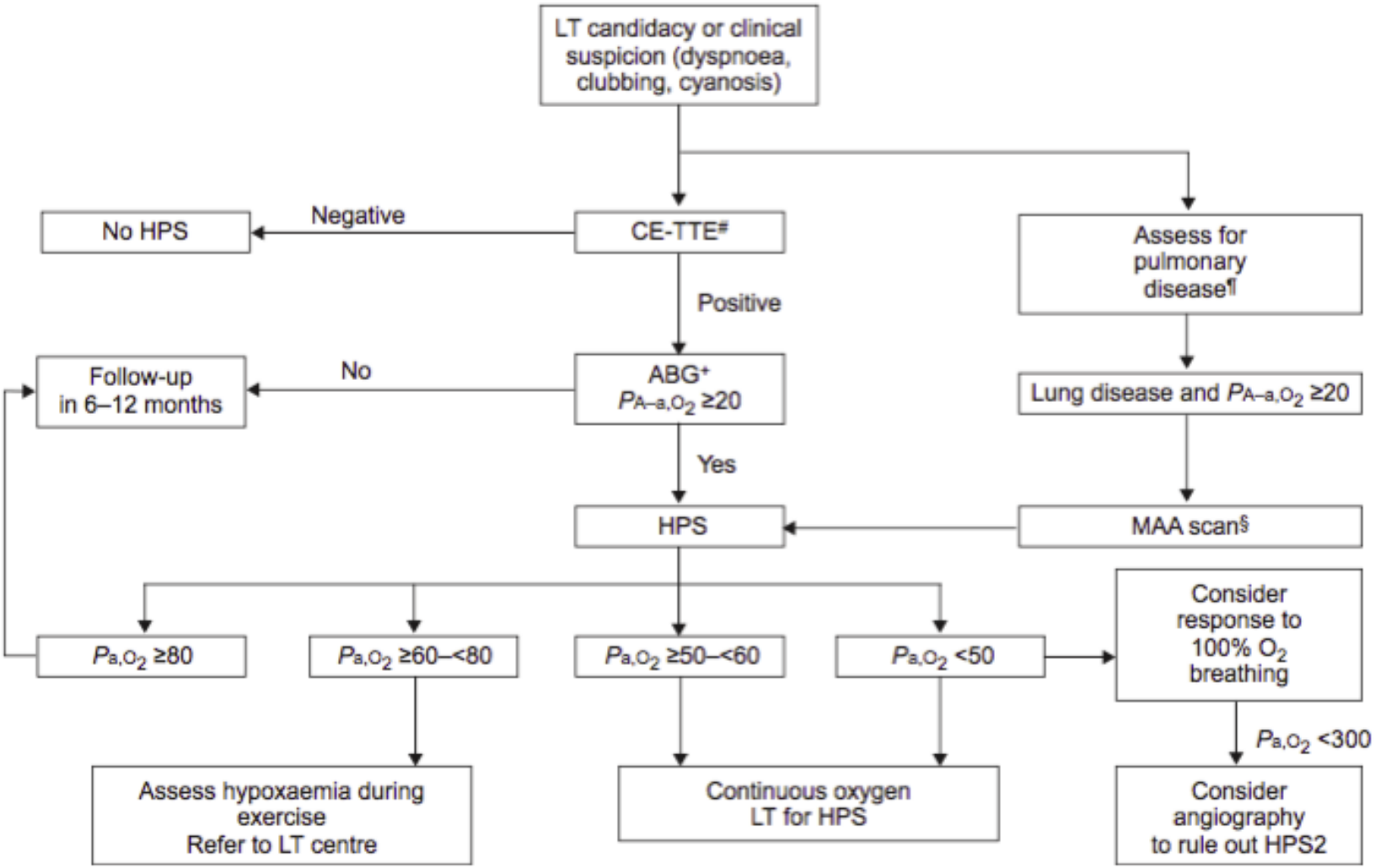
- Most liver nodules benign
  - Metastatic disease in 4% of patients
- Characteristics of benign regenerative nodules:
  - Multiple
  - Well-defined
  - Diameter of 0.5 to 4 cm
  - High signal intensity on T1-weighted images (75% of cases)

Alonso-Gamarra E, *Radiographics*, 2011

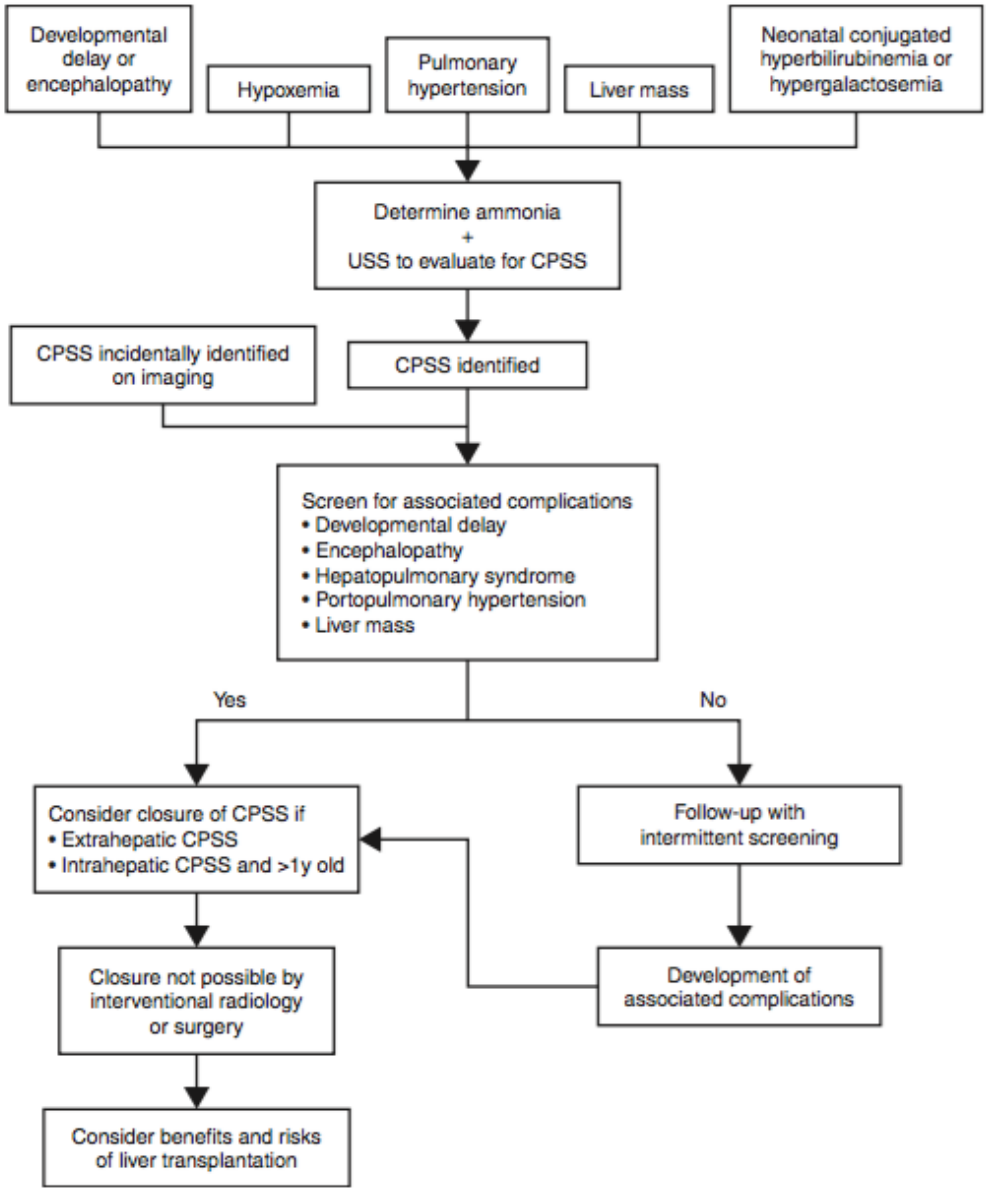
Screening - HPS

- Pulse oximetry is a non-invasive method for screening for HPS
  - SpO2 of > 96% is a sensitive method for excluding a PaO2 < 70mmHg

Porres-Aguilar M, *Eur Respir Rev*, 2012



Porres-Aguilar M, *Eur Respir Rev*, 2012



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