Pernicious Emboli:
An Uncommon Cause of a Common Problem

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MEDICINE

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Have I have a great case for you ….

Debbi Ravert, MD
UMSOM, Class of 2014
Resident, JHH EM

Case Presentation

- 51 year old woman with HTN presents with **sudden-onset shortness of breath**
- Associated with: **diaphoresis**, **lightheadedness** and **near-syncope**
- Occurred while walking outdoors but persisted despite resting on a park bench
- Family members reported recent development of fatigue, drowsiness and forgetfulness

Case Presentation

- **Pertinent negatives:**

  Chest pain, orthopnea, PND, palpitations, cough, wheezing, sputum production, melena, hematochezia, vomiting, fevers or chills

- **Review of systems:**

  Six month gradual development of paresthesia, impaired memory, fatigue and gait instability.

History

- **PMH/PSH:**
  - Hypertension
  - Hyperlipidemia
  - No prior history of heart, lung, or GI disease
- **Social History:**
  - Former smoker – quit a few months ago
  - Denies alcohol, denies illicit drug use
- **FH**: No early MI, no clotting disorders, no thyroid problems
- **Medications**: Lisinopril 10mg daily, not taking reliably
- **Allergies**: None

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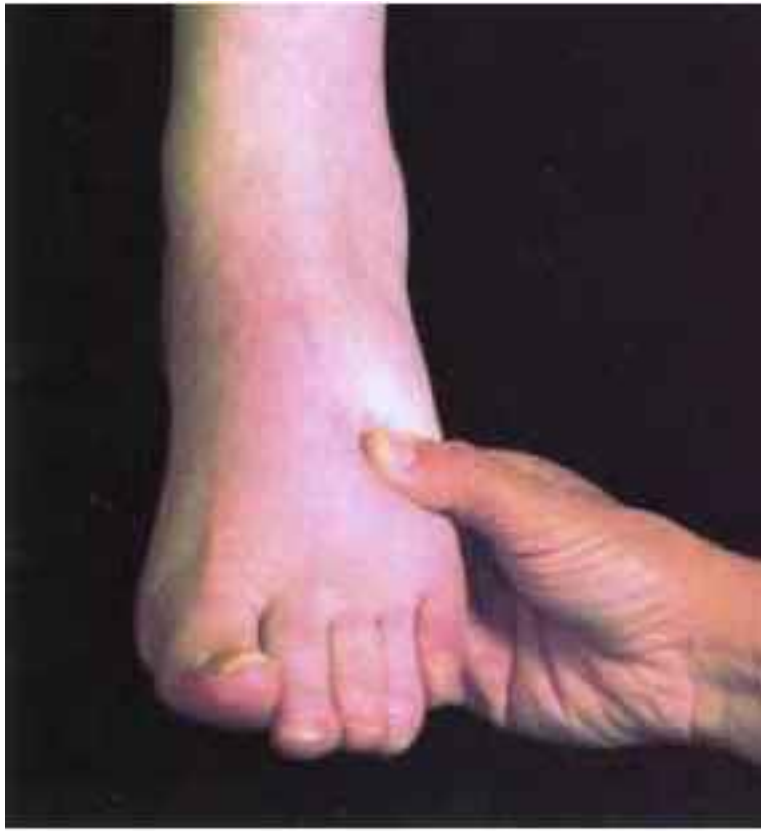
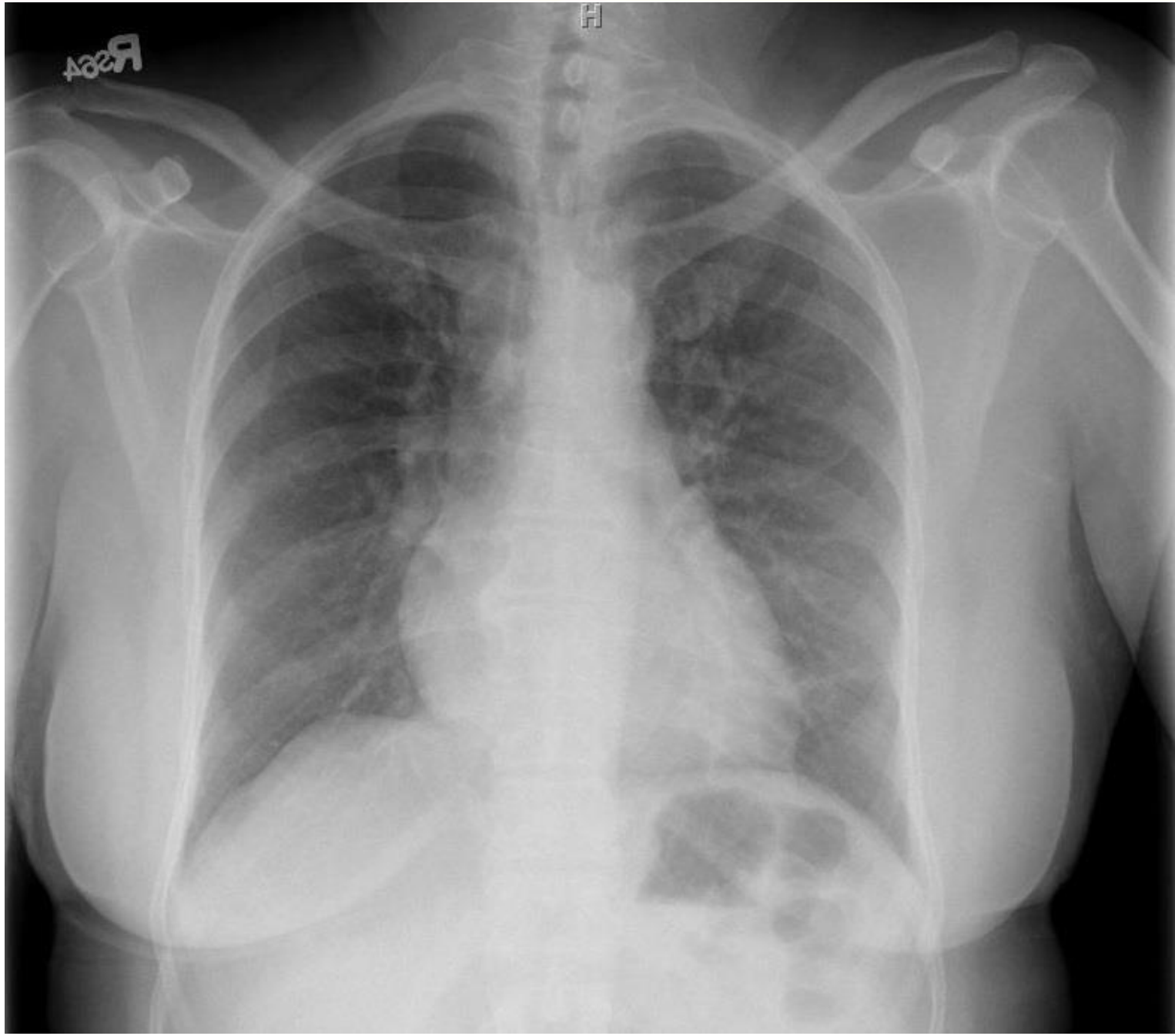
ED VS: T 36.5 | P 112 | BP 130/80 | RR 16 | SpO2 94% on RA

- **General:** Diaphoretic but in no acute distress.
- **CV/PULM:** No RV heave or JVD, lungs clear
- **Extremities:** Shallow pitting edema extending to the knees bilaterally
- **Neuro:**
  - Gait was slightly wide based and showed a tendency for retropulsion
  - Inability to recall three objects, increased irritability
  - Sensation and deep tendon reflexes preserved



Initial imaging:

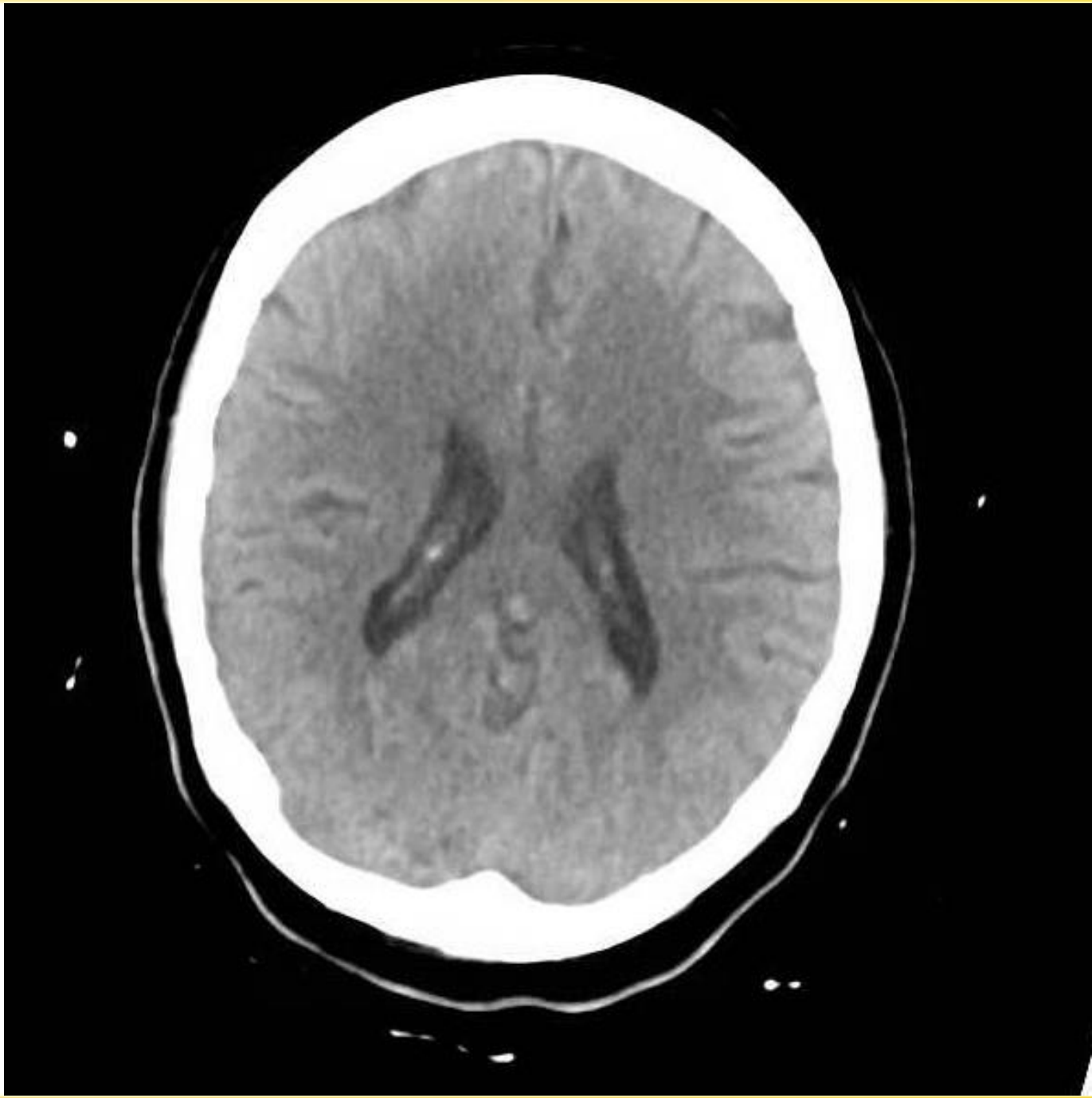
Chest X-Ray: Unremarkable



CT Head/Brain WO Contrast

IMPRESSION:

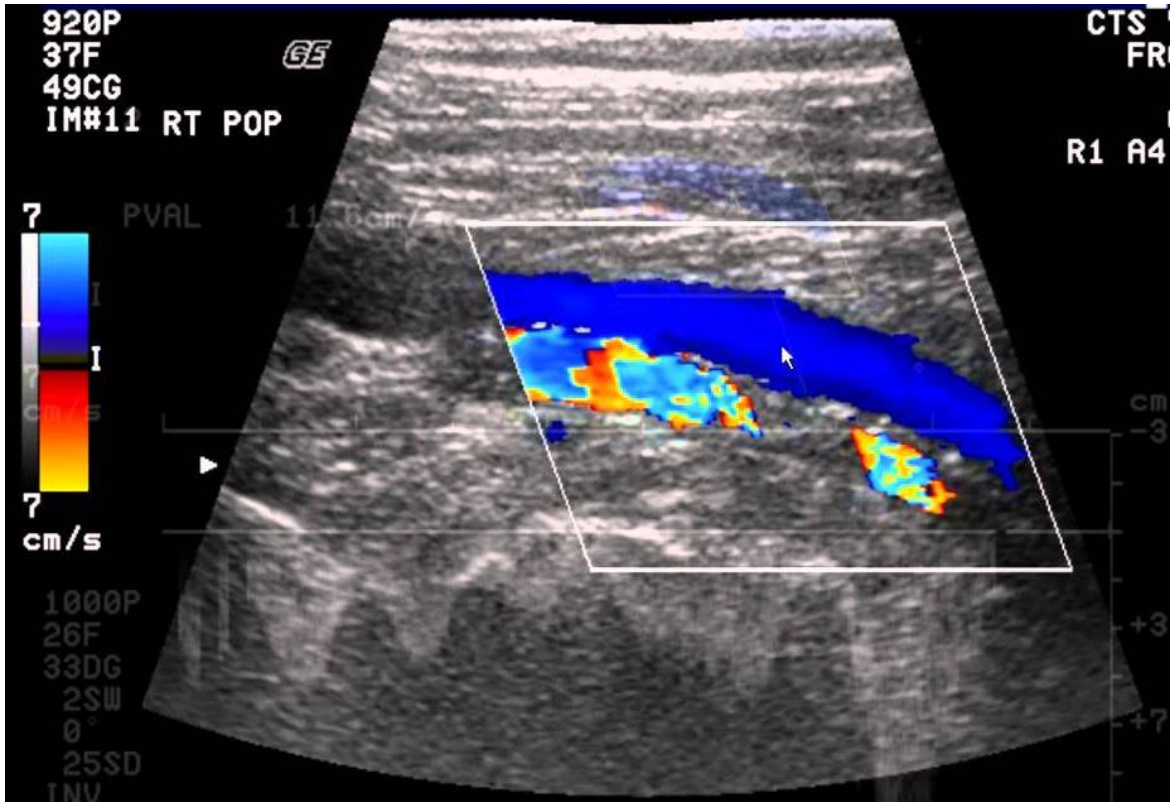
No CT evidence of an acute intracranial abnormality

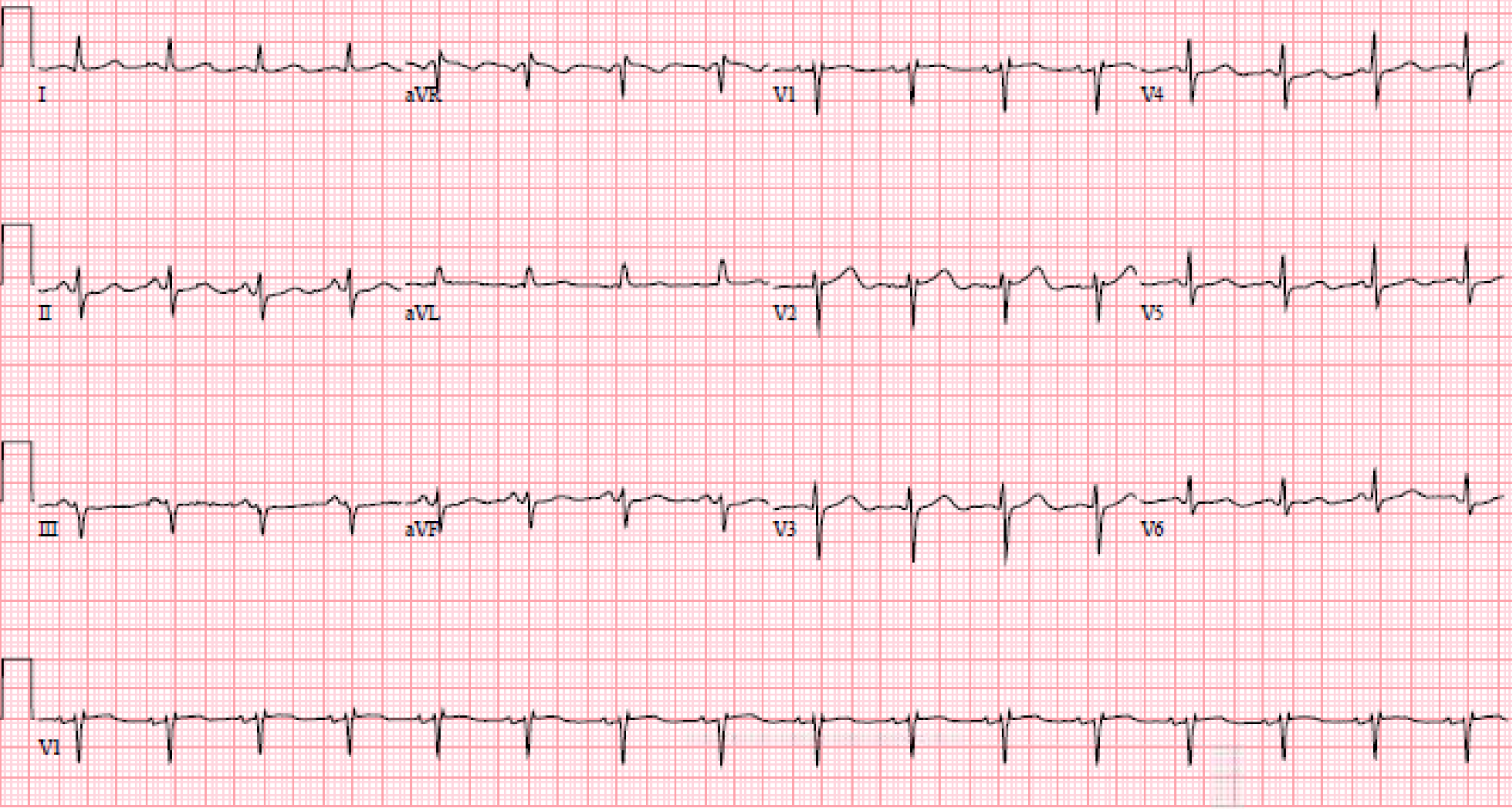


Lower Extremity Doppler

Impression:

No evidence of deep vein thrombosis in the bilateral lower extremities veins as described.




I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

Initial labs

CBC
- Hb: 7.7 g/dL
- HCT: 23.1%
  - MCV 106.9 fL
- WBC: 7.3K
- Plts: 170K

BMP
- Na: 142
- K 3.6
- Cl 105
- COO2 22
- AG: 15
- Glucose 89
- BUN 11
- Cr 1.0
- Ca 8.5
- Mg 1.8

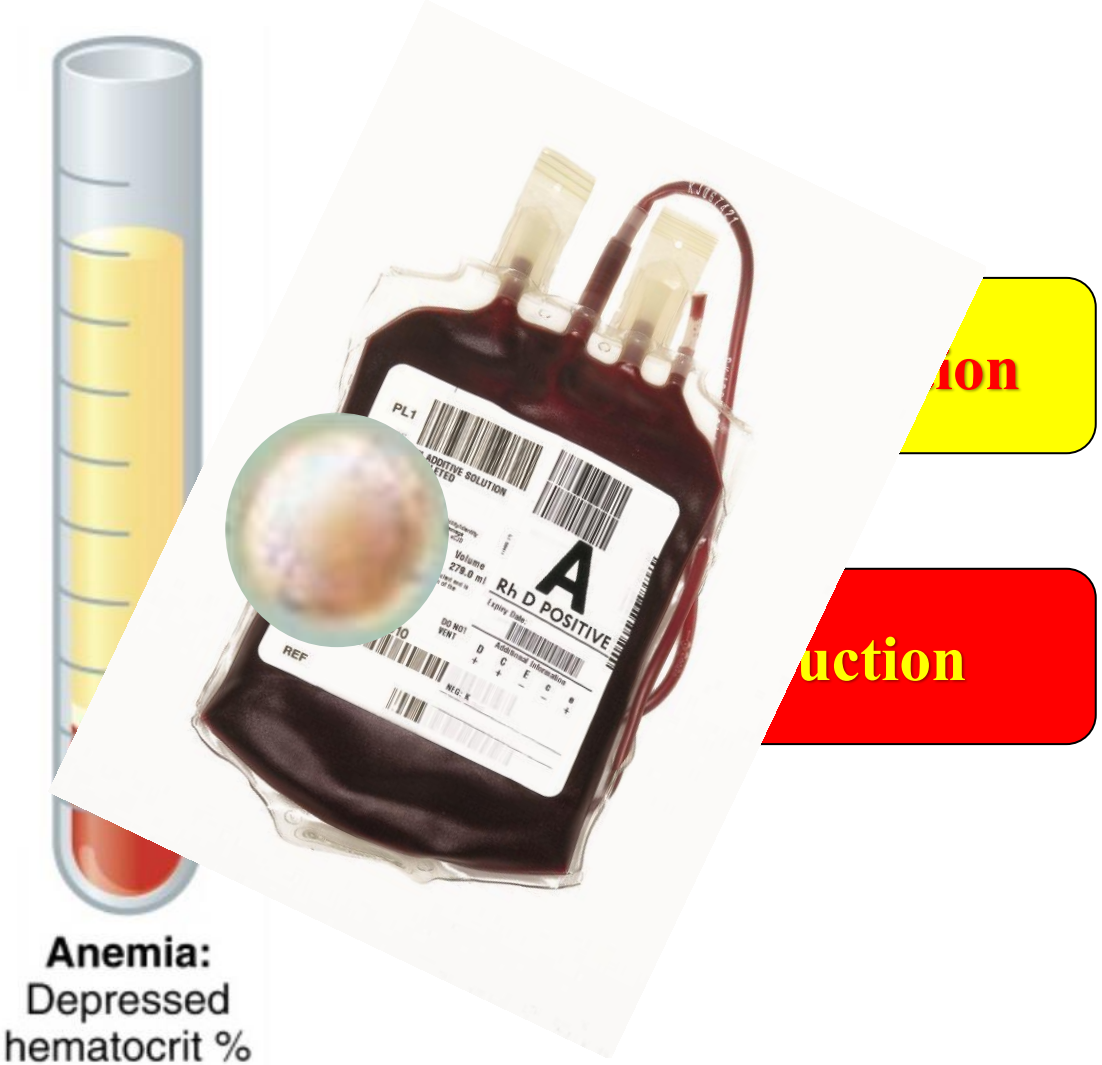
Liver Panel
- AST 22
- ALT 16
- Alk Phos 75
- T Bili: 2.8 / DB 0.5
- T Protein: 7.1
- Albumin 4.1

Troponin I: 0.06 -> 0.2 (9H)
LDH: 650
TSH: 1.20
FOBT: negative

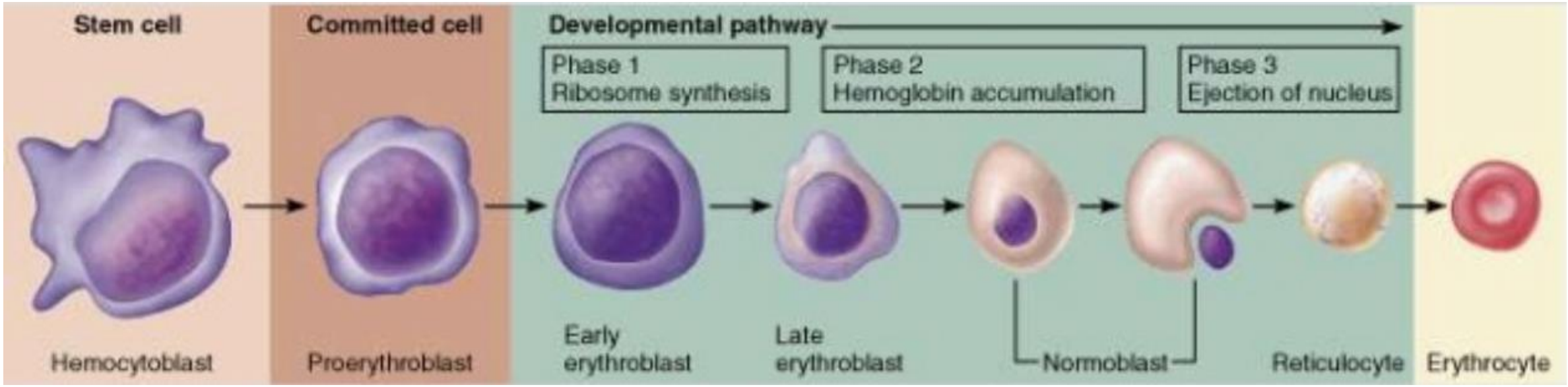
Coags: PT 14.3 | INR 1.4 | aptt 23.7

Hemolytic or Hypoproliferative?

- Hb: 7.7 g/dL | HCT 23.1
  - MCV 106.9 fL
- T Bili : 2.8
- LDH: 650
- PT 14.3 | INR 1.4 | aptt 23.7
- Troponin I: 0.06 -> 0.2 (9H)



Reticulocytes - the first clue

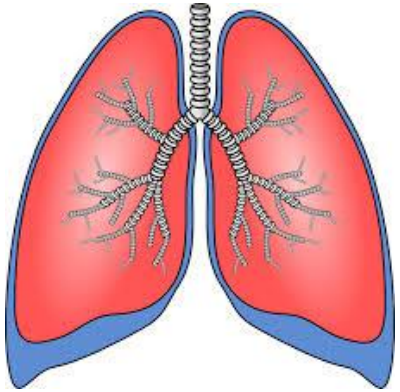


- **Absolute retic count**: 12.9 (24.1-87.7 K)

The Predictive Value of Serum Haptoglobin in Hemolytic Disease

Anthony Marchand, MD; Robert S. Galen, MD, MPH; Frederick Van Lente, PhD

LDH	Haptoglobin



Sudden onset Dyspnea

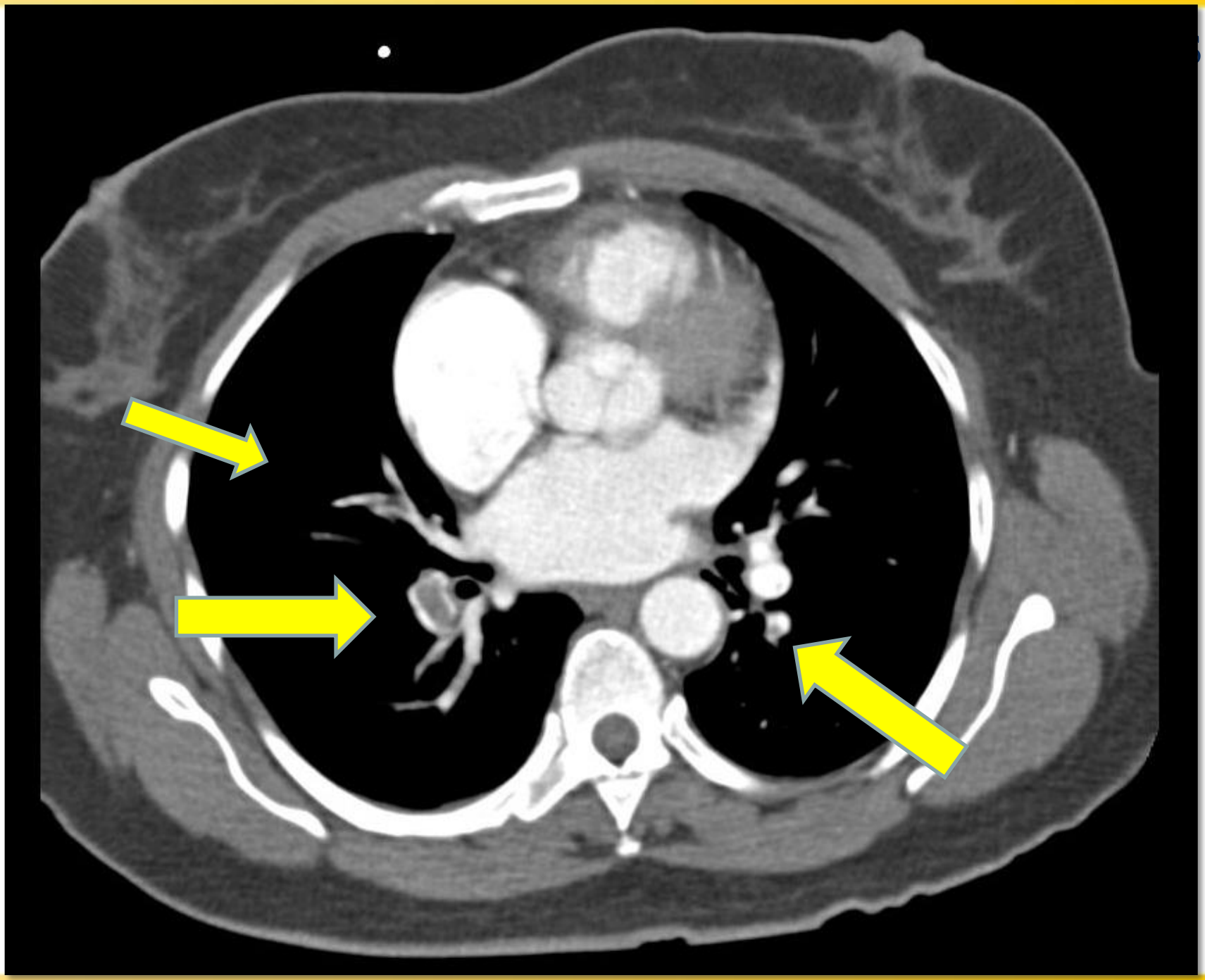
Tachycardia

Bilateral pedal edema X 2 weeks (new)

IMPRESSION:

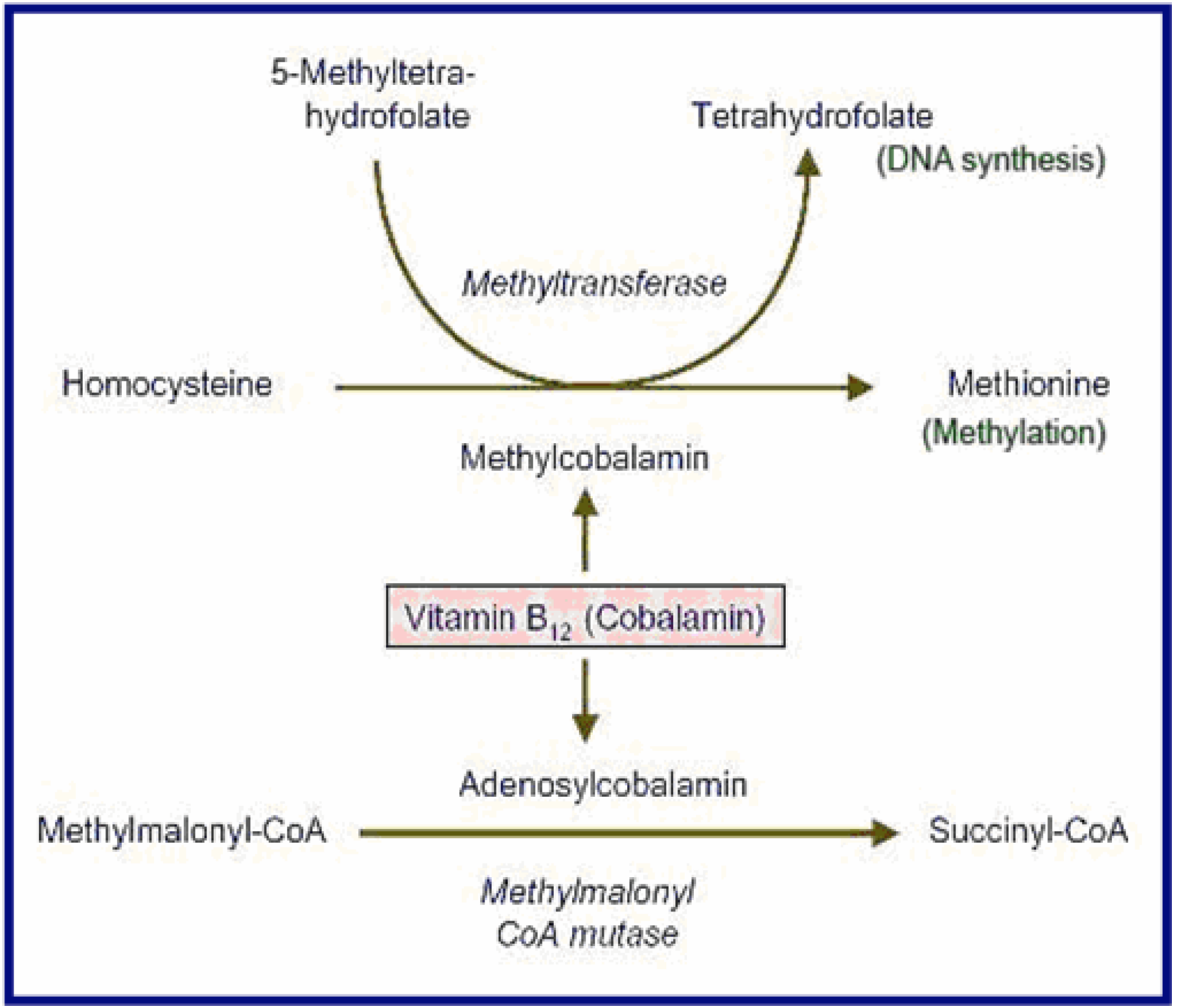
1. Extensive pulmonary emboli within segmental branches of pulmonary arteries throughout both lungs.

2. No CT evidence of right heart strain.



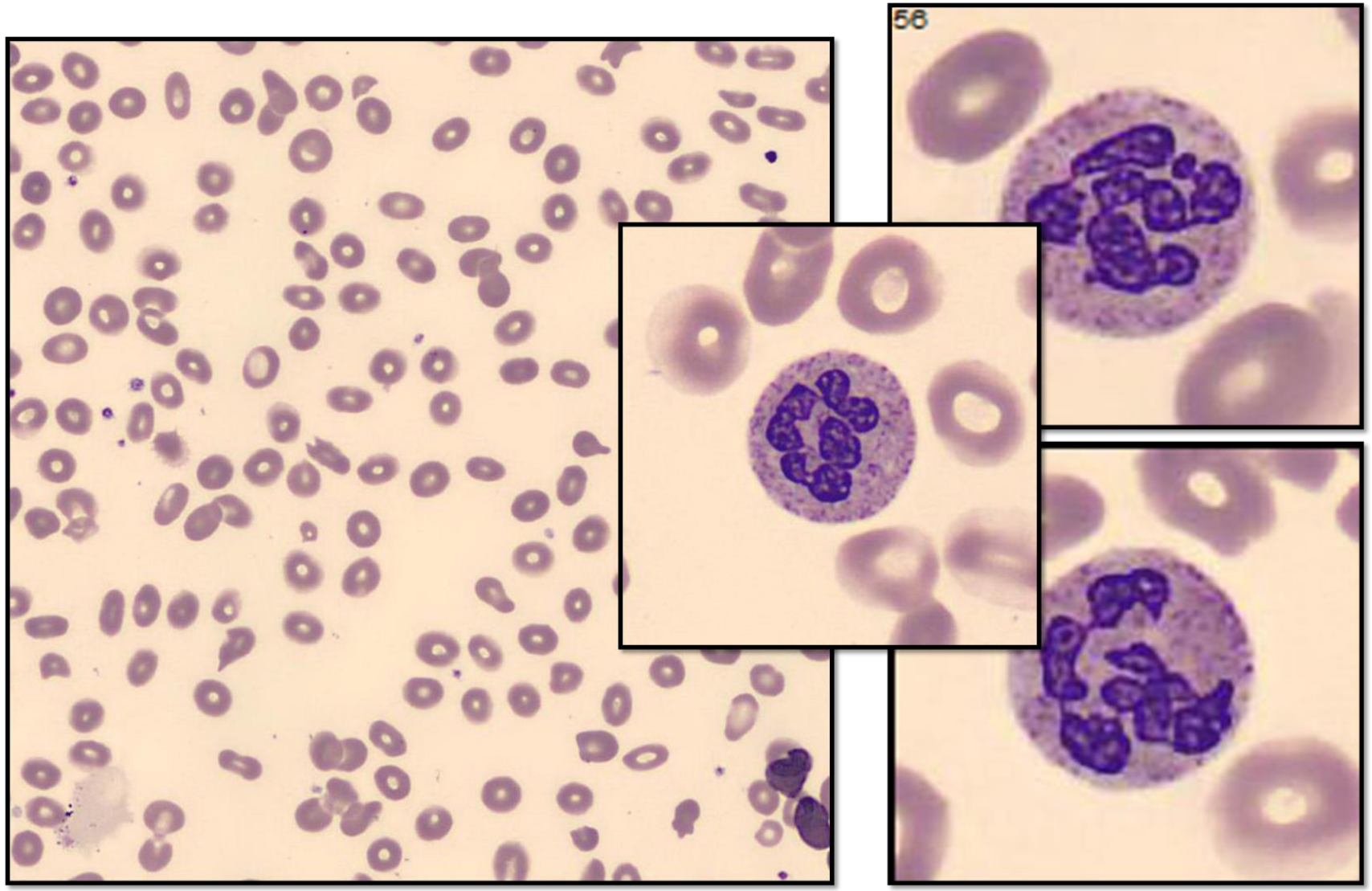
Paresthesia
Impaired memory
Gait instability
Macrocytosis

	Measured	Reference Range
B12, Serum	33 pg/mL	211-946
Homocysteine	200 umol/L	4.0-15.2
MMA	8770 nmol/L	45-325
Intrinsic Factor Ab	Positive	Negative


5-Methyltetra-
hydrofolate
Tetrahydrofolate
(DNA synthesis)
Methyltransferase
Homocysteine
Methionine
(Methylation)
Methylcobalamin
Vitamin B_{12} (Cobalamin)
Adenosylcobalamin
Methylmalonyl-CoA
Succinyl-CoA
Methylmalonyl
CoA mutase

Peripheral Blood Smear

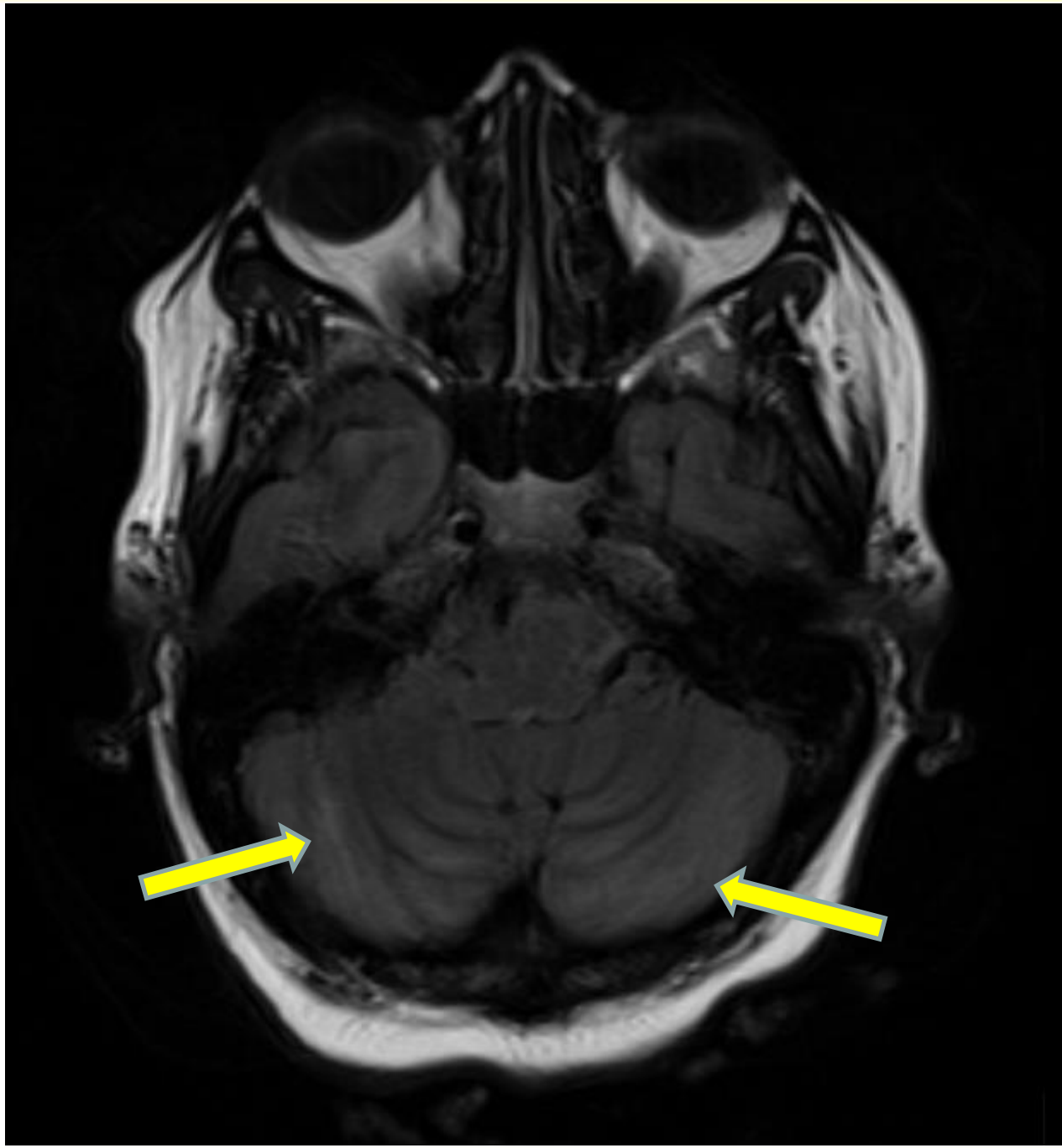
- Hypersegmented neutrophils
- Macrocytosis, poikilocytosis, fragments, bites, ovalocytes and teardrops.

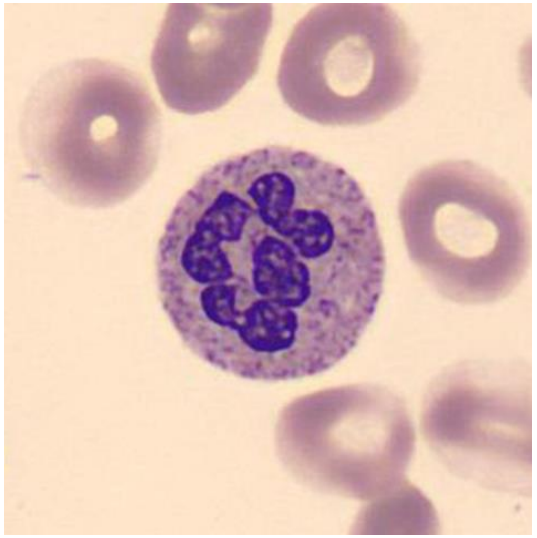


MRI of Brain: T2 FLAIR

IMPRESSION:

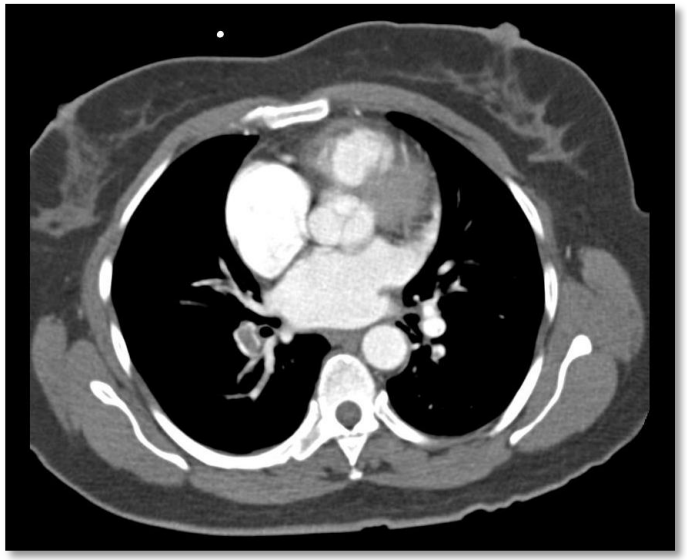
- High signal intensity in the cerebellar hemispheres bilaterally
  - described in the Journal of child neurology 2013 December in **vitamin B12 deficiency**.





Homocysteine

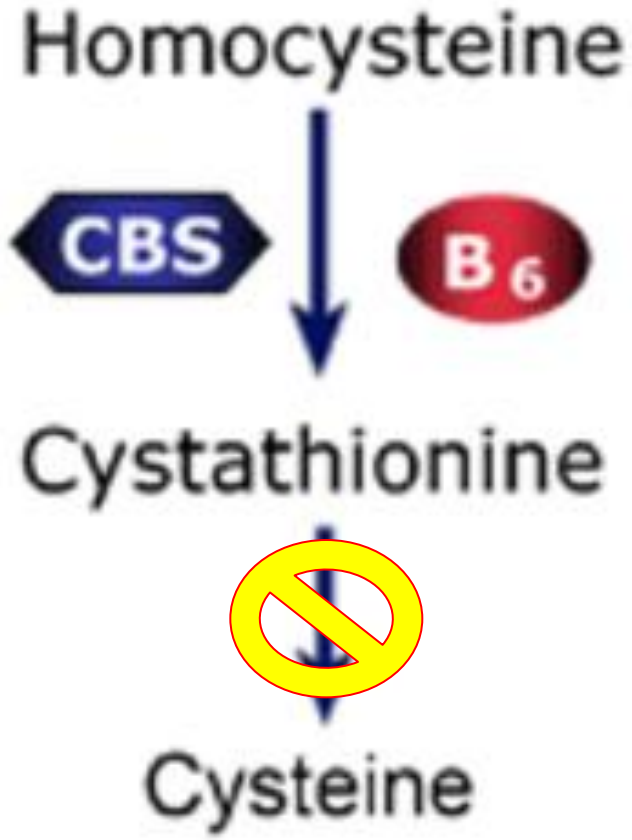
William Occam



YES!!

Congenital Homocystinuria

- Mutation in the cystathionine beta-synthase gene
- Autosomal recessive
- Ectopic lentis, myopia and other abnormalties
- **Thromboembolism is the most common cause of death**



Last 11 cases see at JHH with B12 deficiency

- 4/11 had VTE
- 3/11 referred for TMA and plasma exchange

Age	Sex	Presentation / Diagnosis	B12	HCY 4-12	MMA 90-279	VTE?
49	F	pancytopenia, neuropathy, AMS, TMA	30	108.6	83050	-
42	F	PE	62	144	4160	Y
51	F	PE , anemia, neurological sxs	33	200	8770	Y
56	M	anemia, fatigue, paresthesias	48	49.5	21400	-
57	F	dizzy, anemia, “TMA”	30	123.3	39490	-
53	M	fatigue, jaundice	45	105	5056	-
73	M	glossitis, fatigue, dyspepsia, FTT	33	189.4	175000	-
45	F	syncope, fatigue	42	-	2320	-
67	F	DVT, fatigue	62	-	-	Y
24	M	pancytopenia, “TMA”		-	-	-
44	M	PE (syncope, dyspnea)	95	92.4	431	Y

Management

- IV heparin infusion initiated and bridged with enoxaparin to warfarin with an overlapping regimen of enoxaparin.

- Pernicious anemia was managed with intramuscular vitamin B12 repletion followed by oral B12 indefinitely.

Follow Up

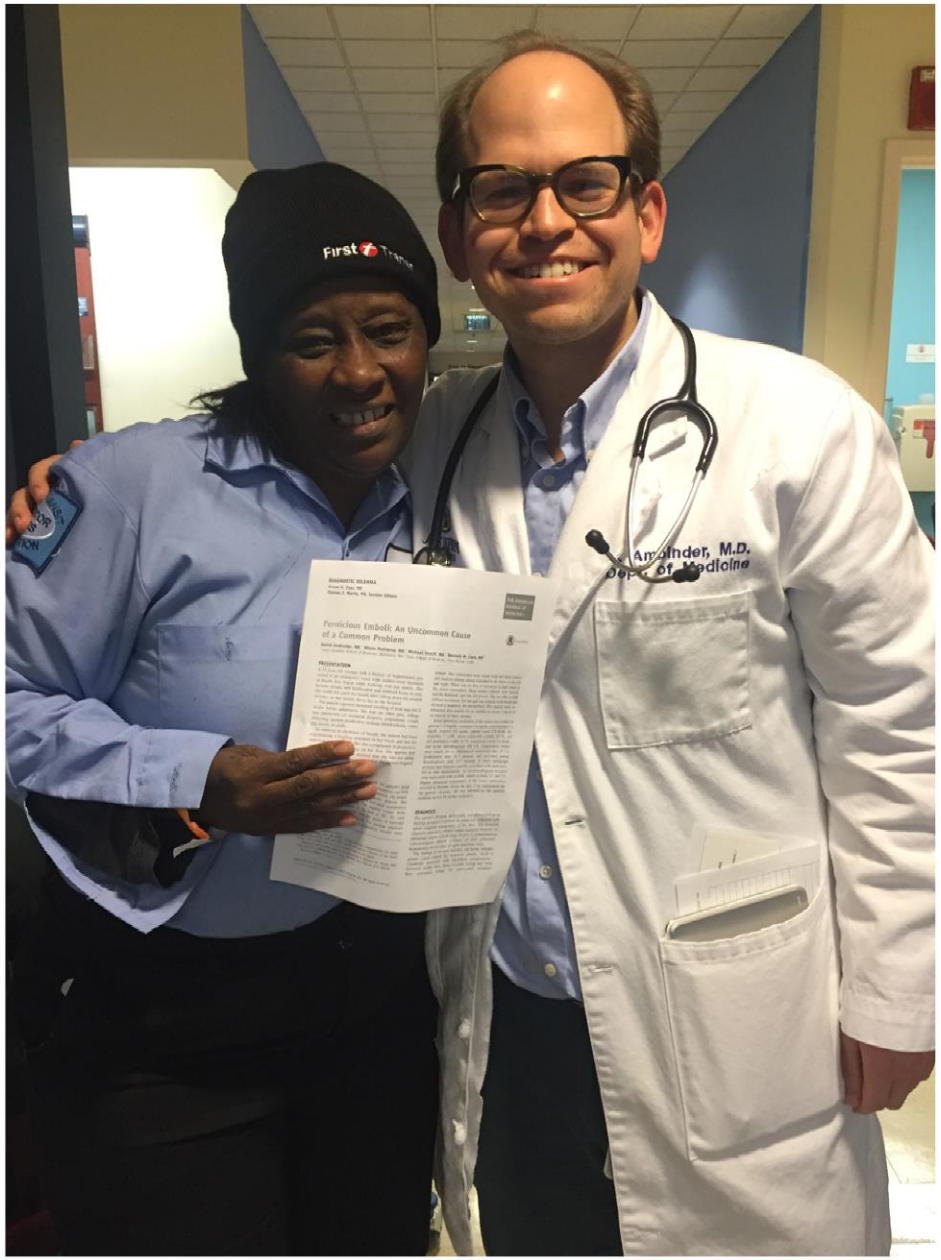
- The patient returned to clinic 7 months later, having continued vitamin B12 supplementation.

- Anticoagulation was discontinued

	2004	9/2014	4/2015
Hemoglobin *12.0-15.0 g/dL*	12.8	7.7 (L)	13.0
Hematocrit *36.0-46.0 %*	39.9	23.1 (L)	41.3
Mean Corpuscular Volume *80.0-100.0 fL*	82.8	106.9 (H)	83.9
Mean Corpus Hgb *26.0-34.0 pg*	26.6	35.6 (H)	26.4
RBC Distribution Width *11.5-14.5 %*	13.6	16.7 (H)	14.0
Bilirubin,Total *0.0-1.2 mg/dL*	0.4	2.8 (H)	0.5
D-Dimer *0.17-0.88 mg/L FEU*		20.84 (H)	0.28
Vitamin B12 *211-946 pg/mL*		33 (L)	922
Methylmalonic Acid, Serum		8770 (H)	88
Homocysteine *4.0-15.2 umol/L*		200.0 (H)	8.5

… But the best part of it is

- Full neurologic recovery
- Moved out of her daughter's home and lives independantly
- Began driving for the MTA



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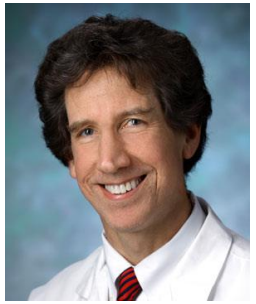
Take home points

- B12 deficiency can present similarly to a micropathic hemolytic anemia
- Decreased reticulocyte count, elevated LDH and normal Haptoglobin can help distinguish the two states
- B12 deficiency is a potentially reversible cause of thrombophilia

Acknowledgements

- Debra Ravert, MD

- Michael Streiff, MD



- Alison Moliterno, MD

- Bennett Clark, MD

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Pernicious Emboli: An Uncommon Cause of a Common Problem

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Department of Medicine, Johns Hopkins University School of Medicine

INTRODUCTION

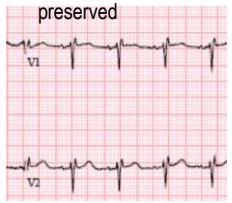
- Vitamin B12 deficiency is a well described condition that leads to macrocytic anemia and neuropsychiatric disorders.
- B12 absorption requires several steps that include stomach acid facilitating breakdown of the vitamin bound to food, secretion of intrinsic factor (IF) by gastric parietal cells, the binding of IF and B12 in the duodenum, and the complex is absorbted in terminal ileum
- Pernicious anemia is an autoimmune process where an autoantibody to intrinsic factor is produced leading to atrophic gastritis and B12 deficiency.
- B12 acts as a cofactor in the conversion of methylmalonic acid (MMA) to succinyl-coenzyme A and homocysteine to methionine.
- In the absence of B12, levels of neurotoxic MMA increase driving peripheral neuropathies, subacute combined degeneration of the spinal cord, dementia and memory loss. Inability to convert homocysteine to methionine leads to a megaloblastic anemia and in severe cases, pancytopenia.

CASE DESCRIPTION

- 51 yo F with HTN presents with sudden-onset shortness of breath associated with diaphoresis and lightheadedness that began while walking but persisted with rest
- Associated with recent development of paresthesia, impaired memory, fatigue and gait instability.
- Family members reported fatigued, drowsy and forgetful.
- Pertinent negatives: chest pain, orthopnea, PND, palpitations, cough, wheezing, sputum production, melena, hematochezia, vomiting, fevers or chills.

EVALUATION

- ED Vitals: T 36.5, P 112, BP 130/80, RR 16, SpO2 94%
- Shallow pitting edema extended to the knees bilaterally. Cardiopulmonary exam was unrevealing
- Gait was slightly wide based and showed a tendency for retropulsion
- Mental status examination was notable for an inability to recall three objects at an interval of three minutes.
- Sensation to light touch and deep tendon reflexes were preserved



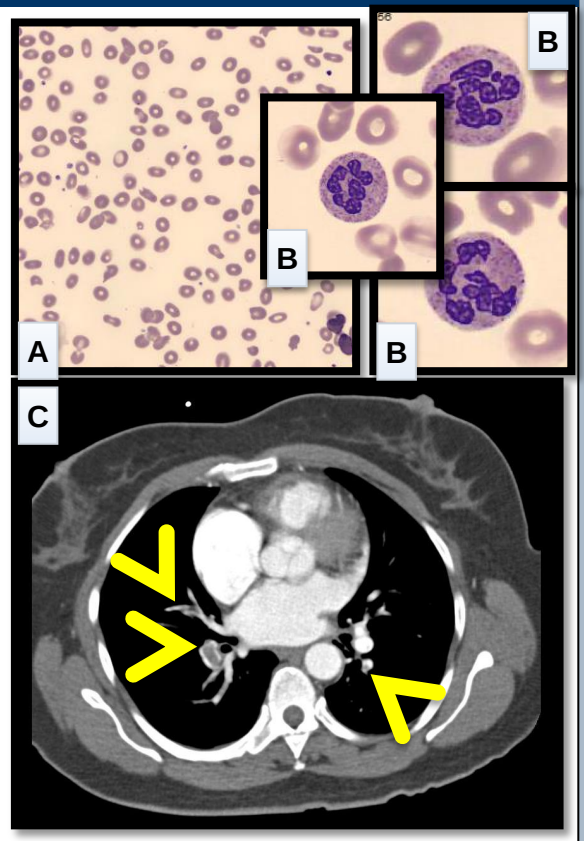
Hemoglobin	7.7 g/dL
Platelets	170 K/cu mm
MCV	107 fL
RDW	16.7%
Reticulocytes	0.6 K/cu MM
T bilirubin	2.5 mg/dL
Troponin	0.6 ng/mL
PT/INR/aPTT	14.3/1.4/23.7

DIAGNOSIS

- Dyspnea, tachycardia, and EKG findings prompted a spiral CT of the chest which revealed extensive pulmonary emboli within segmental branches of pulmonary arteries of both lungs
- Constellation of paresthesia, impaired memory, gait instability, and macrocytosis raised concern for a hypoproliferative anemia caused by vitamin B12
- Serum levels of B12, homocysteine, and methylmalonic acid levels are shown below
- Intrinsic factor antibodies confirmed the diagnosis of pernicious anemia.

B12, Serum	33 pg/mL (nl 211-946)
Homocysteine	200 umol/L (nl 4.0-15.2)
MMA	8770 nmol/L (nl 45-325)

MICROSCOPIC AND RADIOGRAPHIC DATA



A: Peripheral smear demonstrating macrocytic anemia with poikliocytosis, fragments, bites, ovalocytes and tear drops consistent with macrocytic anemia.
B: Hypersegmented neutrophils
C: CT PE protocol demonstrating extensive pulmonary emboli within segmental braches of pulmonary arteries throughout both lungs.

INTERVENTION AND RESPONSE TO RX

- IV heparin infusion initiated and bridged with enoxaparin to warfarin with an overlapping regimen of enoxaparin.
- Pernicious anemia was managed with intramuscular vitamin B12 repletion.
- Evaluation in clinic 7 months later demonstrated a complete resolution of symptoms, patient reentry into the workforce, and normalization of the complete blood count

DISCUSSION AND TEACHING POINTS

- We describe above a unique case of pulmonary embolism associated with pernicious anemia, hyperhomocysteinemia and hemolysis
- Case-control studies of hospitalized patients with VTE suggest that vitamin B12 deficiency is also independently associated with VTE. Mechanism by which vitamin B12 deficiency increases thrombotic risk remains unclear
- B12 deficiency can present similarly to a micropathic hemolytic anemia, as in this case, with elevated total bilirubin, LDH, and RBC fragments seen on peripheral blood smear
- Differentiation between thromboticmicroangiopathies and pseudo-TMA is crucial as the former requires emergent plasmaphoresis and the former does not.
- Decreased reticulocyte count can help distinguish the two as it is decreased in hypoproliferative states, such as B12 deficiency

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