Case review: Pulmonary hypertension induced by Primary Peripheral Pulmonary Artery Stenosis

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CASE 1

29/M

Progression of pulmonary hypertension on echocardiography

Present illness

- mMRC grade 2 dyspnea since age of 7
- 12 years ago (2006.07) chest X-ray for medical check-up
  : enlarged pulmonary artery, r/o pulmonary hypertension
  → Admission
- TR Vmax = 4.5 m/sec on echocardiogram,
  small sized aorta, proximal PA dilatation, multifocal luminal narrowing of segmental PA on chest CT

Present illness

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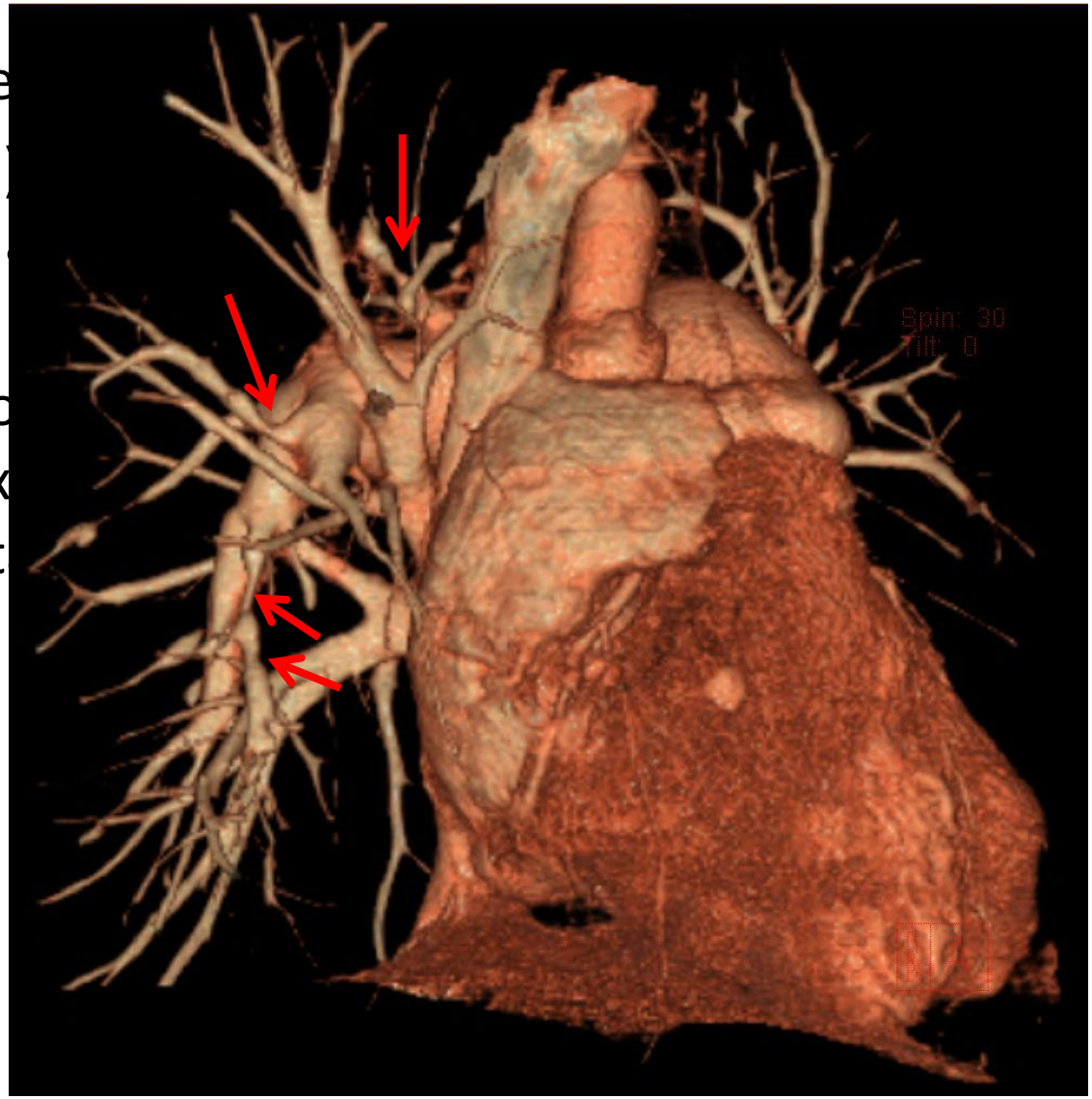
- 12 years ago (2006.07)
  : enlarged pulmonary
  → Admission
- TR Vmax = 4.5 m/sec c
  small sized aorta, prox
  narrowing of segment



Present illness

- mMRC grade 2 dyspnea since age of 7
- 12 years ago (2006.07) chest X-ray for medical check-up
  : enlarged pulmonary artery, r/o pulmonary hypertension
  → Admission
- TR Vmax = 4.5 m/sec on echocardiogram,
  small sized aorta, proximal PA dilatation, multifocal luminal narrowing of segmental PA on chest CT,
  negative for ANCA, rheumatoid factor, FANA
  → Suspicious congenital PPAS or Takayasu arteritis, started beraprost
- 3 months ago, TR Vmax = 5.3 m/sec on routine follow-up TTE

Past medical/familial/social history

- Past medical history: no hypertension/DM/tuberculosis
- Familial history: none
- Social history: non-smoker, social drinking
- Medication: beraprost

Review of systems

- General: not so ill-looking appearance
- HEENT

Headache	(-)	Dizziness	(-)	Visual disturbance	(-)
Photophobia	(-)	Sore throat	(-)	Oral ulcer	(-)
Rhinorrhea	(-)	Hoarseness	(-)		

- Cardiovascular

Palpitation	(-)	Chest pain	(-)

- Respiratory

Cough	(-)	Sputum	(-)	Hemoptysis	(-)
Wheezing	(-)				

- Gastrointestinal, Musculoskeletal, Neurologic

  : non-specific

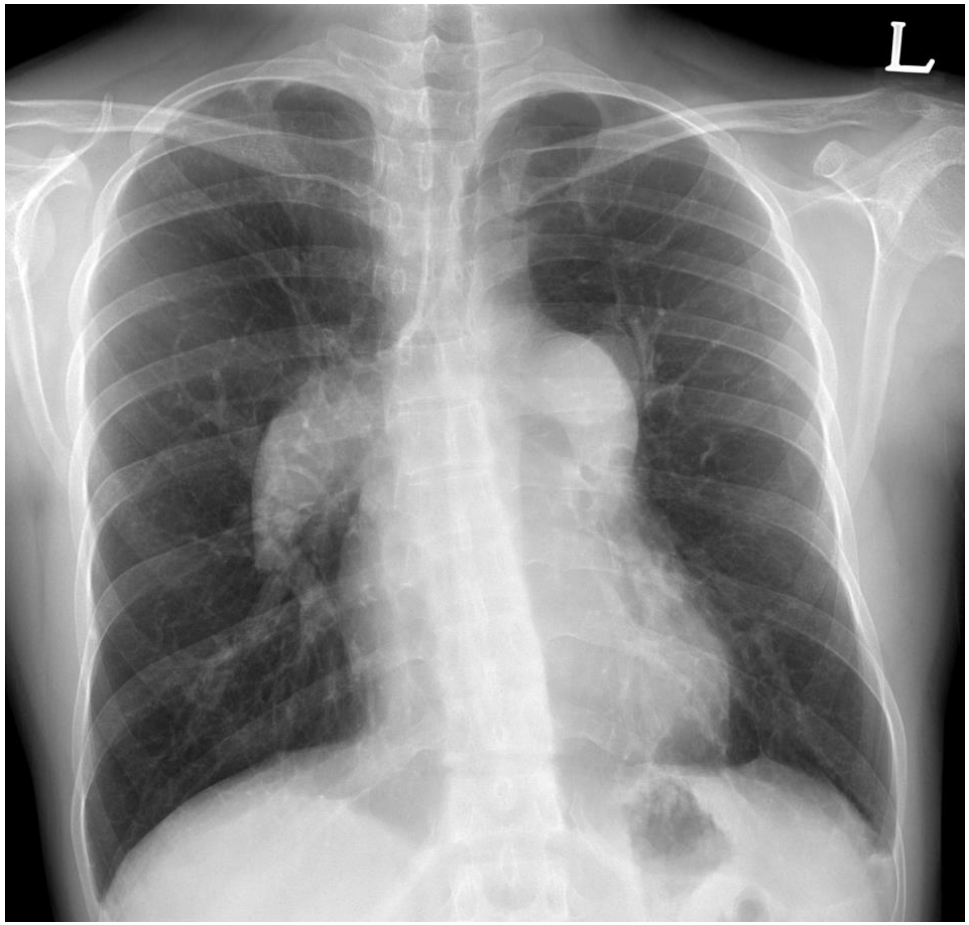
Physical examination

- Vital sign
  BP 132/82 mmHg HR 80/min RR 16/min BT 36.2℃
- General appearance
  Acute ill-looking, alert mental status
- HEENT
  : non-specific, no LN enlargement
- Thorax
  Symmetric expansion
  Normal tactile fremitus
  No abnormal sound on percussion
  Normal breath sound, no murmur, wheezing, ronchi
- Heart, Abdomen, Back and extremity, Neurologic
  : non-specific

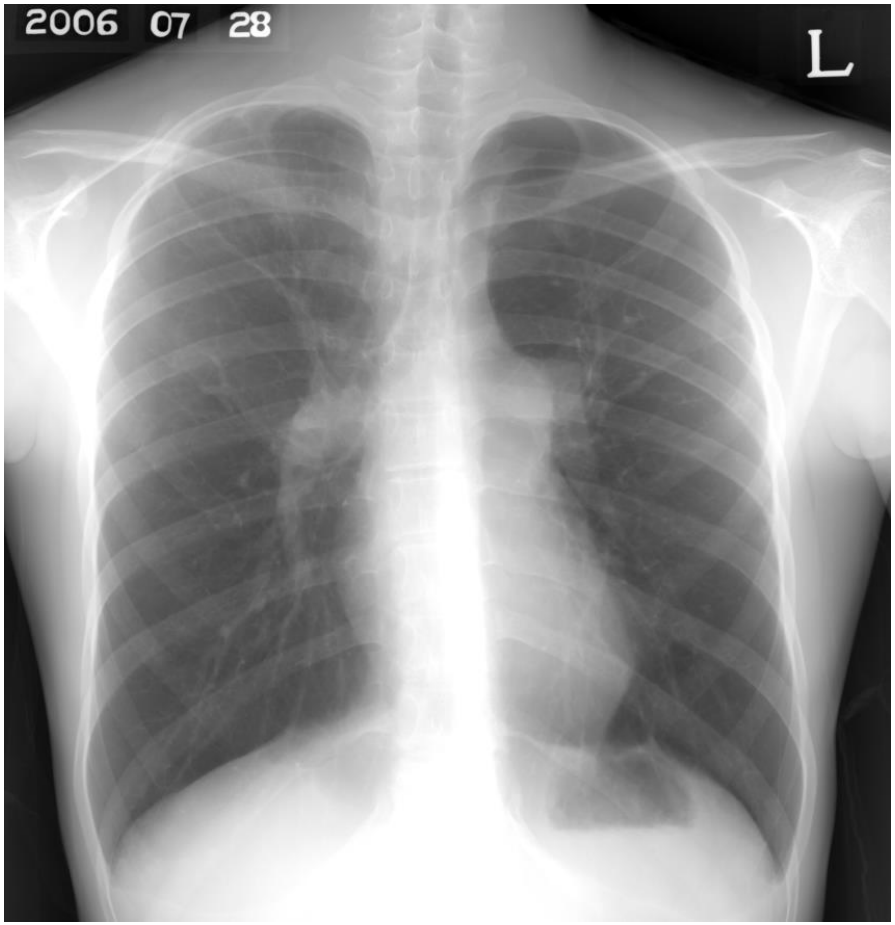
Laboratory data

CBC	8400 (N 63.4%, L 28.1%) – 15.2 – 356K
Chemical battery	
AST/ALT ALP/TB	25/5 398/0.9
BUN/Cr	65/5.7
Pro/Alb	7.3/3.7
ESR/CRP	7/2.5
BNP	128
Coagulation battery	
PT %/ INR	84%/1.08
aPTT	28.1
D-dimer	2.09
Electrolyte	
Na-K-Cl	141-4.7-103
Ca/P	9.5/3.6
ABGA/lactate	7.43-29.3-77.4-19.6 / 1.0

Chest X ray

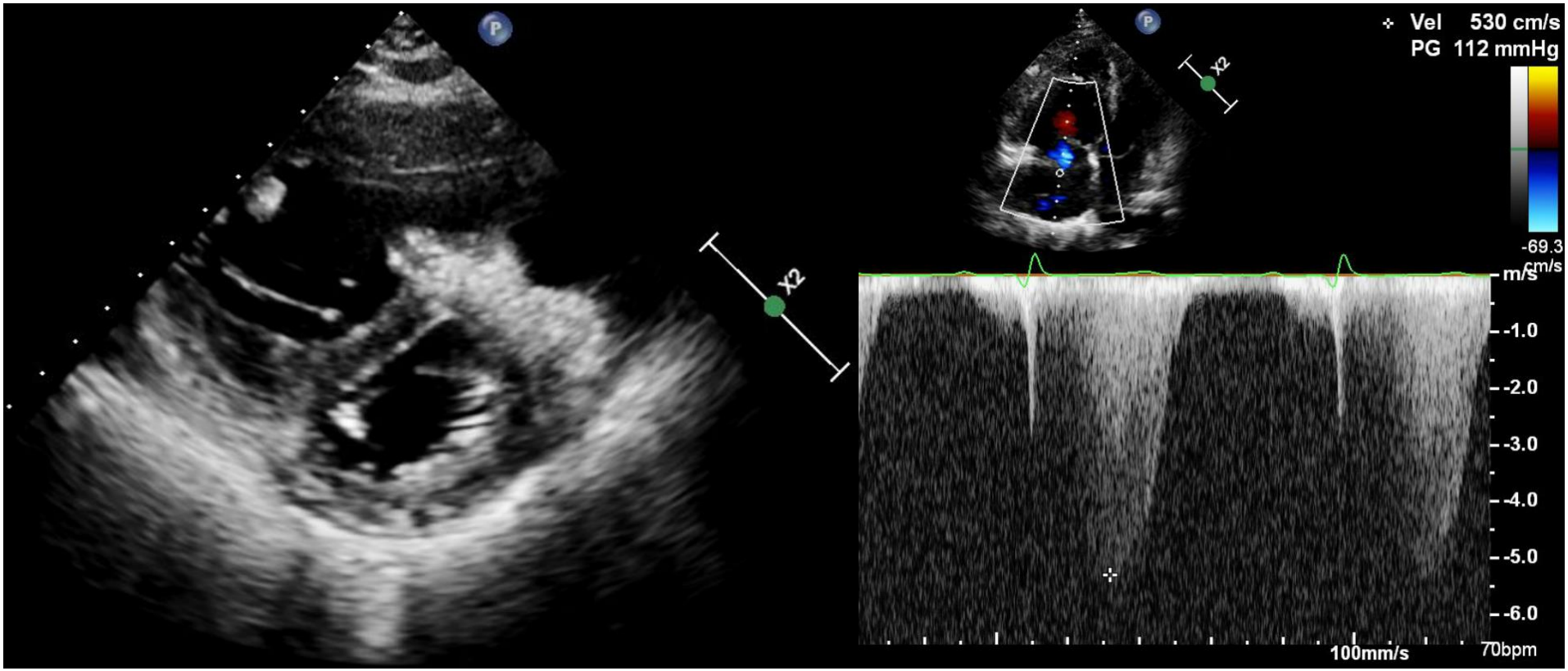


2018-09-07



2006-07-28

Transthoracic echocardiography



LVEF = 61%, thickened RV wall, D-shaped LV

TR Vmax = 5.3 m/s ← 4.5 m/s, severe resting pul. HTN

Assessment & plan

Assessment>

Aggravated pulmonary hypertension in a pt. with peripheral pulmonary artery stenosis of unknown cause

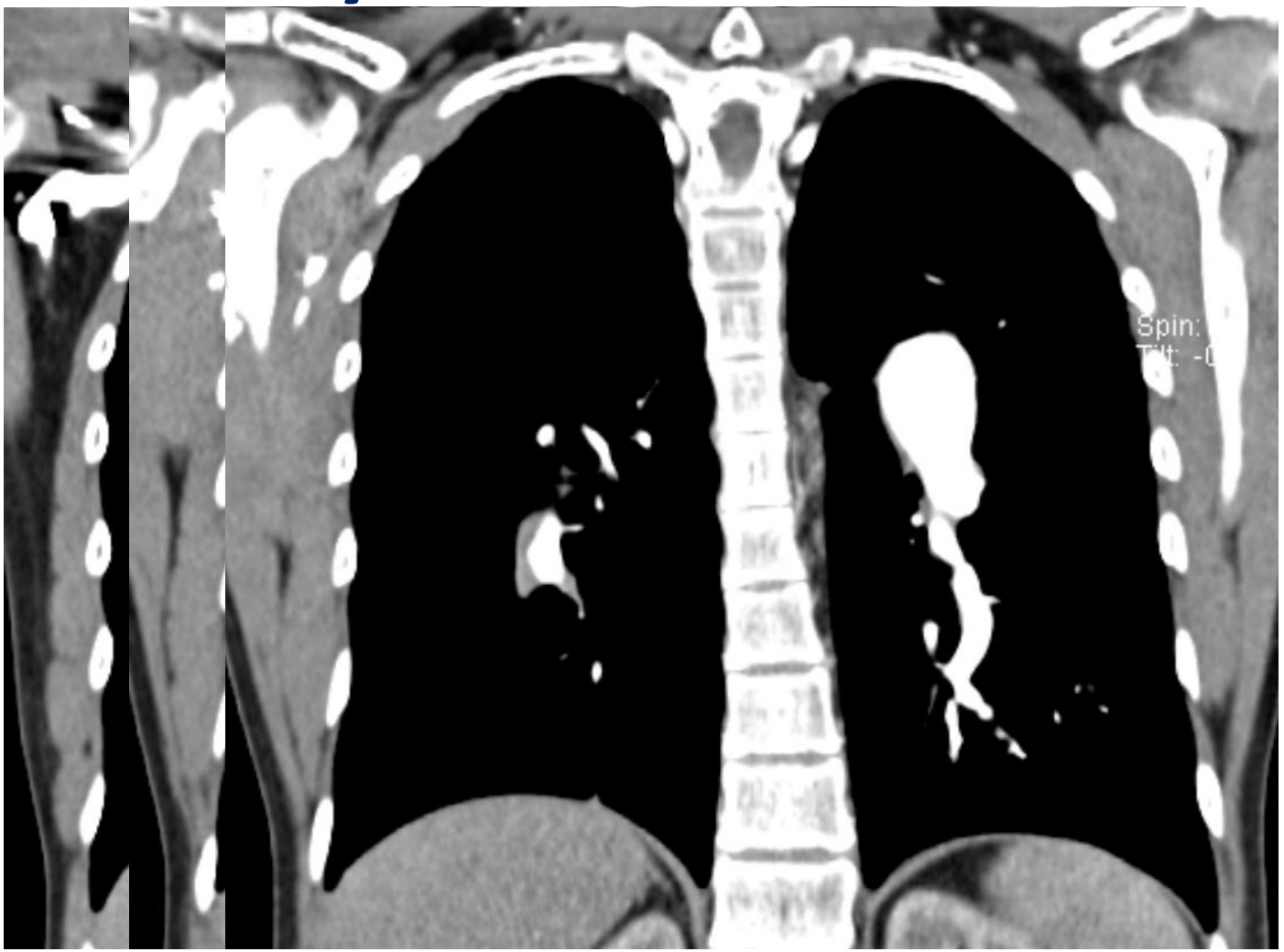
- progression of pulmonary artery stenosis
- combined pulmonary thromboembolism
- increased activity of Takayasu arteritis, less likely

Plan>

Diagnostic: Lung perfusion SPECT, pulmonary embolism CT, Rt heart catheterization, lower extremity US, consider gene test

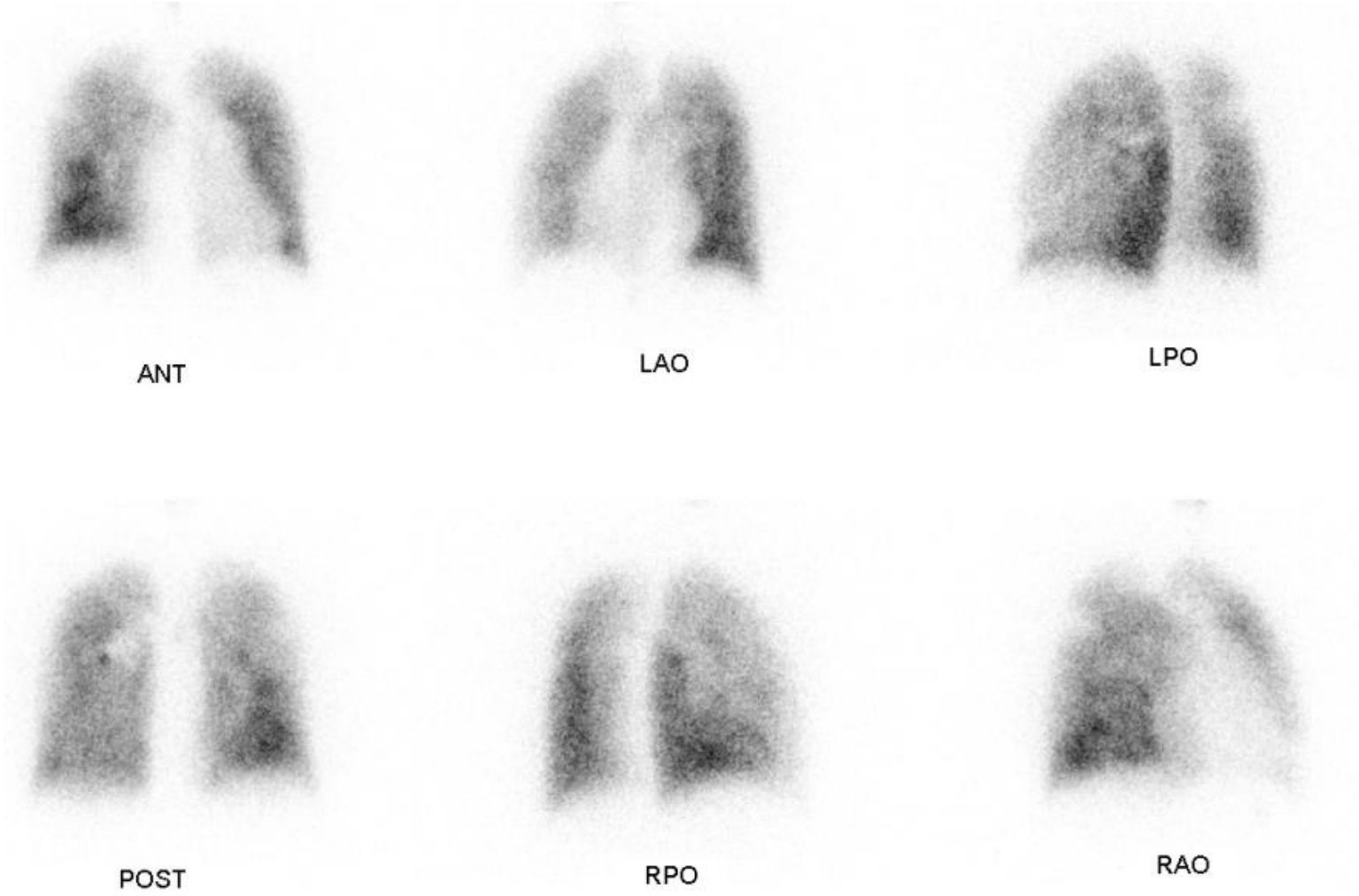
Therapeutic: supportive care

Pulmonary embolism CT



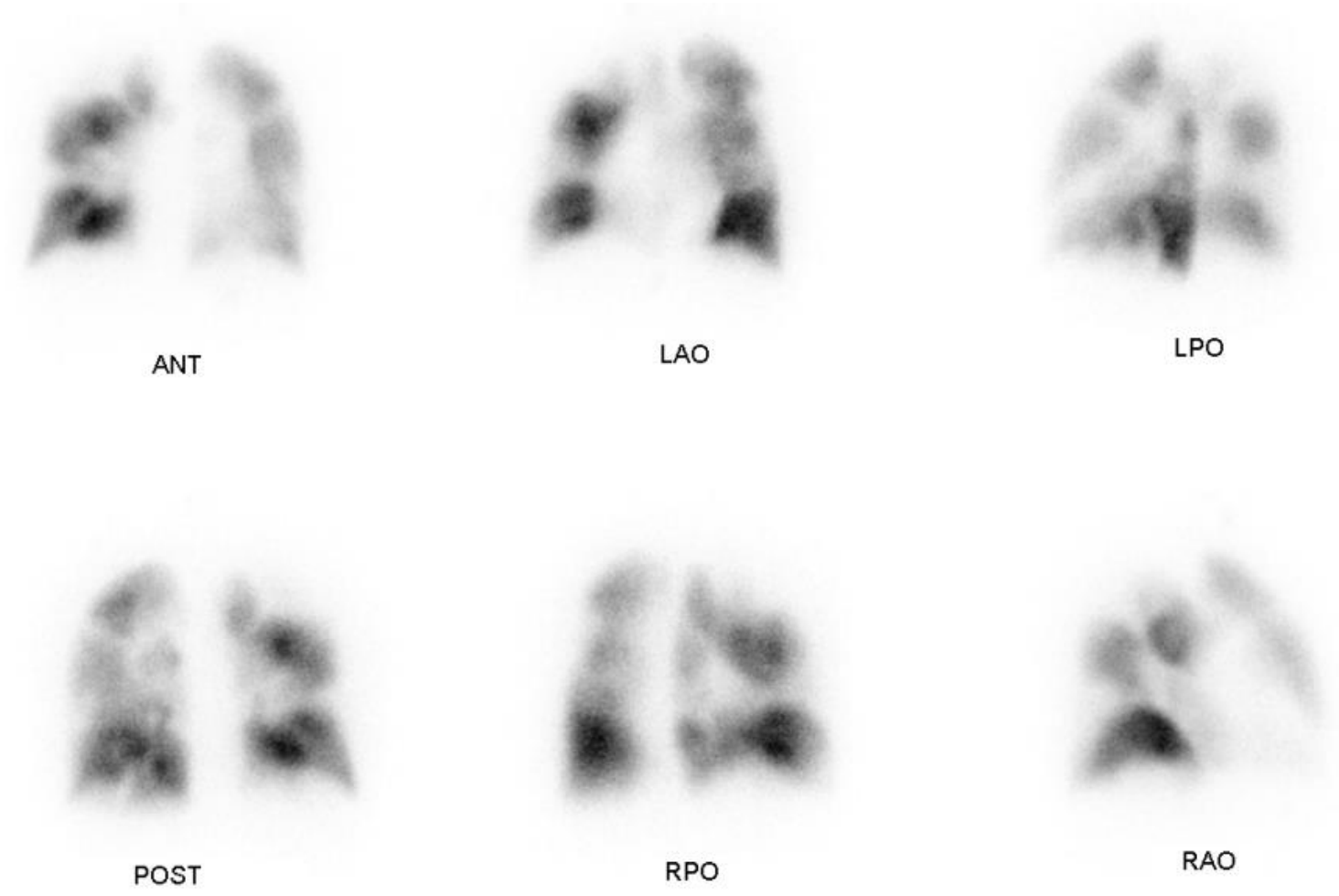
Thrombosis in the Rt. descending, RMLobar, RLLobar, and RLLobar segmental, subsegmental PAs

Lung inhalation / perfusion scan



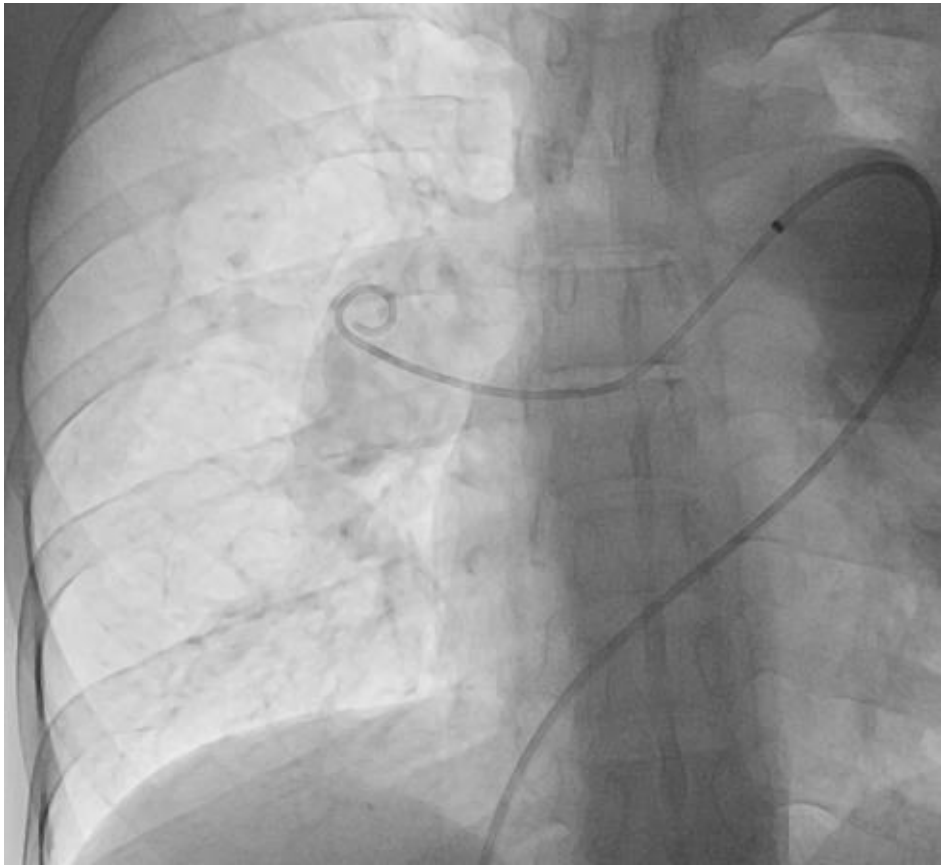
Homogenous tracer distribution, no ventilation defect

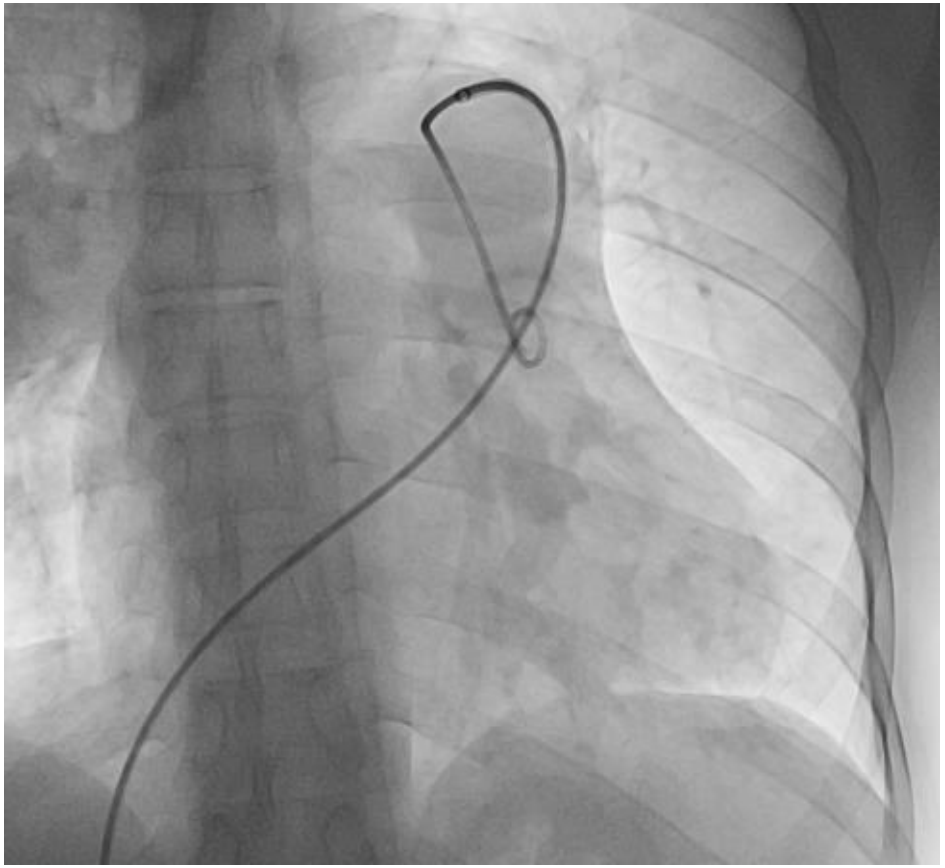
Lung inhalation / perfusion scan



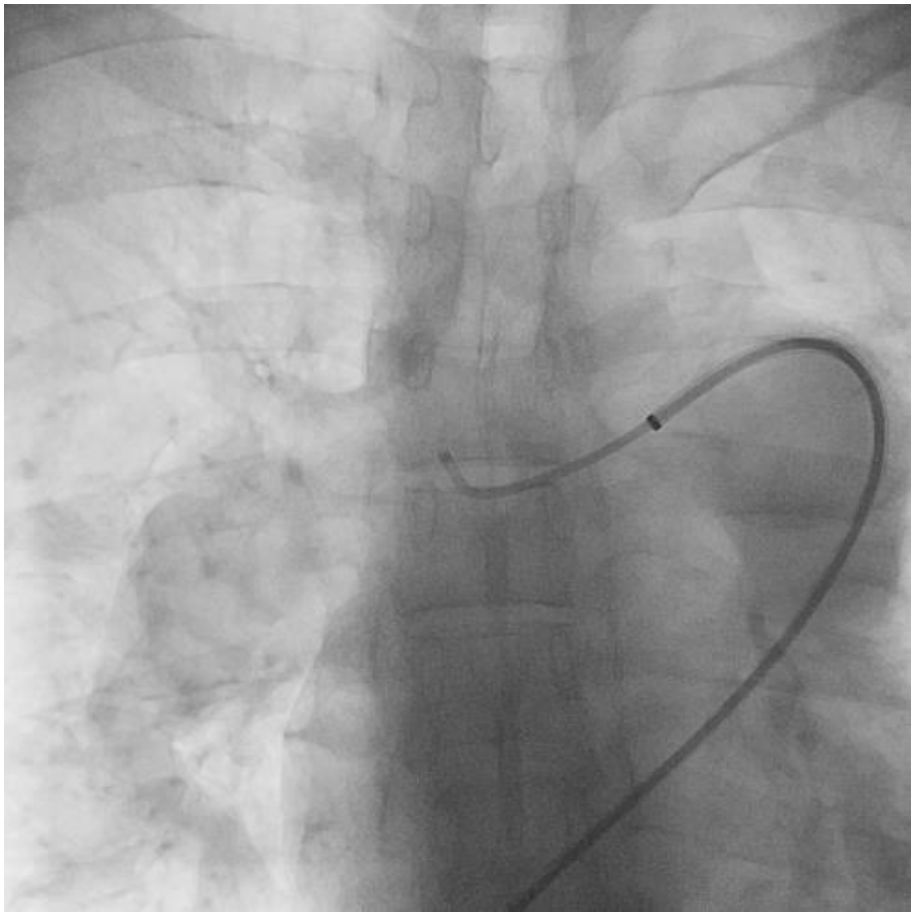
Multiple bilateral segmental large perfusion defects

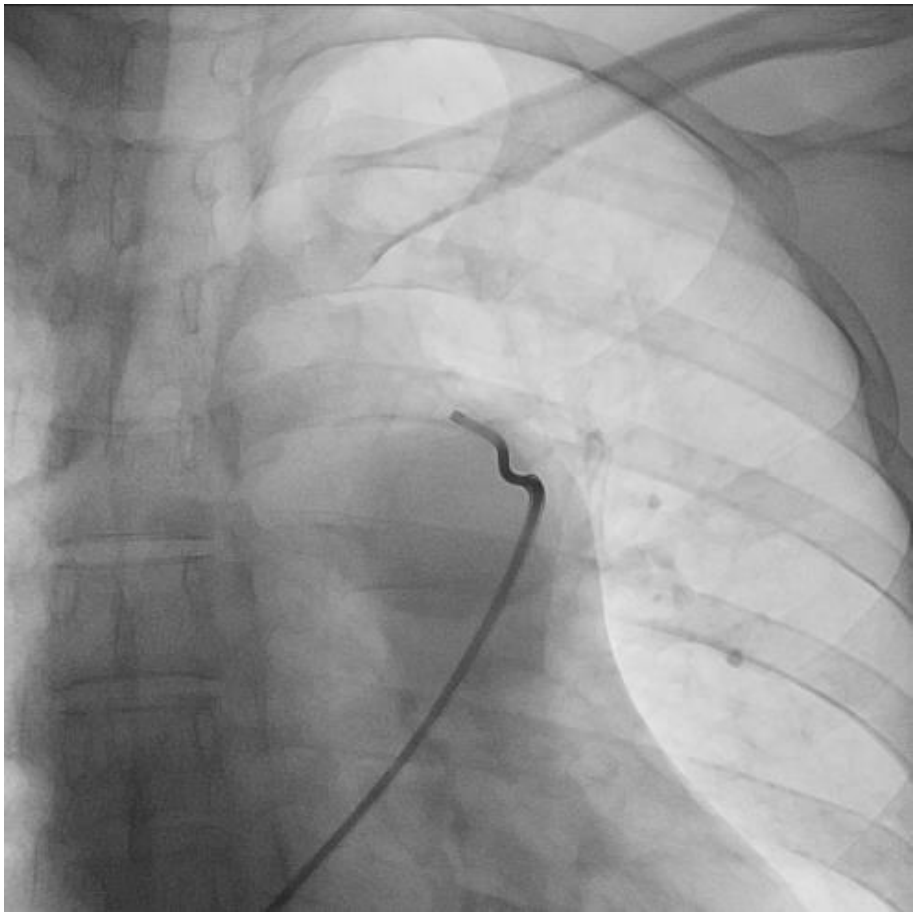
Rt heart cath & angiography





Rt heart cath & angiography





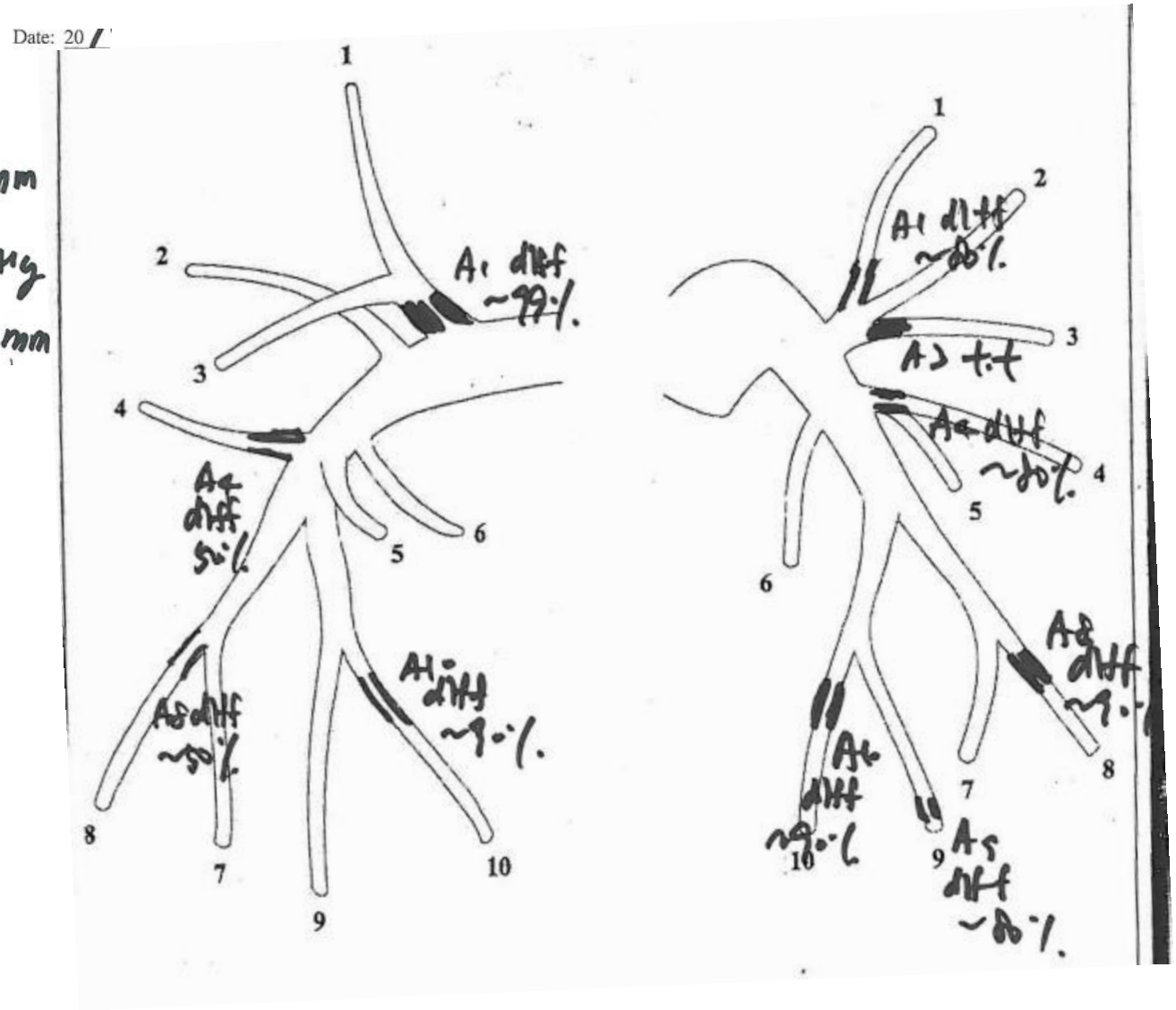
Rt heart cath & angiography

PCWP 6mmHg

MPA 16/4/7(6) mm

RA Pr 9/3(3) mmHg

Aorta 132/79/99 mm



Lower extremity US

- No evidence of DVT

Mutation test

- Homozygote for *RNF213* (Ring finger protein 213) p.Arg4810Lys

Brain, head MR angiography

- No intra- & extra-cranial vessel abnormality

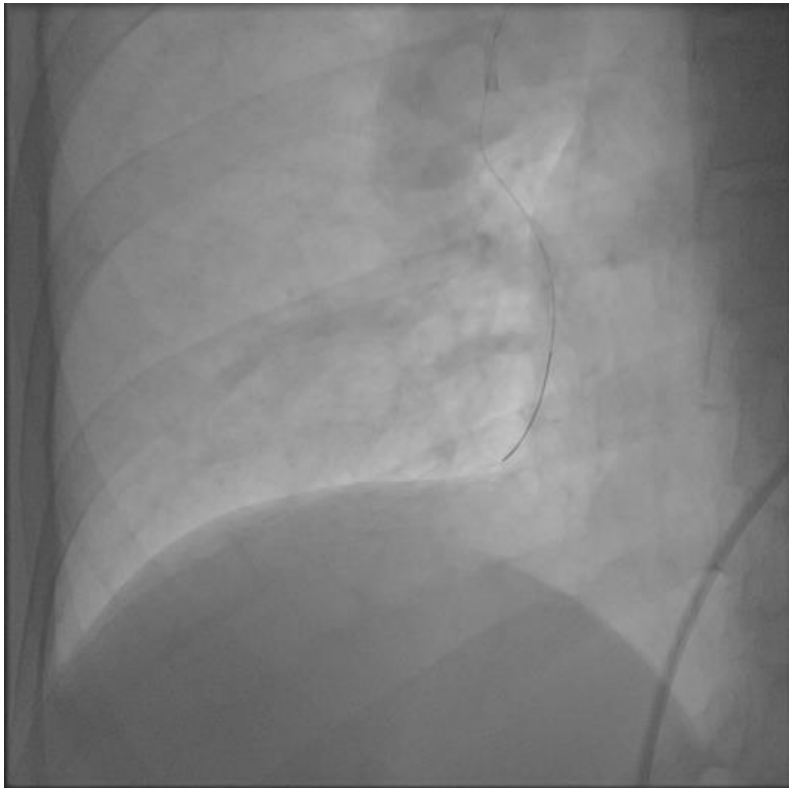
Diagnosis

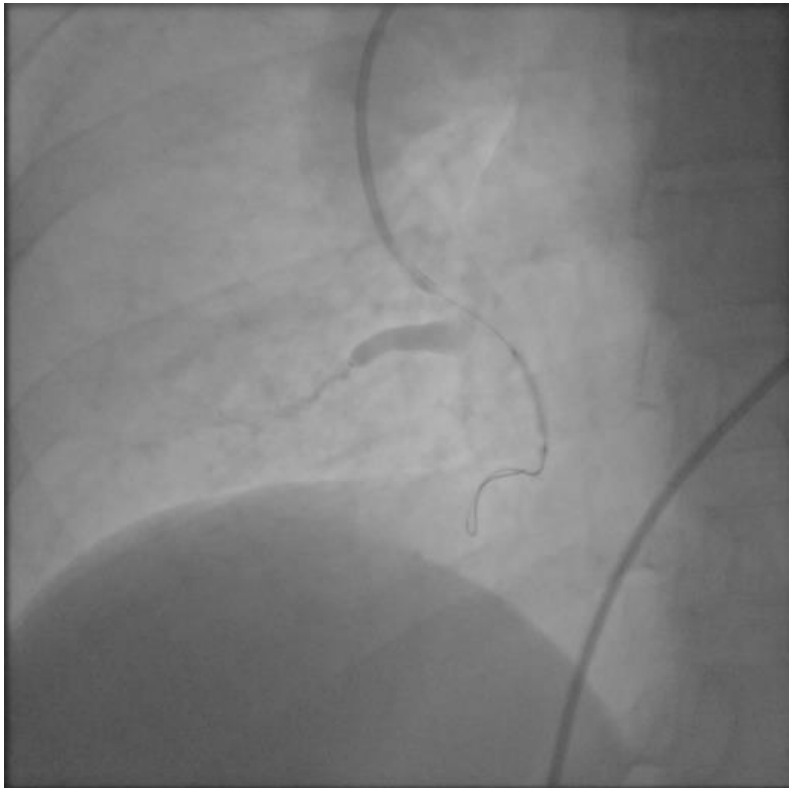
- Primary peripheral pulmonary artery stenosis associated with *RNF213* mutation, combined in situ thrombosis

Treatment

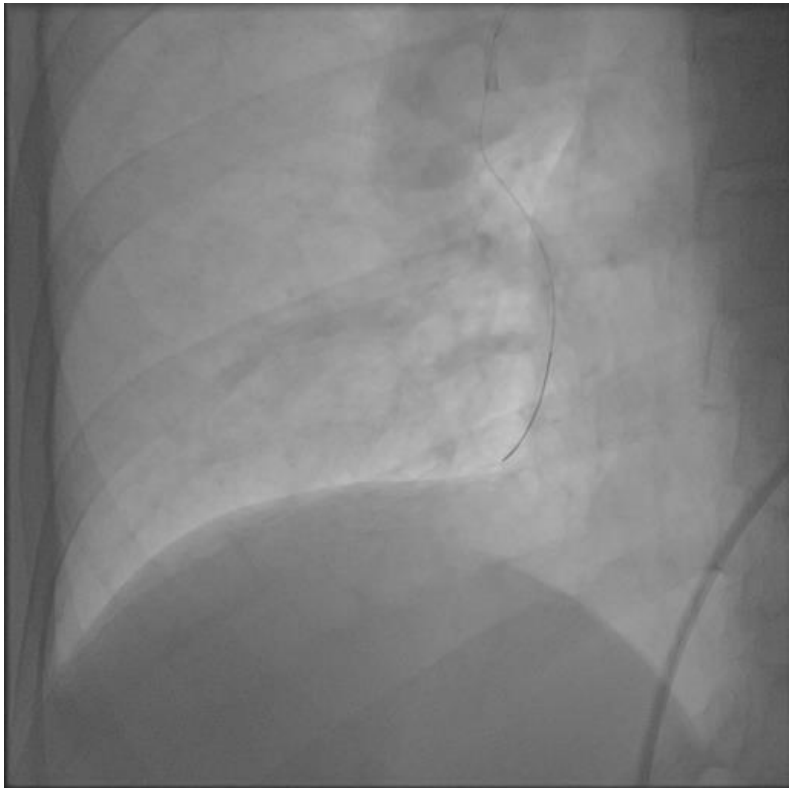
- Anticoagulation for thrombosis
- Balloon angioplasty for PPAS

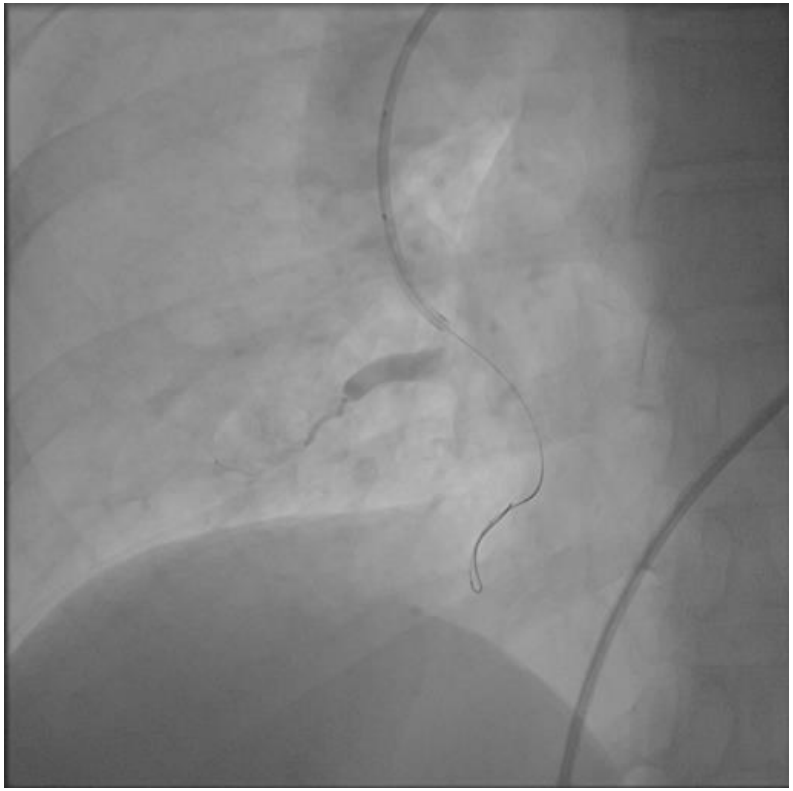
Balloon pulmonary angioplasty (BPA)

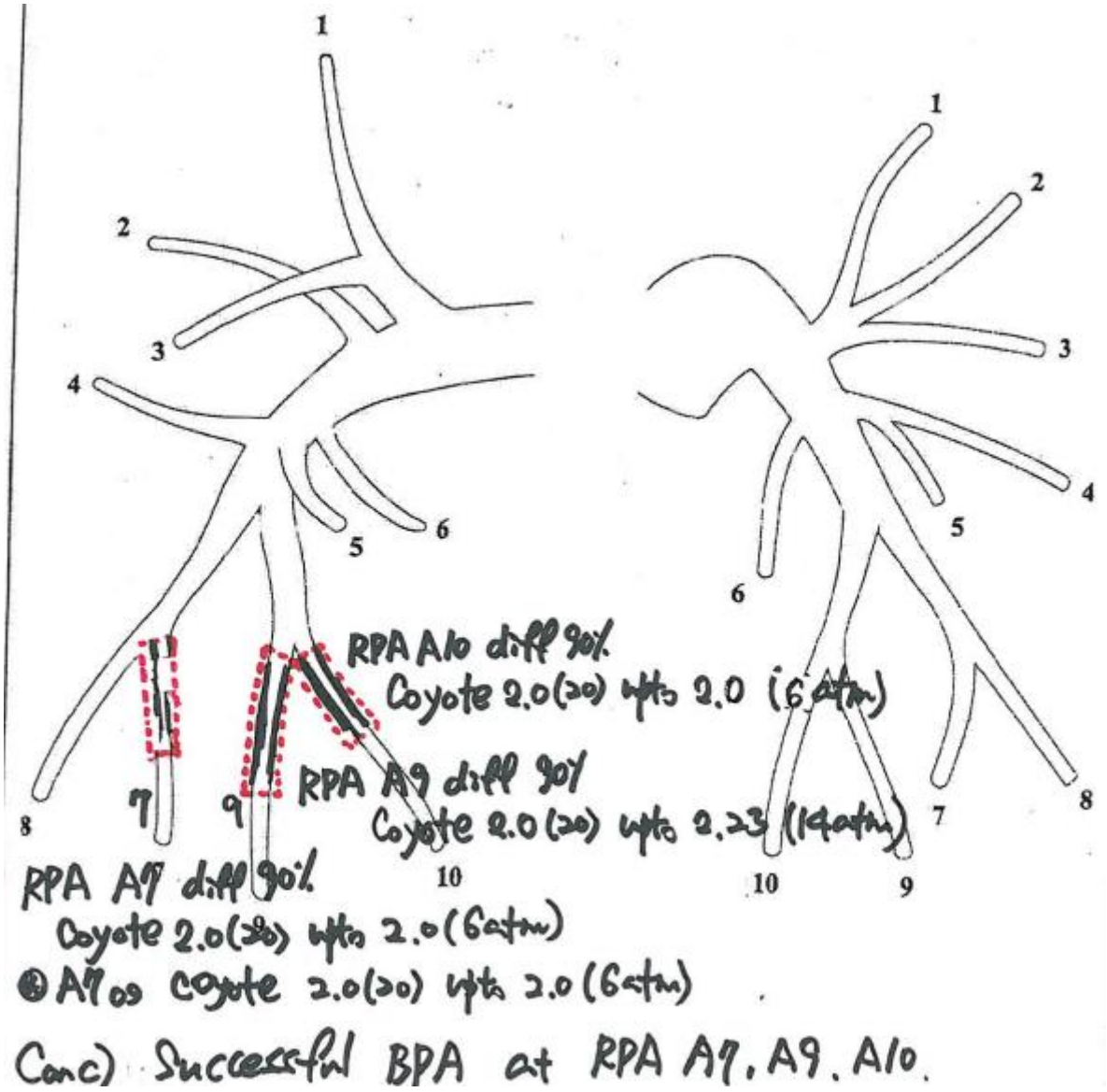




Balloon pulmonary angioplasty (BPA)







RPA pressure

- Pre: 126/46/77
- Post: 118/47/74

CASE 2

32/F
Dyspnea

Medical history with present illness

- mMRC grade 2 dyspnea since 1999 (high school student)
- 11 years ago (2008) r/o pulmonary HTN, TR Vmax = 3.7 m/sec
  → secondary pul. HTN d/t Takayasu arteritis, observation
- 6 years ago (2013) pul. TBc, severe pulmonary hypertension
  → started ambrisentan + beraprost
- Refractory to medical therapy, progressive dyspnea (mMRC Gr 2→3)
- 3 years ago (2016) RHC for disease evaluation
  → CTEPH with multiple PA stenosis, severe pul. HTN
  → septostomy
- Dyspnea not improving → BPA (2017) , but Sx consist

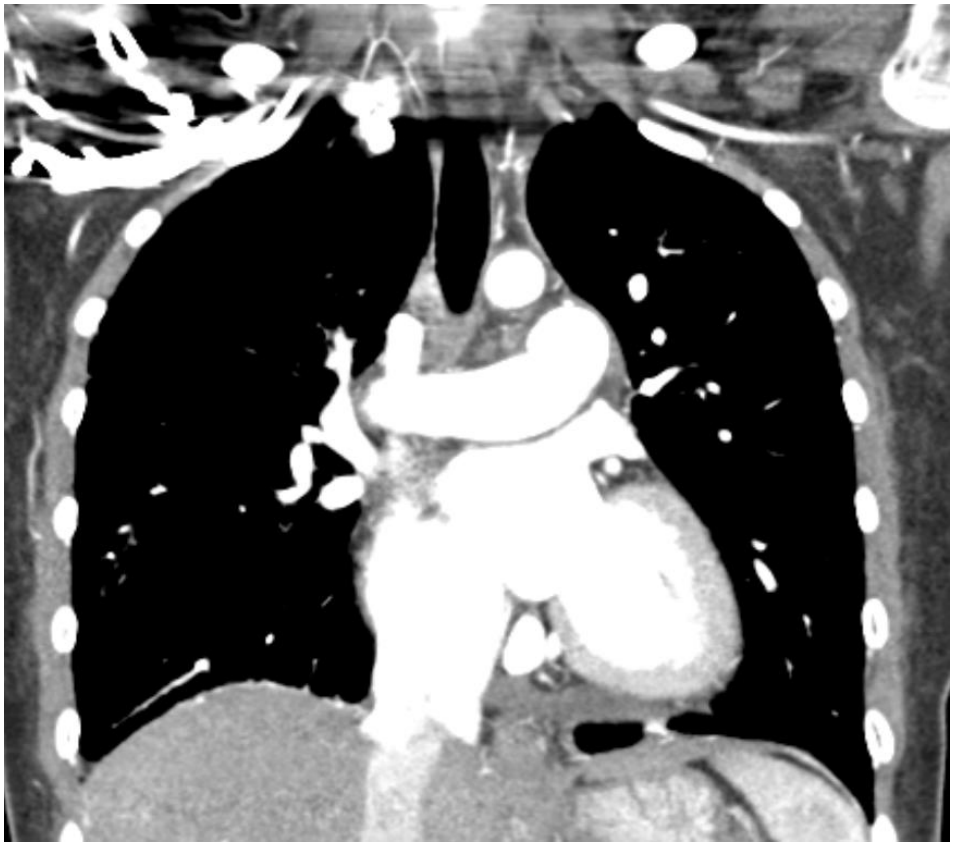
Medication

- Ambrisentan + Beraprost (2013.07.30~2014.05.22)
- Ambrisentan + Sildenafil (2015.05.23~2015.06.24)
- Ambrisentan + Iloprost NEB + PRNSildenafil (2015.06.24~2015.03.22)
- Ambrisentan + Sildenafil(2015.03.23~2015.07.21)
- Remodulin + Ambrisentan (2015.07.22~2016.02.01)
- Ambrisentan + Sildenafil(2016.02.01~)

Familial history

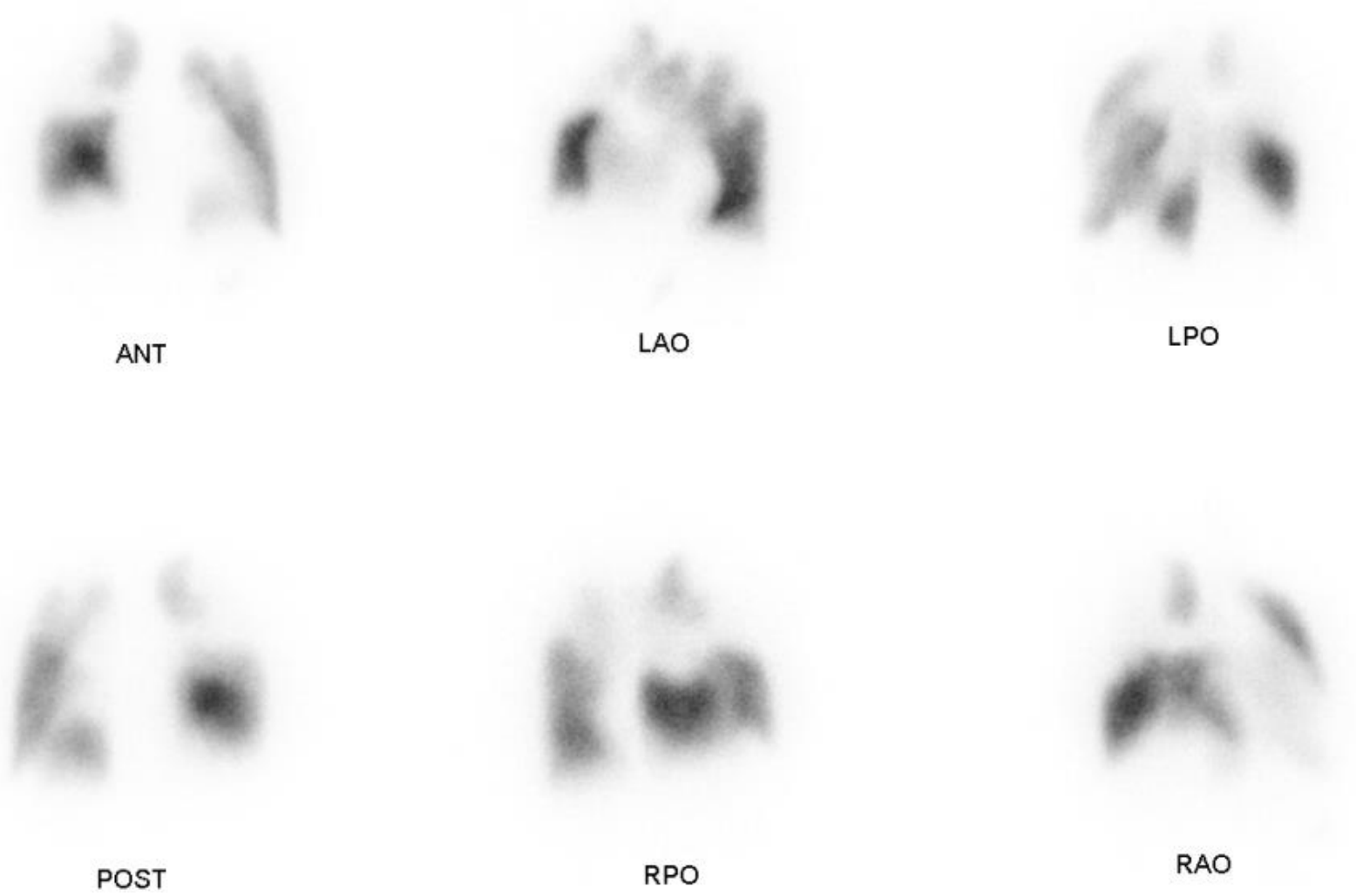
- (+) FHx. For pulmonary hypertension: brother, died at age of 20

Aortic dissection CT



Diffuse narrowing of segmental PA, aorta, and focal narrowing of celiac trunk

Lung inhalation / perfusion scan



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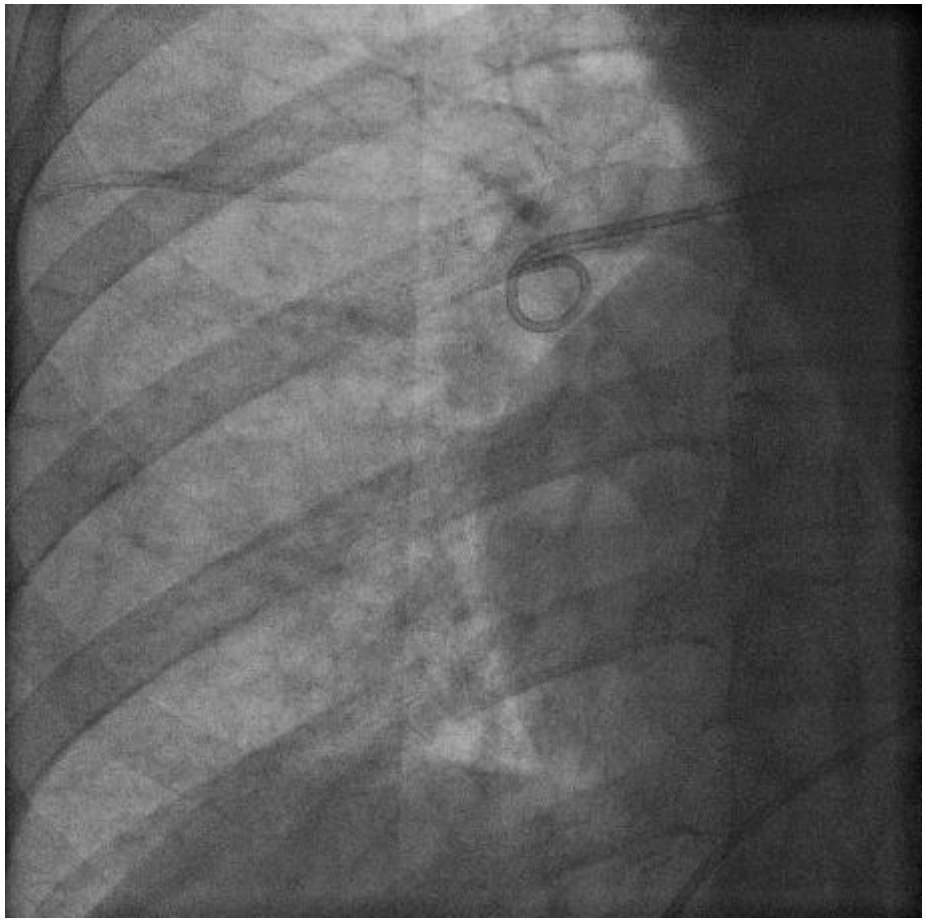

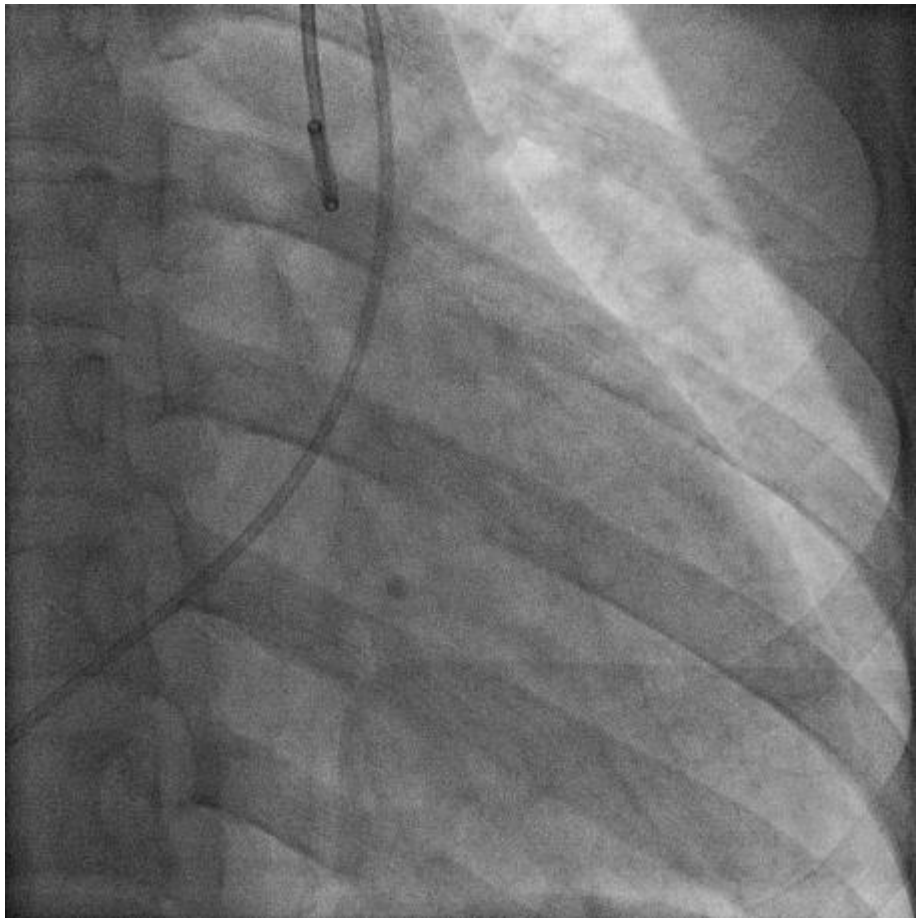

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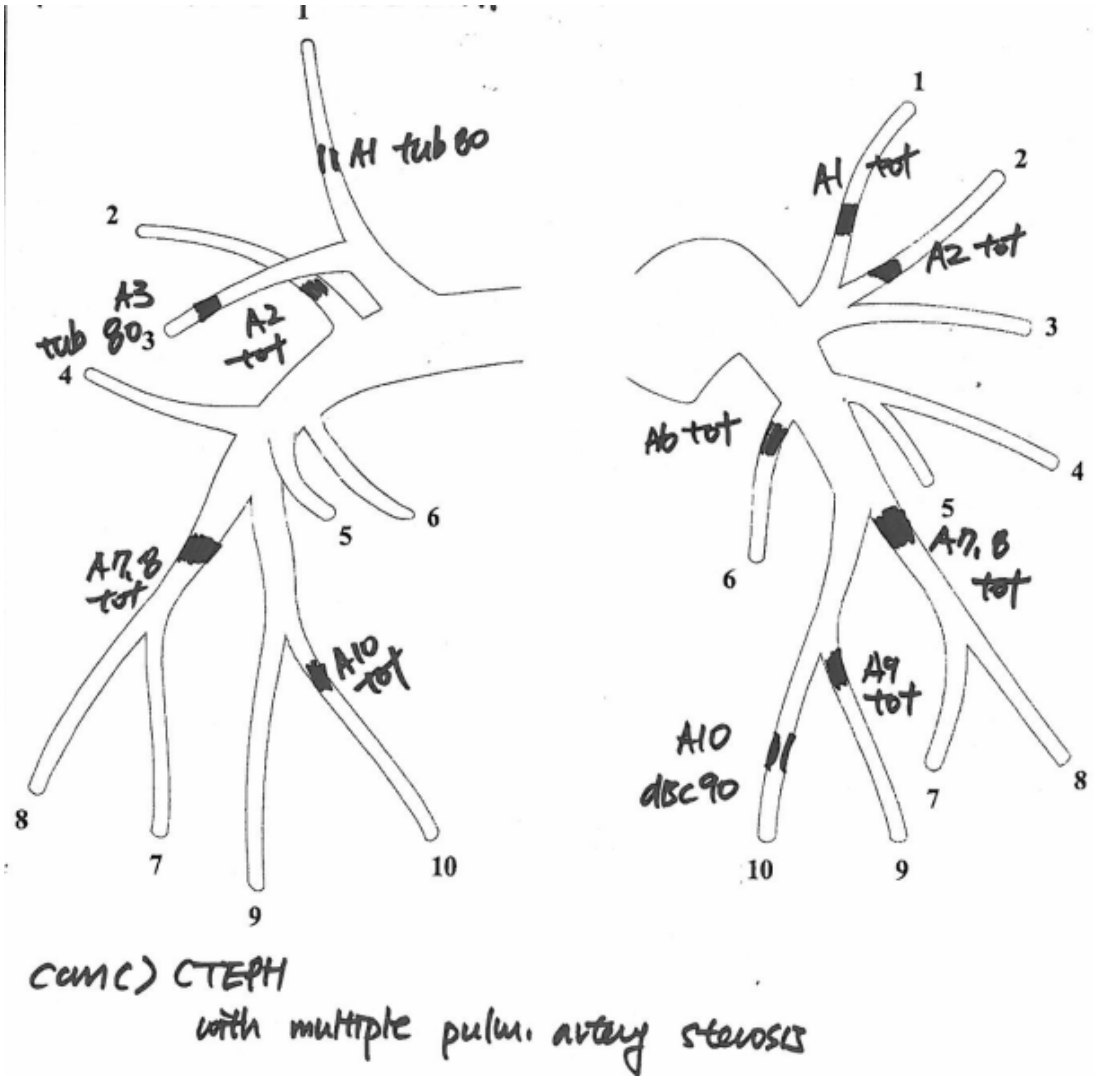
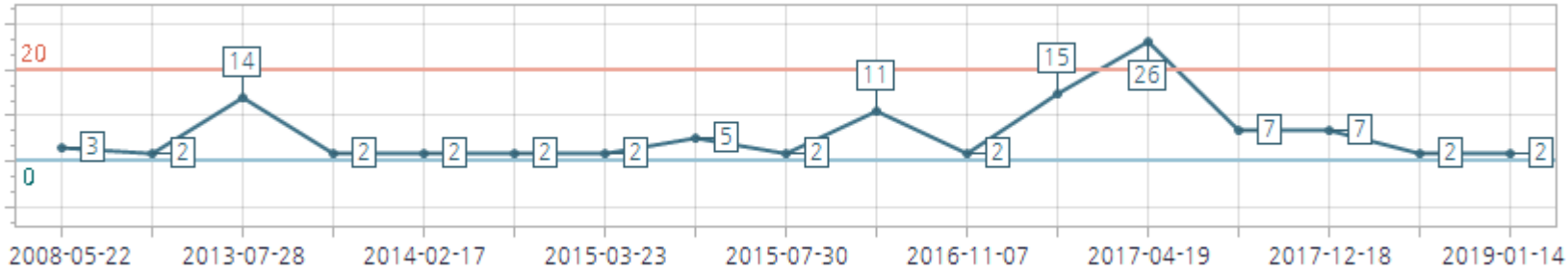


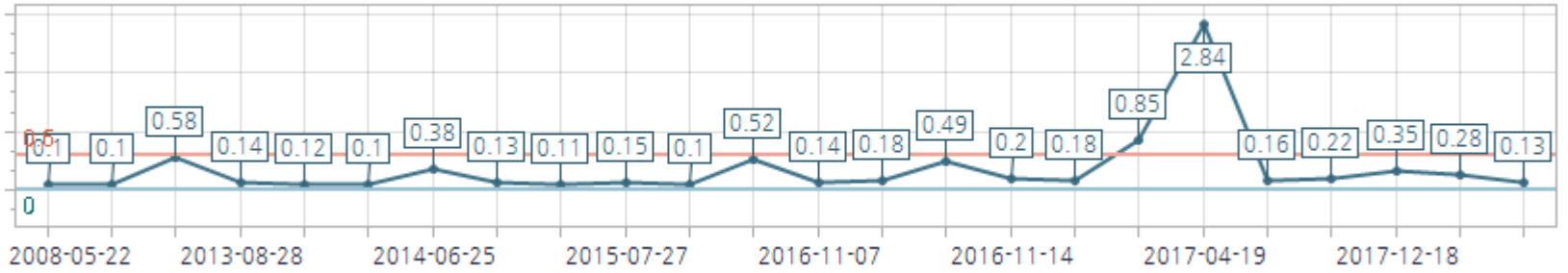
Rt heart cath
PCWP 14
MPA 109/41/69

Activity for Takayasu arteritis

ESR



CRP



Gene mutation test

- Homozygote for *RNF213* (Ring finger protein 213) p.Arg4810Lys

Diagnosis

- Primary peripheral pulmonary artery stenosis associated with *RNF213* mutation, refractory to BPA

Treatment

- Medical treatment, home O2

PERIPHERAL PULMONARY ARTERY STENOSIS

- Associated to *RNF213* mutation

PPAS overview

- Usually found in pediatric patients, ass. With congenital anomalies (ex. Williams, Noonan synd.)
- Isolated PPAS in adulthood without combined anomaly is extremely rare
- Can be misdiagnosed to CTEPH or vasculitis including Takayasu arteritis, pulmonary arteriography golden standard for diagnosis (diffuse narrowing, string beads pattern)
- Treatment: surveillance, balloon angioplasty, stent, surgery → restenosis 35%, difficult pph approach

Am J Med 1963; 35:512–529.
Intern Med 2010; 49:1895–1899.

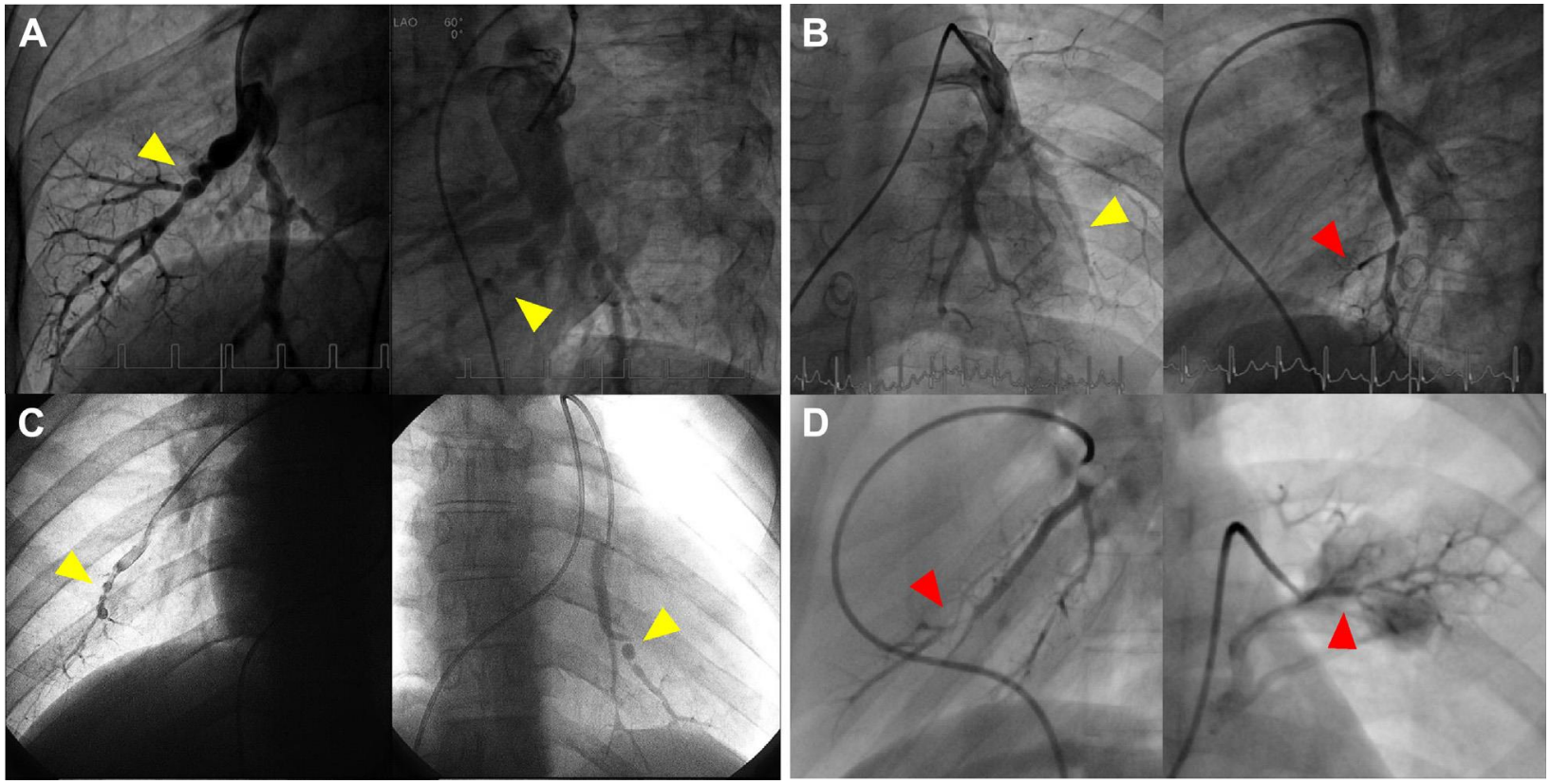
PPAS ass. with *RNF213* homozygosity

Nonsyndromic Peripheral Pulmonary Artery Stenosis Is Associated With Homozygosity of *RNF213* p.Arg4810Lys Regardless of Co-occurrence of Moyamoya Disease

Sung-A Chang, MD, PhD; Ju Sun Song, MD; Taek Kyu Park, MD; Jeong Hoon Yang, MD, PhD; Woo Chan Kwon, MD; So Ree Kim, MD; Sung Mok Kim, MD, PhD; Jihoon Cha, MD, PhD; Shin Yi Jang, PhD; Young Seok Cho, MD, PhD; Tae Jung Kim, MD, PhD; Oh Young Bang, MD, PhD; Jin Young Song, MD, PhD; Chang-Seok Ki, MD, PhD; and Duk-Kyung Kim, MD, PhD

- *RNF213* p.Arg4810Lys : susceptibility variant for Moyamoya disease (7-8% of MMD), prevalent in East asians, rare extracranial manifestations
- Characteristics: adolescent, early adulthood, multiple PA stenosis, slow progression of Sx

Chest 2018; 153(2): 404-413



Case No.	Vasculopathy						*RNF213* pArg4810Lys	Family History of MMD	*RNF213* pArg4810Lys (Father)	*RNF213* pArg4810Lys (Mother)
	Cerebral Artery	Pulmonary Artery	Coronary Artery	Renal Artery	Superior Mesenteric Artery	Celiac Trunk				
1	Y	Y	Y	Y	Y	N	Homozygote	Y	Heterozygote	Heterozygote
2	U[a]	Y	U[a]	U[a]	U[a]	U[a]	Homozygote	N	N/A	N/A
3	N	Y	N	N	N	N	Homozygote	N	N/A	Heterozygote
4	Y	Y	N	N	N	Y	Homozygote	N	Heterozygote	Heterozygote
5	Y	Y	N	Y	Y	N	N/A	N	N/A	N/A

Chest 2018; 153(2): 404-413

Conclusion

- Isolated PPAS in adolescents or adults should be considered in differential diagnosis with CTEPH or other type of vasculitis.
- Association with RNF213 p.Arg4810Lys homozygosity should also be evaluated in this category of patients.

Q&A, COMMENTS