서울아산병원
Asan Medical Center

# A case of Ehlers-Danlos Syndrome presenting as cystic lung disease with recurrent pneumothorax


Min Jee Kim

Department of Internal Medicine

Asan Medical Center

# Case presentation

- **Identifying data**
  - 19/M

- **Reason for admission**
  - Recurrent pneumothorax
    - First detection : 8 months ago

# Case presentation

## Present illness

### 내원 8개월 전

- 가만히 앉아있던 중 갑자기 오른쪽 등으로 찌르는 듯한 통증 발생하여 local 병원 내원하여 우측 기흉 진단, 흉관 삽입 후 호전.
- 당시 흉부 CT상 Rt lower lobe에 atelectasis/consolidation 외 특이 소견 없었음.

### 내원 6개월 전

- 우측 기흉 재발, 흉관 삽입 후 호전.

### 내원 5개월 반 전

- 우측 기흉 재발하여 흉관 삽입술 시행
- 반복되는 기흉으로 diagnostic VATs-wedge resection(Rt upper lobe) 시행하였고, 조직검사 상 Bullae with ossification소견.

### 내원 5개월 전

- 우측 기흉 재발하여 f/u한 chest CT상 RUL에 cystic lesion이 새롭게 발생.
- Percutaneous lung biopsy 시행하였고, chronic inflammation with necrotic debris소견.

# Case presentation

## Present illness

### 내원 2개월 전

- 우측 기흉 재발하여 흉막 유착술 시행.

### 내원 1개월 전

- 좌측 기흉 발생하여 흉관 삽입술 시행.
- Chest CT상 Lt lower lobe에 cavitary nodule이 새롭게 확인.

  이전 RUL의 cystic lesion은 크기가 줄어 호전추세였음.

### 내원 1주 전

- 우측 기흉 재발, 산소치료로 호전.

### 내원 당일

- 반복적으로 재발하는 기흉에 대한 further evaluation 위해 본원 호흡기내과 입원.

# Case presentation

- **Past medical history**
  - H/O Recurrent right shoulder dislocation (eight times)

    s/p ligament repair 2018
  - No trauma history

- **Family history**
  - Father : Sudden death of brain hemorrhage at the age of 43 (2014)

- **Social history** : never-smoker

# Case presentation

- **Associated symptoms**
  - Intermittent cough
  - Hemoptysis whenever pneumothorax developed

- **Physical examination**
  - V/S : 125/83 mmHg-62/min-18/min-36.1℃-99%
  - Body measurements
    - Height 170cm, Weight 64kg, BMI 22kg/$m^2$
  - Thorax
    - Symmetric expansion without retraction
    - Clear breath sound without wheezing or rale

# Case presentation

## Initial laboratory data

### CBC

WBC 7000/uL

Neutrophil 62.4%

Lymphocyte 22.9%

**Eosinophil 6.0% (420/uL)**

Platelet 288/uL

Hb 15.5 g/dL

ESR 2mm/hr

### Chemical battery

| | | | |
|---|---|---|---|
| Ca | 9.9 mg/dL | P | 3.5 mg/dL |
| BUN | 10 mg/dL | Cr | 0.76 mg/dL |
| Glucose | 92 mg/dL | Uric acid | 6.7 mg/dL |
| Protein | 7.4 mg/dL | Albumin | 4.1 g/dL |
| AST | 22 IU/L | ALT | 57 IU/L |
| ALP | 95 IU/L | r-GT | 39 IU/L |
| Total bilirubin | 0.4 mg/dL | LD | 196 IU/L |
| CRP | 0.17 mg/dL | | |

# Case presentation

## Initial laboratory data

**Coagulation battery**

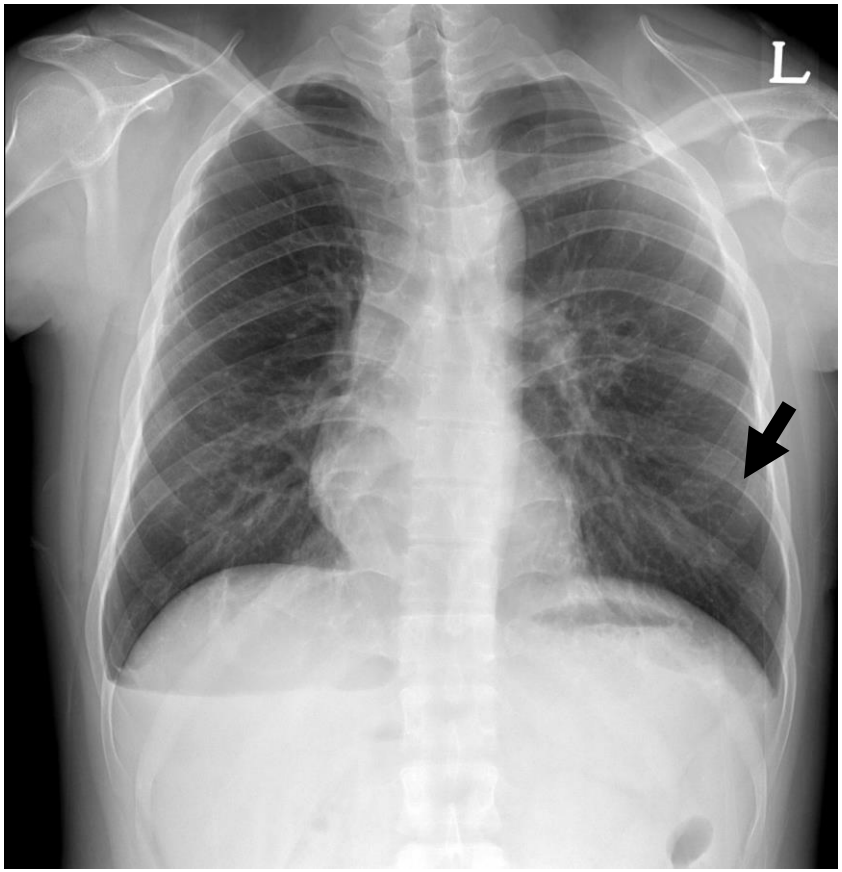
| | |
|---|---|
| PT(sec) | 12.0 sec |
| PT(%) | 96.2 % |
| PT(INR) | 1.02 |
| aPTT | 26.3 sec |

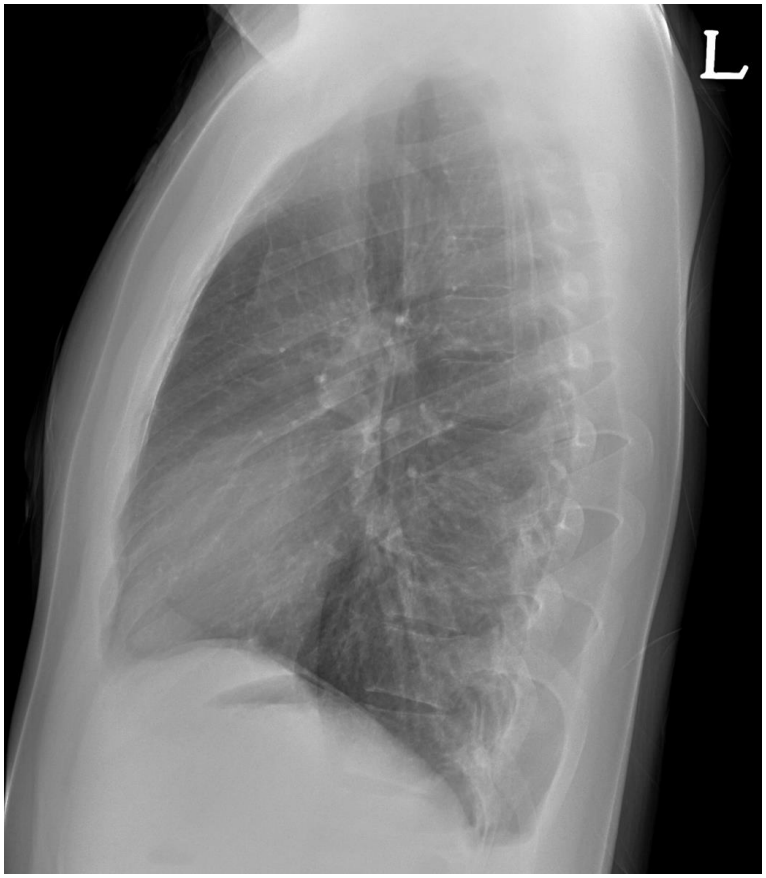
**Routine urinalysis**

| | |
|---|---|
| pH | 7.0 |
| Albumin | (-) |
| Glucose | (-) |
| Ketone | (-) |
| Occult blood | (-) |
| Nitrite | (-) |
| WBC | (-) |
| RBC | 0~2/HPF |
| WBC | 0~2/HPF |
| Squamous cell | 0~2/HPF |

# Case presentation

- **Chest X ray at admission**

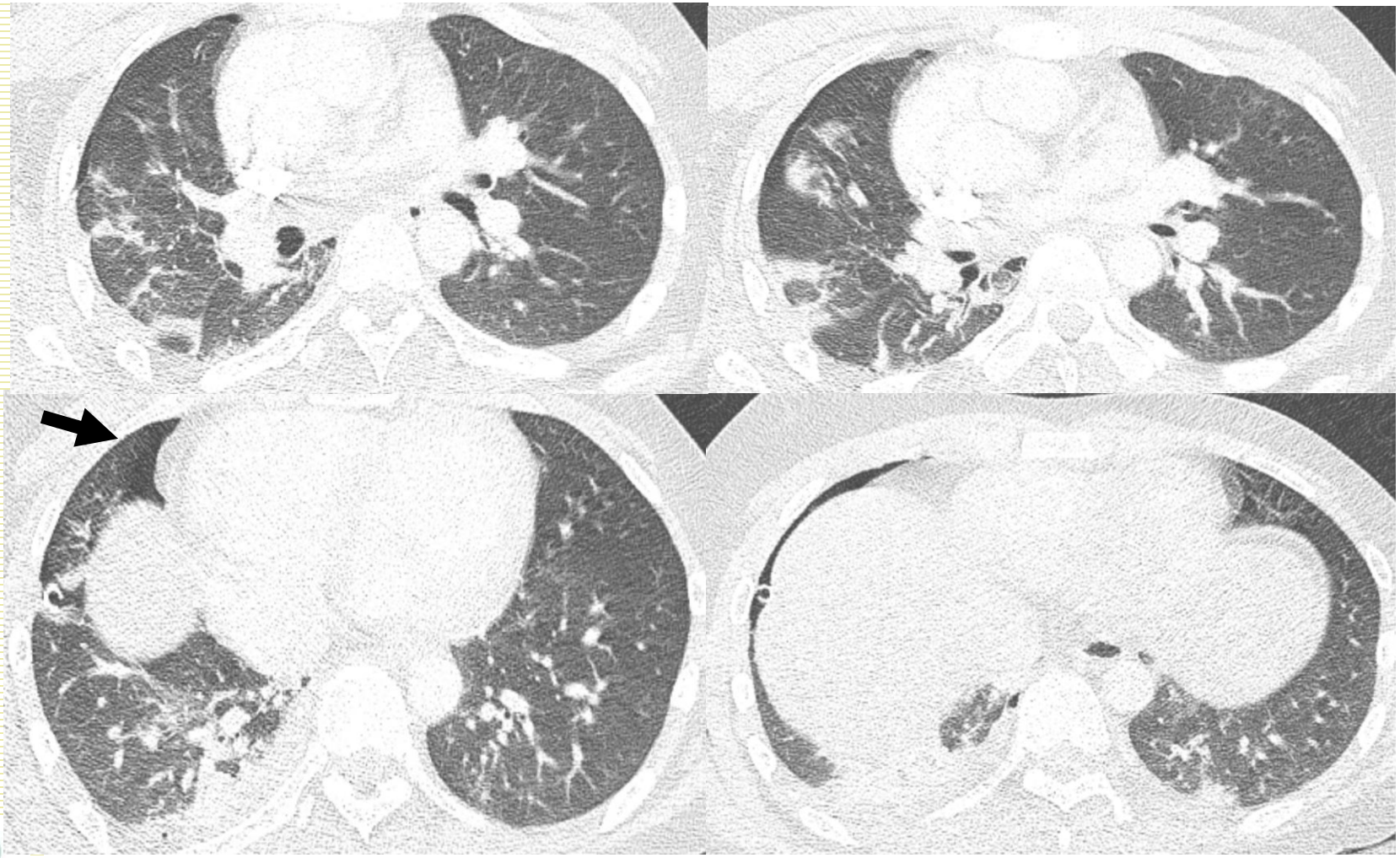


# Previous chest CT images

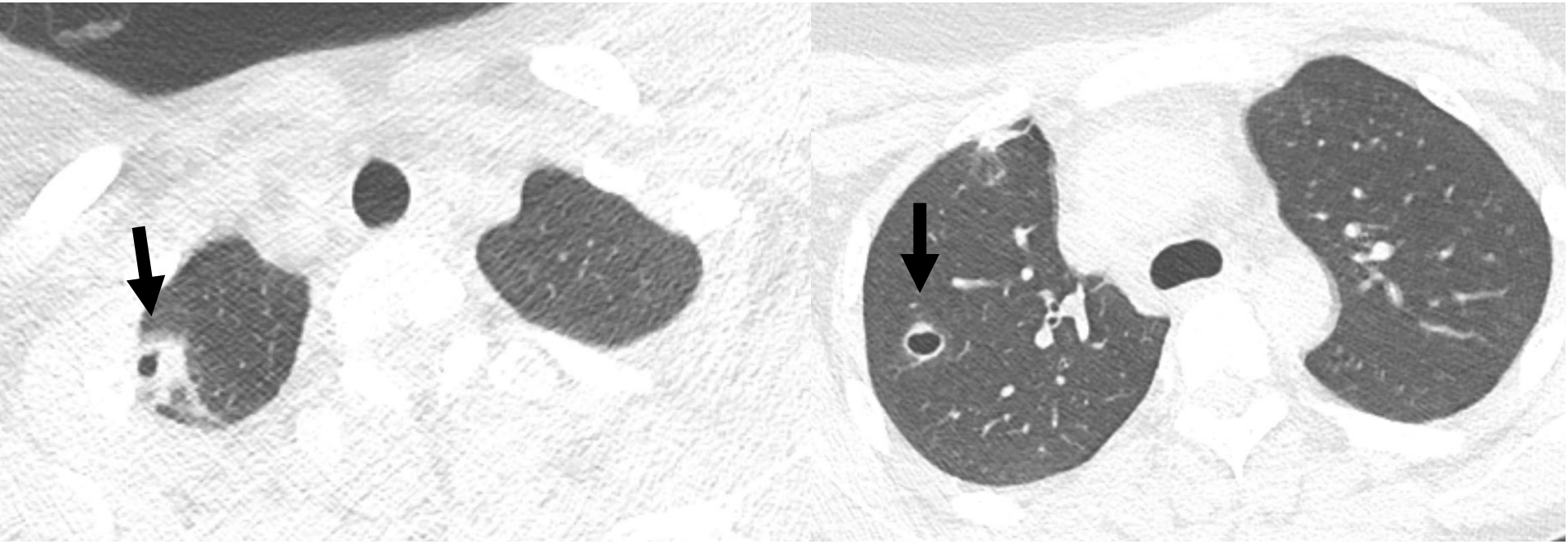
# Case presentation

- 1st event, (8 months ago)



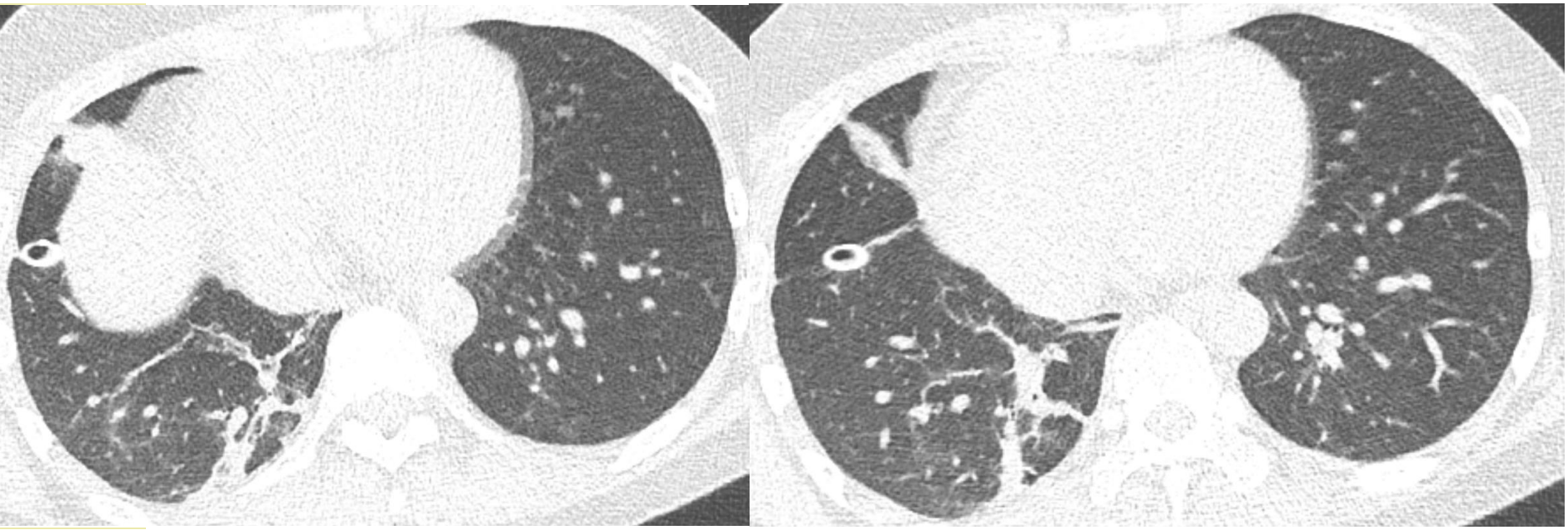
# Case presentation

- 4th event, (3 months after the initial CT)



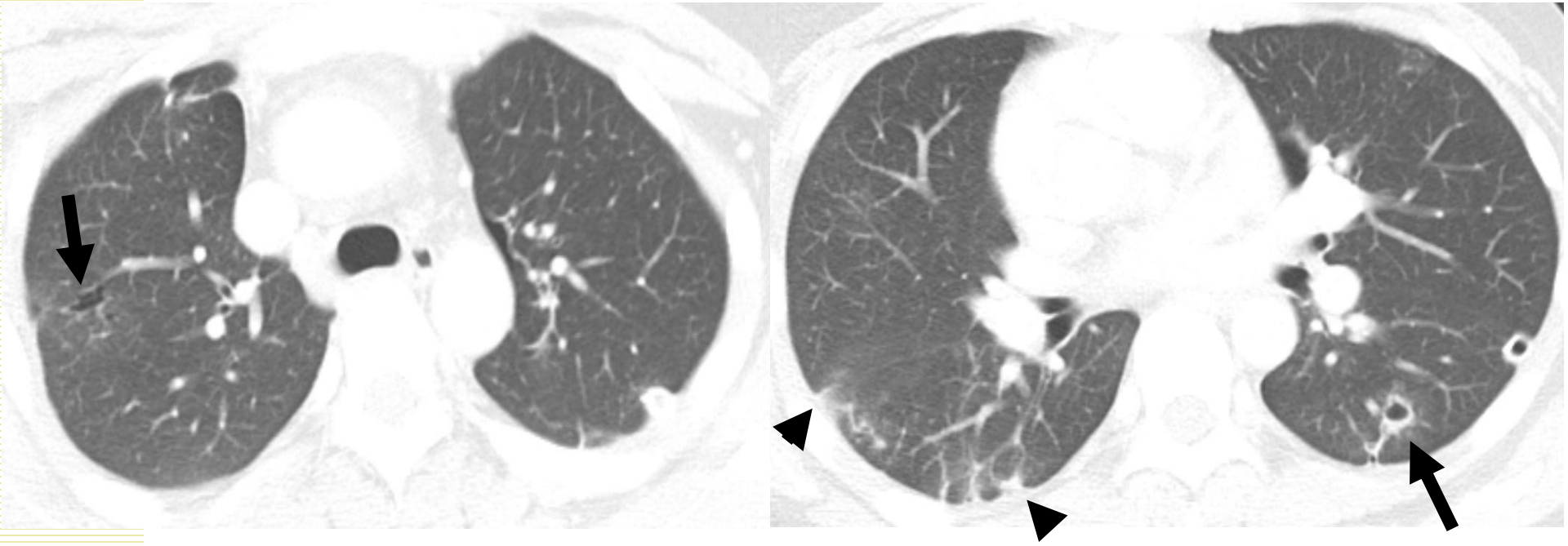
# Case presentation

- 4th event, (3 months after the initial CT)



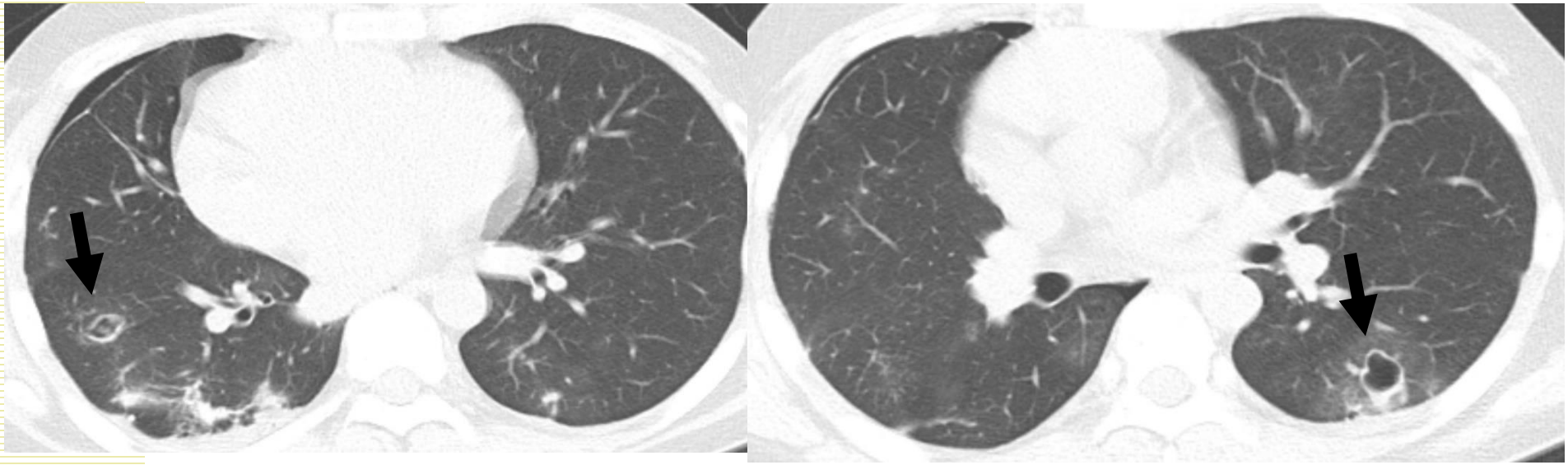
# Case presentation

- 6th event,  (7 months after the initial CT)



# Case presentation

- Chest CT on admission



# Case presentation

## Assessment

- Cystic lung disease causing secondary pneumothorax
  - **Infection (*Paragonimus westermani*)**
  - **Vasculitis**
    - Eosinophilic granulomatosis with polyangiitis
    - Granulomatosis with polyangiitis
  - **Interstitial lung disease**
    - Pulmonary Langerhans cell histiocytosis
    - Lymphocytic interstitial pneumonia
    - Birt-Hogg-Dube' syndrome

# Case presentation

- **Assessment**
  - Cystic lung disease causing secondary pneumothorax
    - **Infection (*Paragonimus westermani*)**
    - **Vasculitis (EGPA, GPA)**
    - Interstitial lung disease (PCLH, LIP, BHD)
- **Plan**
  - Serologic test/Bronchial washing for *P.westermani*
  - EMG/NCV, ANCA, PNS series

# Case presentation

## Additional Information

- Parasites work up
  - No intake history of raw food
  - *P.westermani* Ab IgG : negative
  - Bronchial washing for *P.westermani* : negative
- Vasculitis work up
  - No symptoms or signs of vasculitis or asthma
  - EMG/NCV : normal
  - PNS series : normal
  - ANCA : negative

# Case presentation

## Assessment

- Cystic lung disease causing secondary pneumothorax
  - Infection (*Paragonimus westermani*)
  - Vasculitis (EGPA, GPA)
  - **Cystic interstitial lung disease**
    - Pulmonary Langerhans cell histiocytosis
    - Lymphocytic interstitial pneumonia
    - Birt-Hogg-Dube' syndrome

## Plan

- Outside pathology review
- Auto Ab (ANA, RF, Anti-CCP Ab, Anti-Ro/La Ab) test
- *FCLN* (folliculin) gene mutation test

# Case presentation

## Additional Information

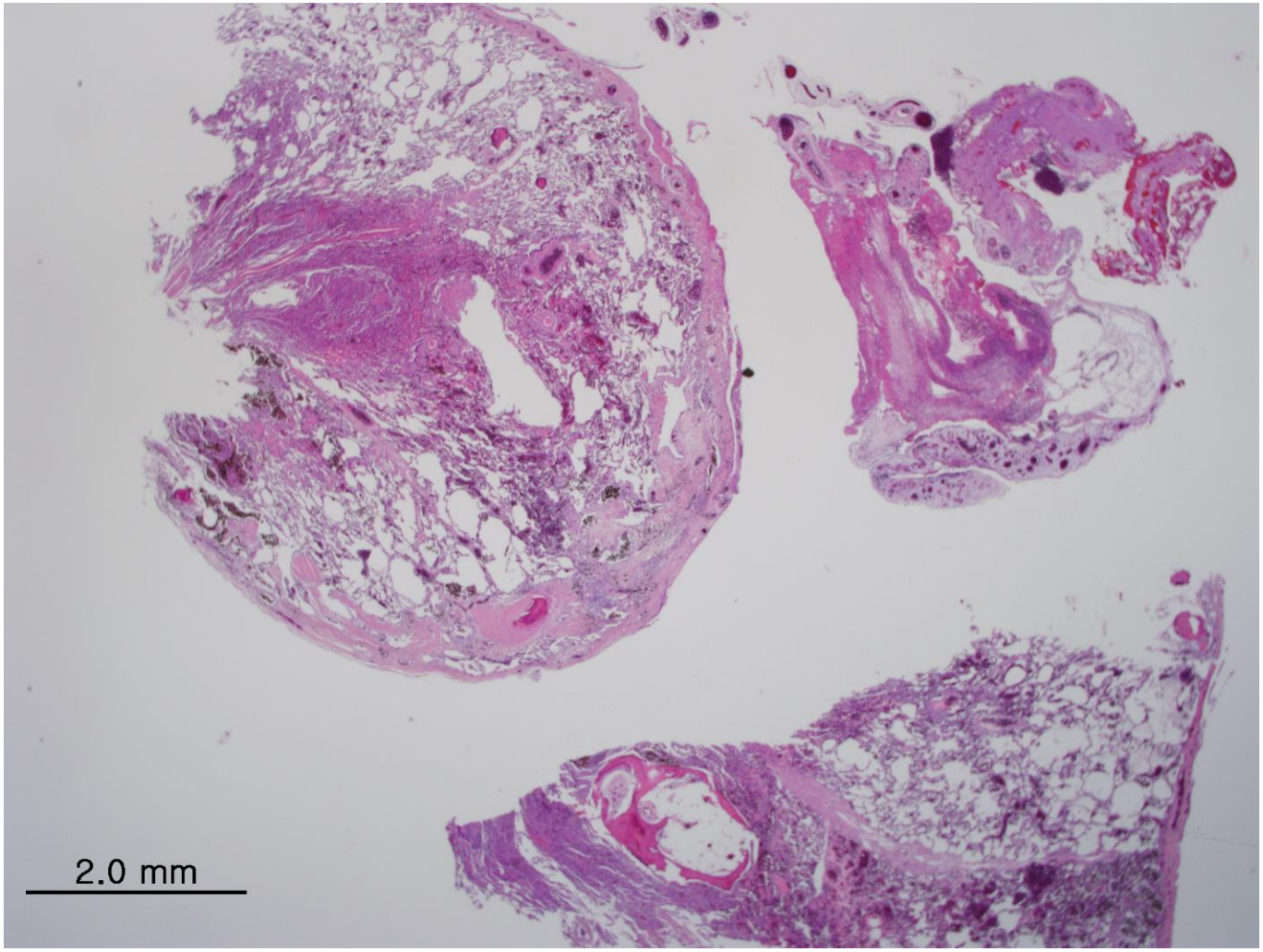
- Physical examination
  - No skin tumors or connective tissue disease- related symptoms
- FCLN gene mutation (-)
- Auto antibody test
  - ANA, RF, Anti-CCP Ab, Anti-Ro Ab, Anti-La Ab : negative

# Case presentation

## Outside pathology

VATs-wedge resection, RUL

# Case presentation



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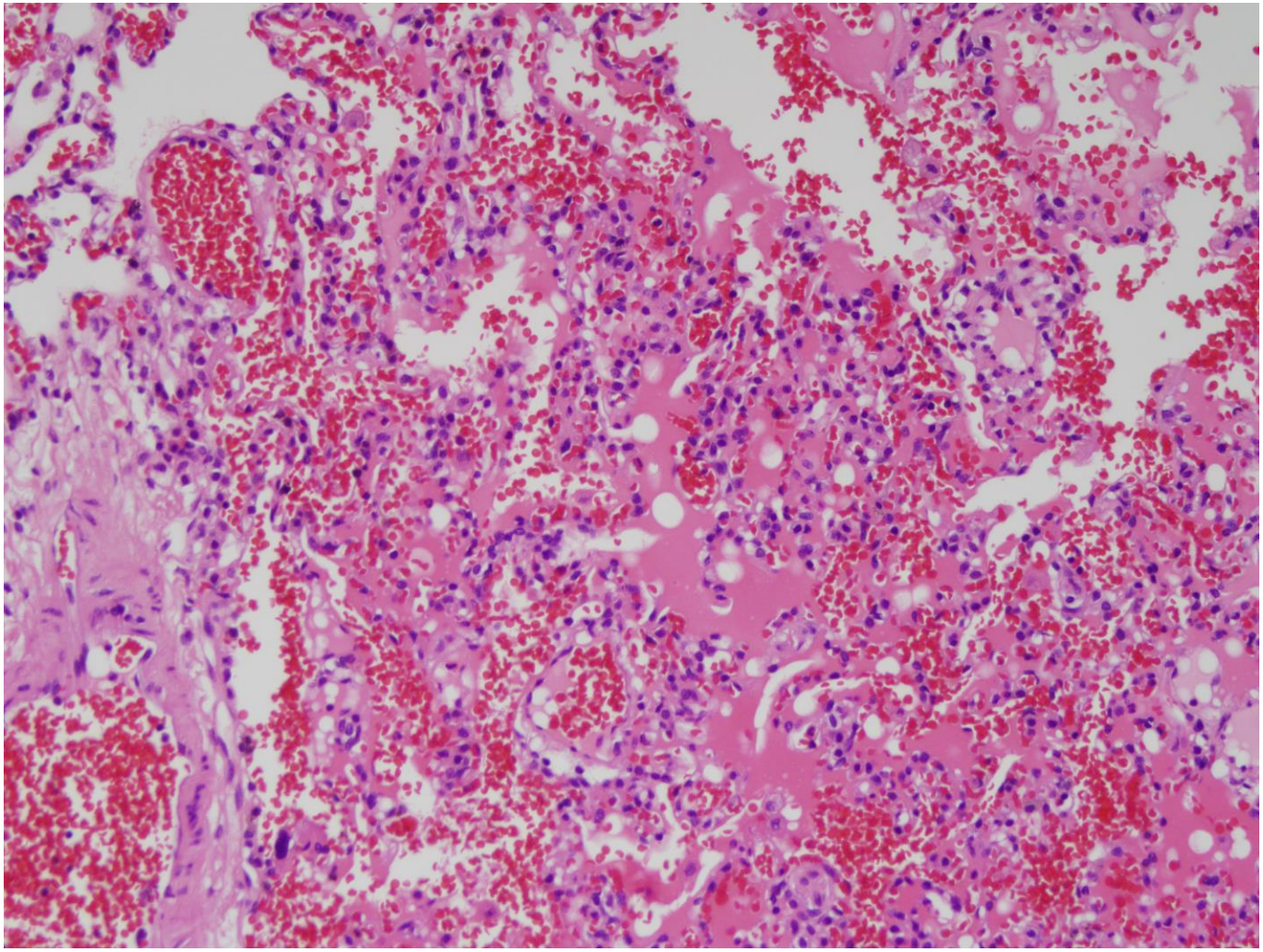

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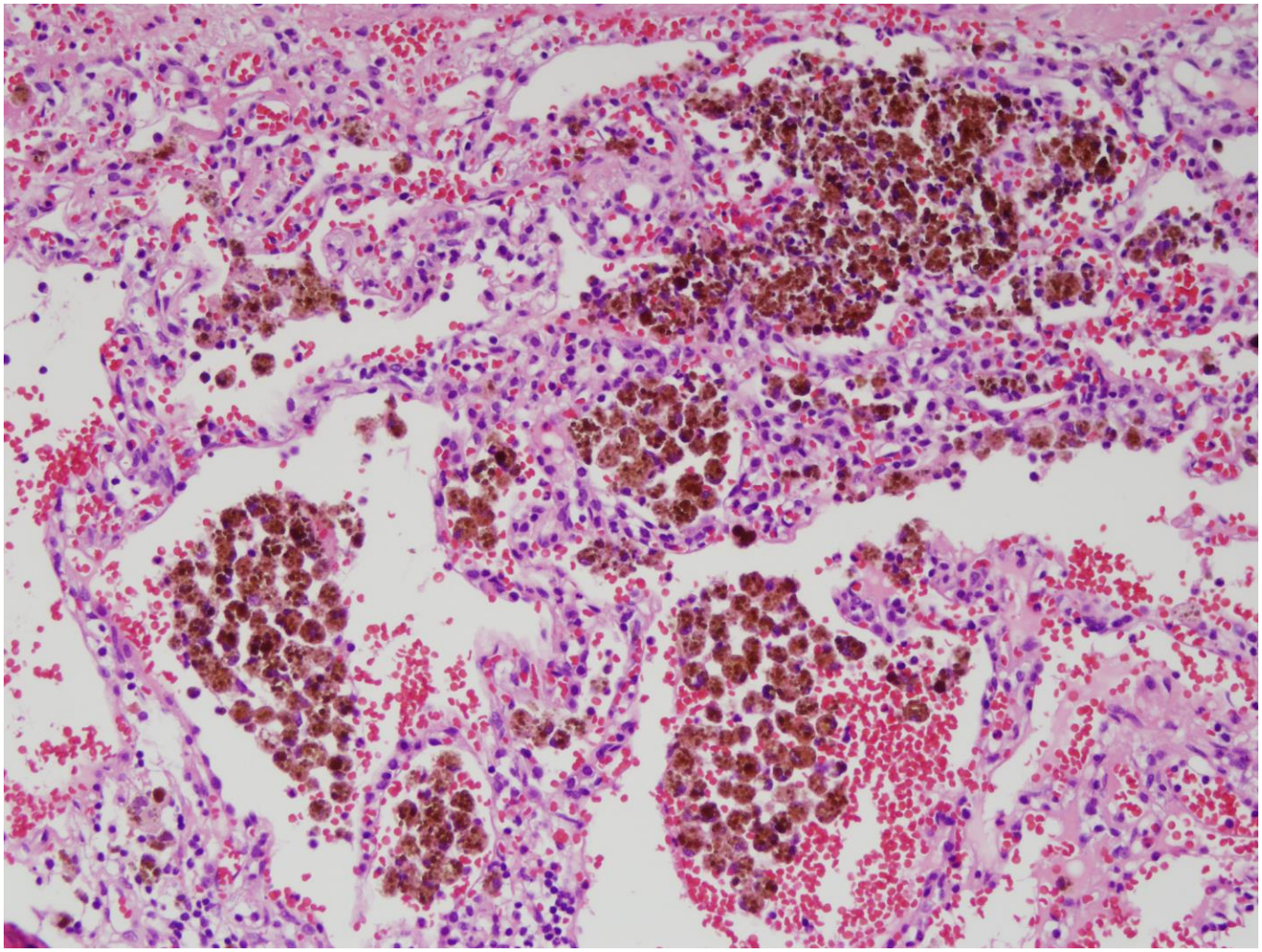
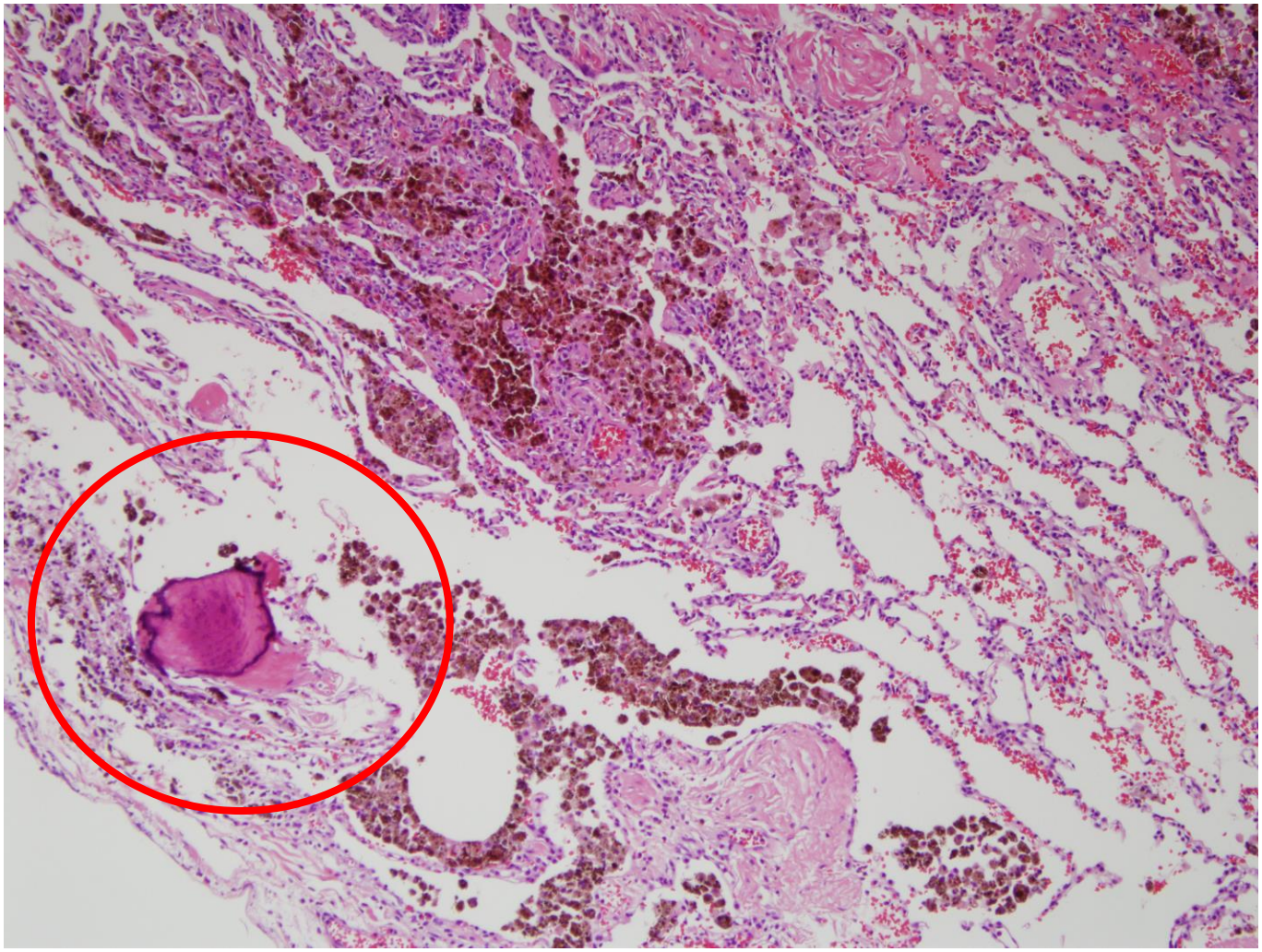
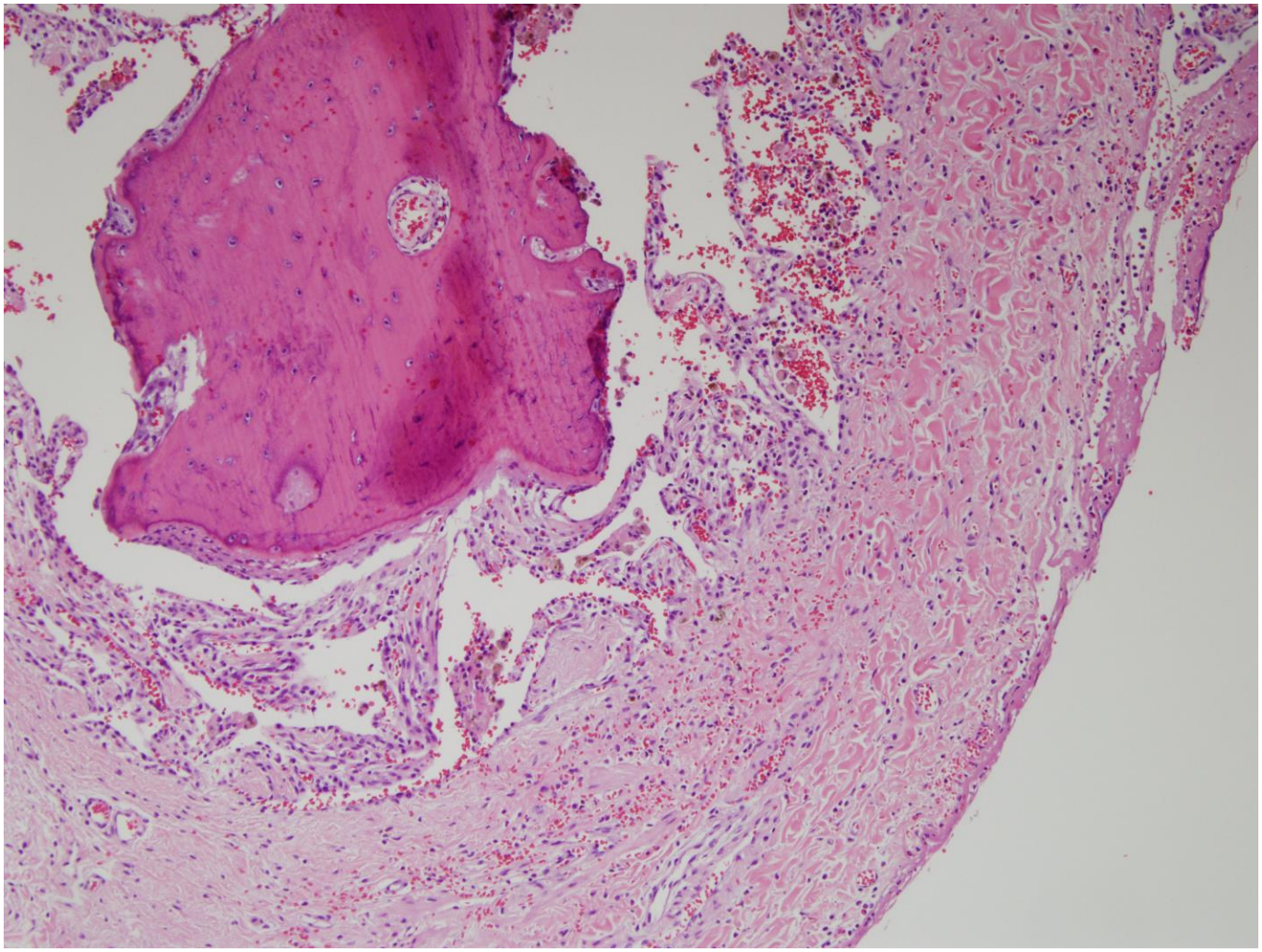


# Case presentation



# Case presentation



# Case presentation

Lung, (right), wedge resection :

- Multiple parenchymal cysts with intra-alveolar hemosiderin-laden macrophages collection and multifocal heterotopic ossification.

# Case presentation

## Updated problem list

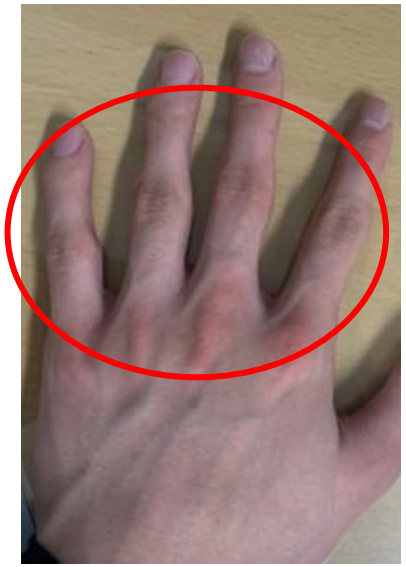
- Repeated recurrent spontaneous pneumothorax
- Pathological findings suggesting the fragility of lung tissue
- Family history of father's death
- History of recurrent right shoulder dislocation for 8 times

**"Vascular Ehlers Danlos Syndrome?"**

# Case presentation

## Progress note HD#5

- S>
  - 어릴 때부터 쉽게 멍들고, 상처가 잘 났어요.
  - 아버지가 이전에 원인모를 간동맥 파열로 수술한 적이 있어요.
- O>
  - Skin : Thin and increased venous visibility



# Case presentation

## Progress note HD#5

- A>
  - Vascular Ehlers Danlos syndrome
- P>
  - Genetic test for vascular EDS (*COL3A1*)
  - Baseline arterial imaging studies (Brain MRA, Chest/APCT)
  - Echocardiography for cardiac surveillance

# Case presentation

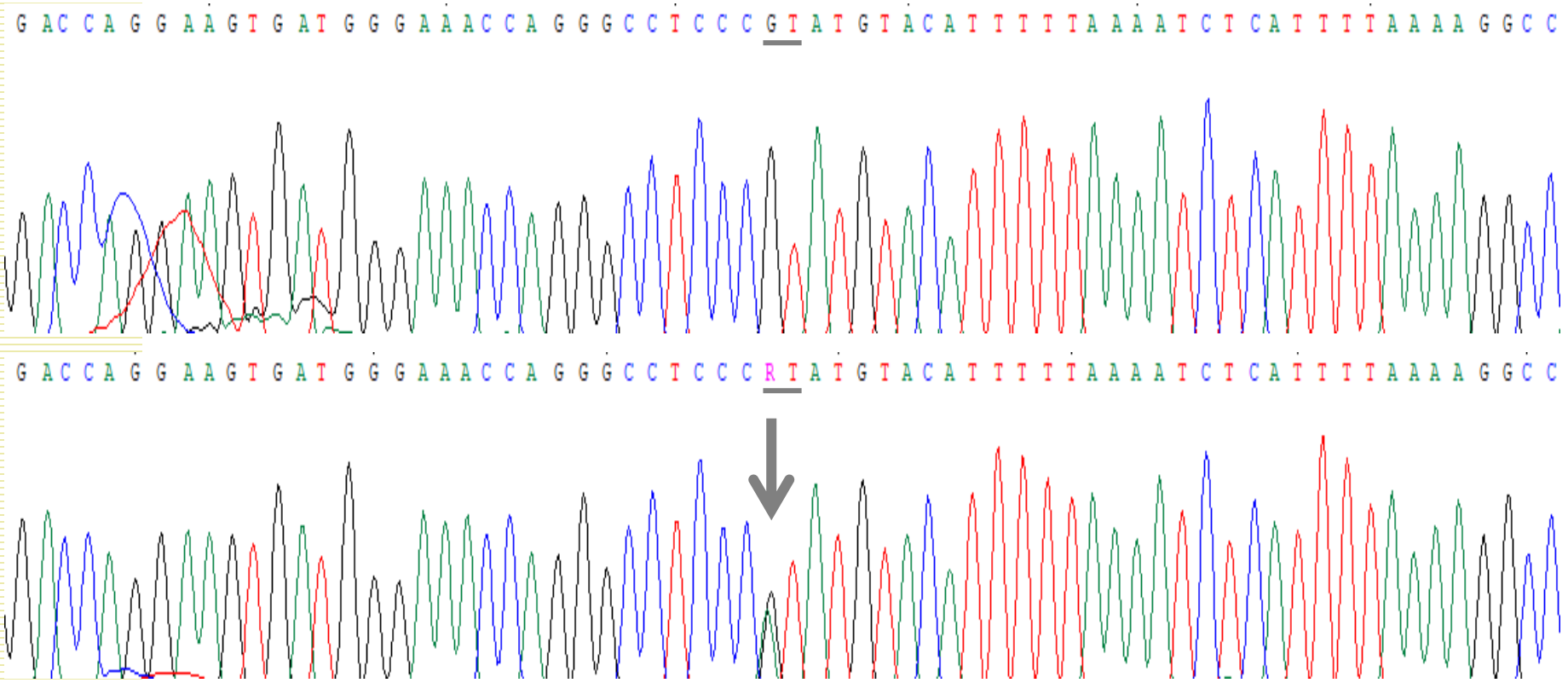
## Progress note HD#6

- Brain MRA : normal
- Chest/APCT : No vascular abnormalities
- Echocardiography : normal

# Case presentation

OPD f/u

Partial sequence of *COL3A1* gene




**c.1662+1G>A (IVS23(+1)G>A), Heterozygote**

# Ehlers-Danlos syndrome

# Discussion

- **Ehlers-Danlos syndrome (EDS)** describes a group of heritable disorders of connective tissue comprising mutations in the genes involved in the structure and/or biosynthesis of collagen.
- Thirteen EDS subtypes are recognized, with a wide degree of symptom overlap among subtypes and with other connective tissue disorders.
- The clinical hallmarks of EDS are tissue fragility, joint hypermobility, and skin hyperextensibility.

*Journal of the American Academy of PAs, 33(4), 23-28.*

# Discussion

| *Name of EDS Subtype* | *IP** | *Genetic Basis* | *Protein Involved* |
|---|---|---|---|
| Classical EDS (cEDS) | AD | Major: *COL5A1, COL5A2* | Type V collagen |
| | | Rare: *COL1A1* c.934C>T, p.(Arg312Cys) | Type I collagen |
| Classical-like EDS (clEDS) | AR | *TNXB* | Tenascin XB |
| Cardiac-valvular EDS (cvEDS) | AR | *COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro ¤2(I) collagen chains) | Type I collagen |
| Vascular EDS (vEDS) | AD | Major: *COL3A1* | Type III collagen |
| | | Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys) | Type I collagen |
| Hypermobile EDS (hEDS) | AD | Unknown | Unknown |
| Arthrochalasia EDS (aEDS) | AD | *COL1A1, COL1A2* | Type I collagen |
| Dermatosparaxis EDS (dEDS) | AR | *ADAMTS2* | ADAMTS-2 |
| Kyphoscoliotic EDS (kEDS) | AR | *PLOD1* | LH1 |
| | | *FKBP14* | FKBP22 |
| Brittle cornea syndrome (BCS) | AR | *ZNF469* | ZNF469 |
| | | *PRDM5* | PRDM5 |
| Spondylodysplastic EDS (spEDS) | AR | *B4GALT7* | ß4GalT7 |
| | | *B3GALT6* | ß3GalT6 |
| | | *SLC39A13* | ZIP13 |
| Musculocontractural EDS (mcEDS) | AR | *CHST14* | D4ST1 |
| | | *DSE* | DSE |
| Myopathic EDS (mEDS) | AD or AR | *COL12A1* | Type XII collagen |
| Periodontal EDS (pEDS) | AD | *C1R* | C1r |

*Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):8-26.*

# Discussion

## Vascular Ehlers-Danlos syndrome

- Ehlers–Danlos syndrome type IV, the vascular type, results from mutations in the gene for type III procollagen (*COL3A1*).
- Autosomal dominant disorder
- Increased risk for arterial, bowel, and uterine rupture
  - The timing of these events, their frequency, and the course of the disease are not well documented.

*N Engl J Med 2000; 342:673-680*

# Discussion

## Vascular Ehlers-Danlos syndrome

- Because of its rarity, the diagnosis is often made only after a catastrophic complication or at postmortem examination
- Patients with vascular EDS have decreased intima-media thickness

*N Engl J Med 2000; 342:673-680*
*J Vasc Surg. 2016 Dec;64(6):1869-1880.*

# Discussion

## Vascular Ehlers-Danlos syndrome

- The majority of these complications are arterial in nature.
  - Aneurysm formation , dissection or rupture of medium sized vessels
- Respiratory system involvement is not common in EDS-IV .
  - However, when present, pneumothoraces are the most common respiratory complications
- Hemoptysis , bullae formation , cavitary pulmonary lesions and fibrous pseudotumor have also been described .

*Eur Respir J 2002; 19: 195–198*

# Discussion

## Causes of death in patients with type IV EDS

**TABLE 2.** CAUSES OF DEATH IN 26 INDEX PATIENTS WITH EHLERS–DANLOS SYNDROME TYPE IV AND 105 AFFECTED RELATIVES.

| CAUSE OF DEATH | TOTAL | MALE SUBJECTS | FEMALE SUBJECTS |
|---|---|---|---|
| | | no. of subjects | |
| All causes | 131 | 77 | 54 |
| Arterial rupture | 103 | 62 | 41 |
| Organ rupture | 13 | 7 | 6 |
| Uterus | 5 | 0 | 5 |
| Heart* | 3 | 2 | 1 |
| Liver or spleen | 5 | 5 | 0 |
| Gastrointestinal rupture | 10 | 7 | 3 |
| Other causes† | 5 | 1 | 4 |

*The cause of death was left ventricular rupture.

†Two relatives died of other causes: an adolescent boy died in a motor vehicle accident at the age of 17 years, and a 70-year-old woman died of an apparent heart attack.

Thoracic/abdominal vessels
CNS hemorrhages

*N Engl J Med 2000; 342:673-680*

# Discussion

**Table 2** Diagnostic criteria for vascular Ehlers-Danlos syndrome

Major criteria

1. Family history of vascular Ehlers-Danlos syndrome with a documented causative variant in the COL3A1 gene
2. Arterial rupture at a young age
3. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
4. Uterine rupture during the third trimester in the absence of previous Caesarean section and/or severe peripartum perineum tears
5. Carotid–cavernous sinus fistula (CCSF) formation in the absence of trauma

Minor criteria

1. Bruising unrelated to identified trauma and/or in unusual sites, such as the cheeks and back
2. Thin, translucent skin with increased venous visibility
3. Characteristic facial appearance
4. Spontaneous pneumothorax
5. Acrogeria
6. Talipes equinovarus
7. Congenital hip dislocation
8. Hypermobility of small joints
9. Tendon and muscle rupture
10. Keratoconus
11. Gingival recession and gingival fragility
12. Early onset varicose veins (younger than age 30 and nulliparous if female)

Minimal criteria suggestive for vEDS :

- FHx of the disorder, arterial rupture or dissection in individuals <40 years of age
- Unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features

*Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):8-26.*

서울아산병원 Asan Medical Center

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# Discussion

## Medical management of vascular EDS

- Education of visiting ER immediately if symptoms suggestive of bleeding (sudden pain, dizziness, etc) occur.
- Vascular/cardiac surveillance using noninvasive measures
  - Ultrasound, MRI, CT, Echocardiography
- Avoidance of vascular trauma (arterial and intramuscular punctures)
- The use of fluoroquinolone antibiotics should be avoided
  - Increased risk of aortic dissection, tendonitis, and tendon rupture.

*J Vasc Surg. 2016 Dec;64(6):1869-1880.*
*Chron Respir Dis. 2021 Jan-Dec;19* 14799731211025313

# Discussion

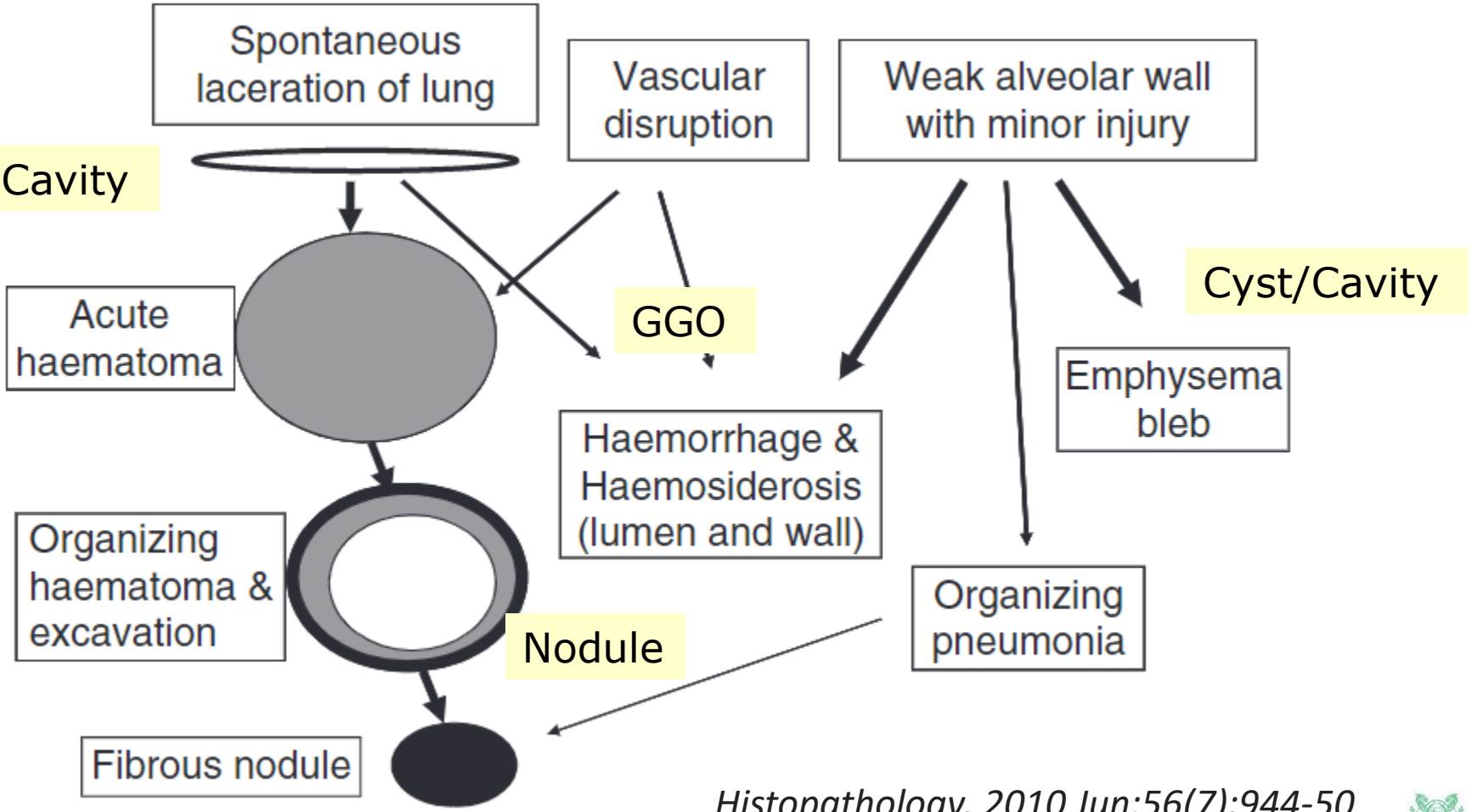
## Medical management of vascular EDS

- Contact sports should be avoided
- Antiplatelet therapy and anticoagulants should be avoided whenever possible.
- Routine colonoscopy should be avoided (risk of bowel rupture)
- Reproductive-age females with vascular EDS should receive counseling.
  - High risk for uterine and vascular ruptures in pregnancy

*J Vasc Surg. 2016 Dec;64(6):1869-1880.*

# Thank you for listening

## Relationship of each lung lesion in vascular Ehlers-Danlos syndrome




*Histopathology. 2010 Jun;56(7):944-50*