Cryobiopsy for diffuse parenchymal lung disease (DPLD): the better mousetrap or irrational exuberance

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Disclosures

- Consulting fees
  - Olympus America
  - Becton Dickinson

Objectives

- 1) Review the current trials of cryobiopsy in DPLD
- 2) Review the perils associated with cryobiopsy
- 3) Review the limitations of existing data for cryobiopsy
- 4) Propose a path forward

What is a cryobiopsy (CBx)?

in.erbe-med.com

- 1.9, 2.4 mm probes
- Joule-Thompson Effect
- -80 to -90°C

Christmas story triple dog dare

Cryobiopsy clinic trials

- First description in tracheobronchial pathology in 1979 in Romania
- PubMed/Ovid search cryobiopsy – roughly 70 manuscripts
- First DPLD paper - 2009
- 23 single center manuscripts reporting CBx experience

Babiak, et al (2009) Respiration 78(2):203-208

Why is there interest in CBx?

- 15% of pulmonary consultations DPLD
- Differentiating the subtype of DPLD has treatment and prognostic relevance
- Traditional transbronchial biopsies (TBBx) limited by size and crush artifact
- Surgical lung biopsy concerns of morbidity (~30%) and mortality (2-6%)

Hutchinson et al (2016) AJRCCM 193:1161-7; Utz et al (2001) Eur Resp Jl 17:175-9

What diagnoses are we interested in?

- UIP
- NSIP
- Sarcoidosis
- HSP
- COP/BOOP
- Drug toxicity
- LIP
- Pleuroparenchymal fibroelastosis
- AIP
- Eosinophilic lung diseases
- ILD NOS

What randomized data exists?

- DPLD – randomized to TBBx or CBx
- Excluded patients with UIP pattern
- Three biopsies from affected areas
- Histopathological – 74% vs. 34%
- Limitations:
  - Interpatient variability
  - Only 3 biopsies taken
  - Pathologist not completely blinded

Pajares et al (2014) Respirology 19:900-906

What randomized data exists?

- Patients underwent both TBBx and CBx
- Multi-D decision to biopsy

Clinical Diagnosis	TBLB and TBLC Similar and Diagnostic	TBLB Diagnostic TBLC Non-Diagnostic	TBLB Non-Diagnostic TBLC Diagnostic	Neither TBLB nor TBLC Diagnostic
ILD*	4	0	3	3
OP	6	2	1	0
HSP	1	0	2	0
Sarcoid	1	0	1	1
Malignancy	5	0	0	0
Drug Reaction	5	1	1	0
Other**	4	1	3	11
Total (56)	26	4	11	15***

Ramaswamy et al (2016) J Bronch Interv Pulmonol 23:14-21

Concerns with this trial

- Retrospective
- Pathologists not blinded
- CBx taken from involved areas only, TBBx from each lobe
- Grouped ILD - ? NSIP vs. UIP
- 20% pneumothorax rate

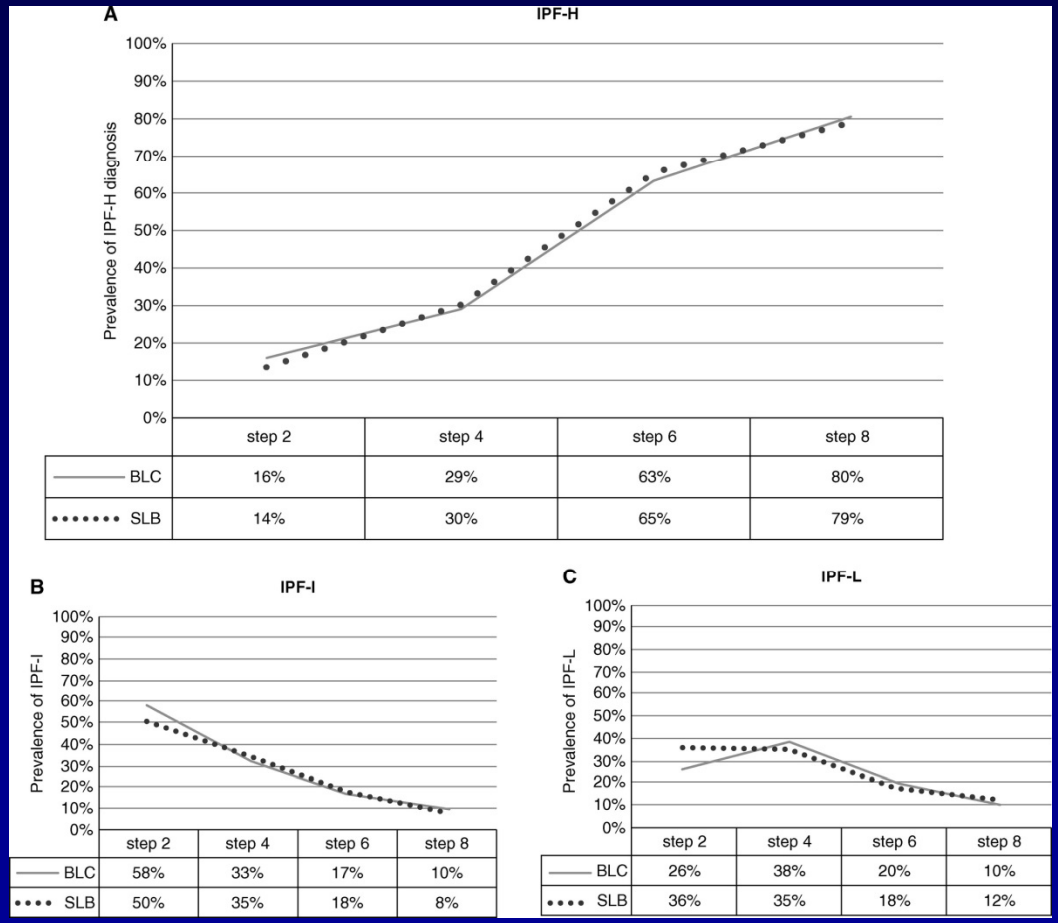
Ramaswamy et al (2016) J Bronch Interv Pulmonol 23:14-21

Novel study design

- Cross sectional study separate clinicians, radiologists, and pathologists
- Report diagnostic confidence as add clinical, radiographic, BAL, biopsy, and follow up data
- Individually
- Group

STEP	DATA	PARTICIPANTS	DISCUSSION
1	Clinical-Radiological data	C + R	Individual
2			Group
3	BAL	C + R + P	Individual
4			Group
5	BIOPSY	C + R + P	Individual
6			Group
7	FOLLOW-UP data	C + R + P	Individual
8			Group

Limitations



- Indication bias
- No description of how bx taken
- Pathologists least confident in high
  - 85% vs. 52%
- ?Pathologist experience
- 33% pneumothorax

Tomassetti et al AJRCCM (2016) 193:745-52

Better mousetrap?
or
Irrational exuberance?

Cryobiopsy: perils and pitfalls

- Complications
- What diagnoses are we trying to make?
- Trial design limitations
- What century are we practicing pulmonary medicine in?
- Does a “hard and fast” diagnosis really matter?

Table 4 Major complications of cryobiopsy

Lentz J Thorac Dis. 2017 Jul;9(7):2186-2203

First author	Year	PTX: all[a]	PTX: chest tube[b]	Serious bleed[c]	Escalation of care[d]	AE	Death	Overall CR
Babiak (1)	2009	2 (4.8%)	2 (4.8%)	0	–	–	–	2 (4.8%)
Griff (4)	2011	0	0	0	–	–	–	0
Kropski (30)	2013	0	0	0	2 (8%)	–	–	2 (8%)
Fruchter (31)	2013	0	0	0	–	–	–	0
Fruchter (32)	2013	0	0	0	–	–	–	1 (2.5%)
Yarmus (33)	2013	1 (4.8%)	1 (4.8%)	0	0	0	0	1 (4.8%)
Casoni (25)	2014	19 (28%)	14 (20%)	1 (4%)	–	1 (4%)	1 (4%–AE)	20 (29%)
Griff (34)	2014	0	0	0	–	–	–	0 (0%)
Pajares (29)	2014	3 (8%)	?	0	3 (8%)	–	0	3 (8%)
Fruchter (35)	2014	2 (2.6%)	?	3 (4%)	–	0	0	5 (7%)
Pourabdollah (36)	2014	(No safety data reported)						
Hernandez-Gonzales (37)	2015	4 (12%)	1 (3%)	0	1 (3%)	0	0	4 (12%)
Hagmeyer (38)	2015	6 (19%)[e]	6 (19%)	2 (6%)[f]	–	–	–	8 (26%)
Gershman (39)	2015	15 (5%)	6 (2%)	16 (5%)[g]	10 (3%)	–	0	47 (15.5%)
Ravaglia (5)	2016	60 (20%)	46 (15.5%)	0	?[h]	1 (0.3%)	1 (0.3%–AE)[i]	66 (22%)
Ramaswamy (40)	2016	11 (20%)	?	1 (2%)	–	0	0	12 (22%)
Tomassetti (41)	2016	19 (33%)	15 (25%)	0 (0%)	7 (12%)	1 (1.7%)	1 (1.7%–AE)[i]	19 (33%)
Hagmeyer (42)	2016	5 (26%)	4 (21%)	8 (42%)	–	1 (2%)	1 (2%–AE + MI)	–
Echevarria (43)	2016	3 (3%)	3 (3%)	10 (10%)	–	–	1 (1%–PTX, cancer)	16 (16%)
Sriprasart (44)	2017	5 (7%)	5 (7%)	1 (1%)	8 (11%)	–	3 (4%–AS, OP, PE)	8 (11%)
DiBardino (45)	2017	2 (8%)	1 (4%)	3 (12%)	6 (24%)	–	0	6 (24%)
Bango-Alvarez (46)	2017	5 (4.7%)	?	0	–	0	0	5 (5%)
Kronborg (47)	2017	10 (26%)	8 (21%)	3 (8%)	–	0	0	18 (47%)
Berim (48)	2017	–	–	2 (20%)	–	–	–	2 (20%)
Ravaglia (49)	2017	7 (16%)	?	0	–	–	0	7 (16%)
Ussavarungsi (50)	2017	1 (1.4%)	1 (1.4%)	9 (12%)	2 (3%)	–	0	12 (16%)

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UIP/IPF: is tissue obsolete?

- Current guidelines characteristic radiographic pattern HRCT scan
  - 90-100% PPV for IPF
- Only 50% with ultimate dx of IPF meet this characteristic criteria
  - Biopsy is recommended to confirm UIP

Raghu et al AJRCCM (2011) 183:788-824; Travis et al AJRCCM 188:733-48

Retrospective UIP Dx on TBBx

- Roughly 30-35% characteristics of UIP
- Biopsies considered “adequate” if 1-3 TBBx available for review
- Sheth et al trial – TBBx vs. SLB in DPLD
  - Median 3 alveolated lung bx (0-7)
  - 50% felt to be diagnostic of relevant DPLD
  - Could we do any better with more TBBx from more lobes with less complications?

Barbescu et al (2006) Chest 129:1126-1131
Tomasetti et al (2012) Resp Res 13:96
Sheth et al (2017) 151:389-399

Sarcoidosis

- EBUS TBNA
- Transbronchial biopsy
- Endobronchial biopsy

HSP – does the timing and yield of bx matter?

- Acute – diffuse centrilobular micronodular pattern
- Subacute – GGO, interlobular septal thickening/fibrosis, centrilobular micronodularity, early honeycombing
- Chronic – worsening of above, can assume UIP-like pattern
- Either last two – NSIP, granulomas, UIP, BOOP

Drug toxicity

- Radiography
  - GGO, interseptal lobular thickening, infiltrates
- Pathology
  - BOOP/COP
  - Granulomas – well and poorly formed
  - NSIP
- Clinical diagnosis of exclusion, not pathologic

BOOP/COP/OP

- May be very characteristic radiography
- Not a disease – injury pattern
- Can be seen in drug toxicity, HSP, idiopathic, associated with tumors
- Clinical correlation always indicated

How many current cryobx trials?

- Clinicaltrials.gov website
  - 3 actively recruiting trials for DPLD
  - 3 trials listed as complete, not recruiting
  - None exclusion criteria for UIP pattern
  - Only 1 has exclusion criteria for typical sarcoid pattern

Trial design

- DPLD - SLB ideally from at least 2 lobes
- Interpatient disease heterogeneity is problematic
- Ideal design
  - Every patient serves as their own control
  - Each patient gets the comparative biopsy modality
  - Each modality biopsies in at least 2 lobes

Trial Design

- Hypotheses
  - CBx is superior to conventional TBBx
  - CBx is equivalent to SLB
- The pathologist should be blinded to prevent interpretation bias
- The multi-disciplinary team should be blinded to the report description of bx size

Statistical considerations

- Statistical considerations
  - Superiority trials – CBx to conventional TBBx
    - require a much lower N
  - Non-inferiority trials – CBx to SLB
    - require a much higher N

Current best clinical trial

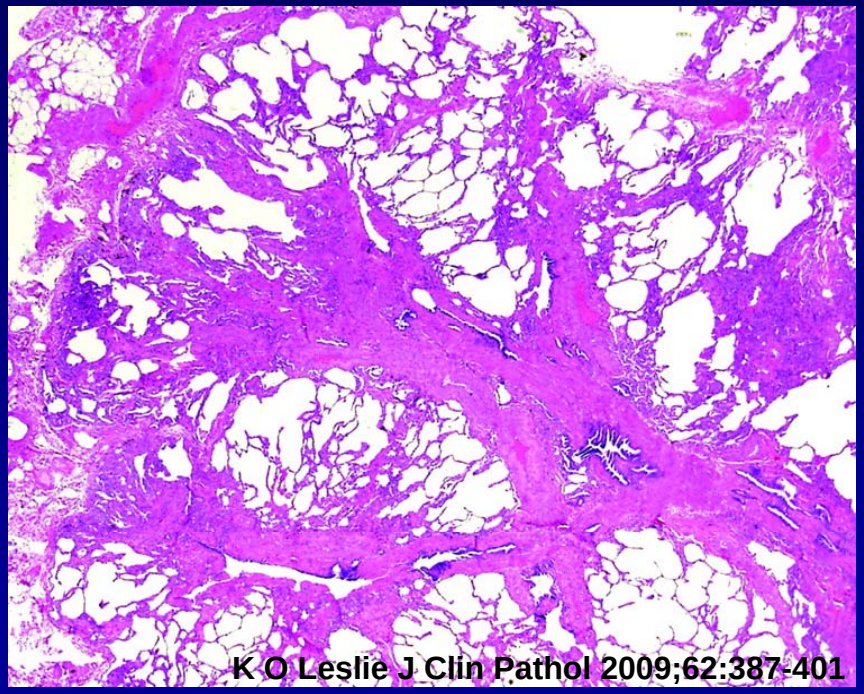
- All patients get all 3 modalities
- Planned enrollment 20 patients at 4 centers
- Trial opened June 2013
  - Have not completed enrollment
- What is the limitation?
  - Are multi-disciplinary teams moving away from bx of any kind?
  - Patients' perception of CBx safety compared to SLB

What century are we practicing in?

1590

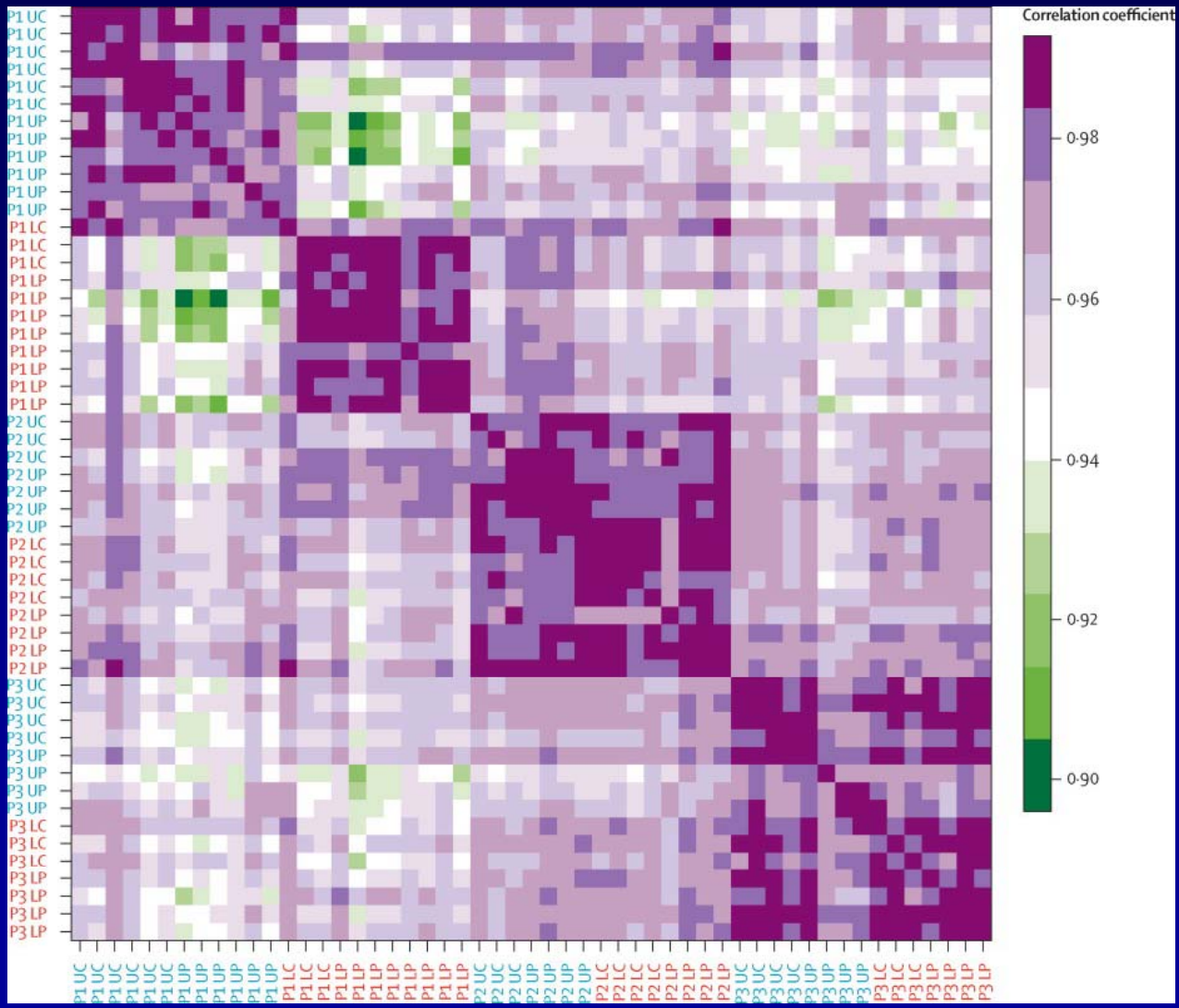
https://en.wikipedia.org/wiki/Zacharias_Janssen

1876



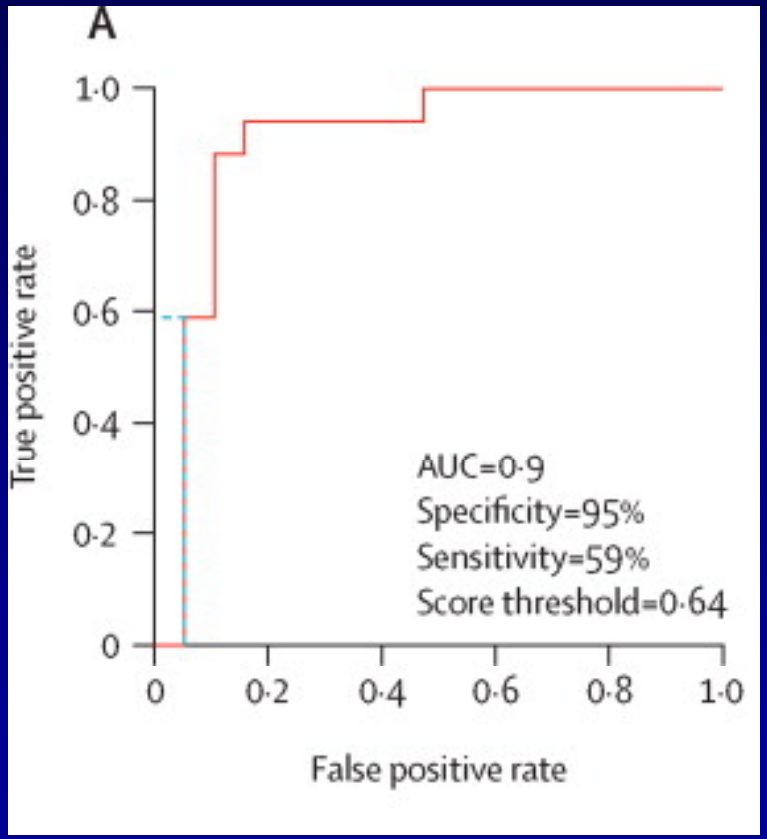
K O Leslie J Clin Pathol 2009;62:387-401

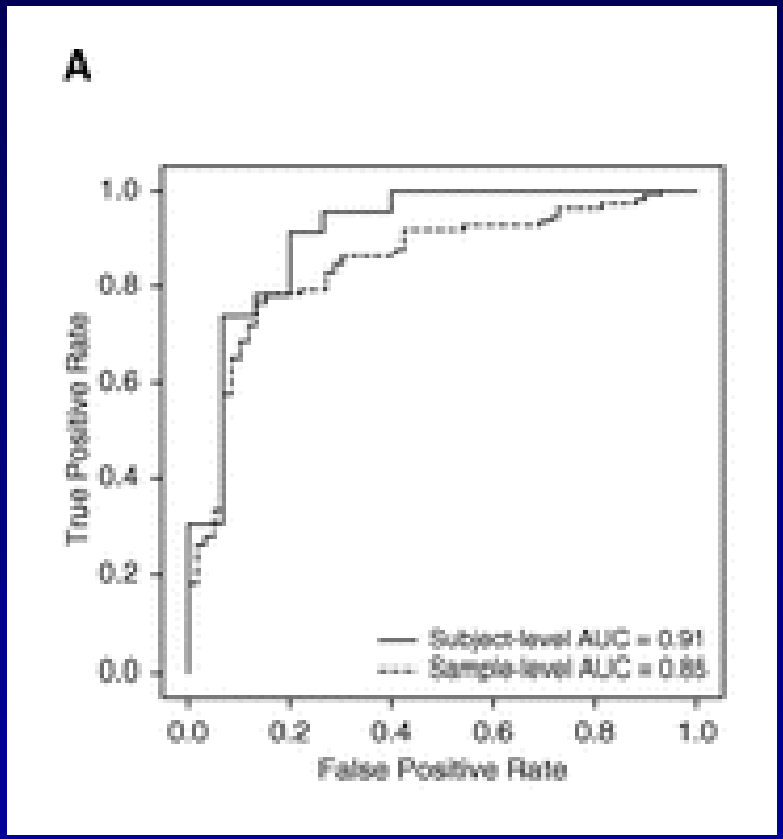
21st Century Microscope and H&E Stain



Kim et al. Lancet Resp Med (2015) 3:473-482; Pankratz et al. (2017) AnnalsATS 14:1646-1654

ROC Curves for SLB and TBBx





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Does a “definitive” diagnosis matter?

- All patients (except UIP) get steroids anyway
- Exceptions:
  - UIP discovered when CT scan not classic
  - Clinical trial enrollment if “confidence” in the diagnosis is necessary

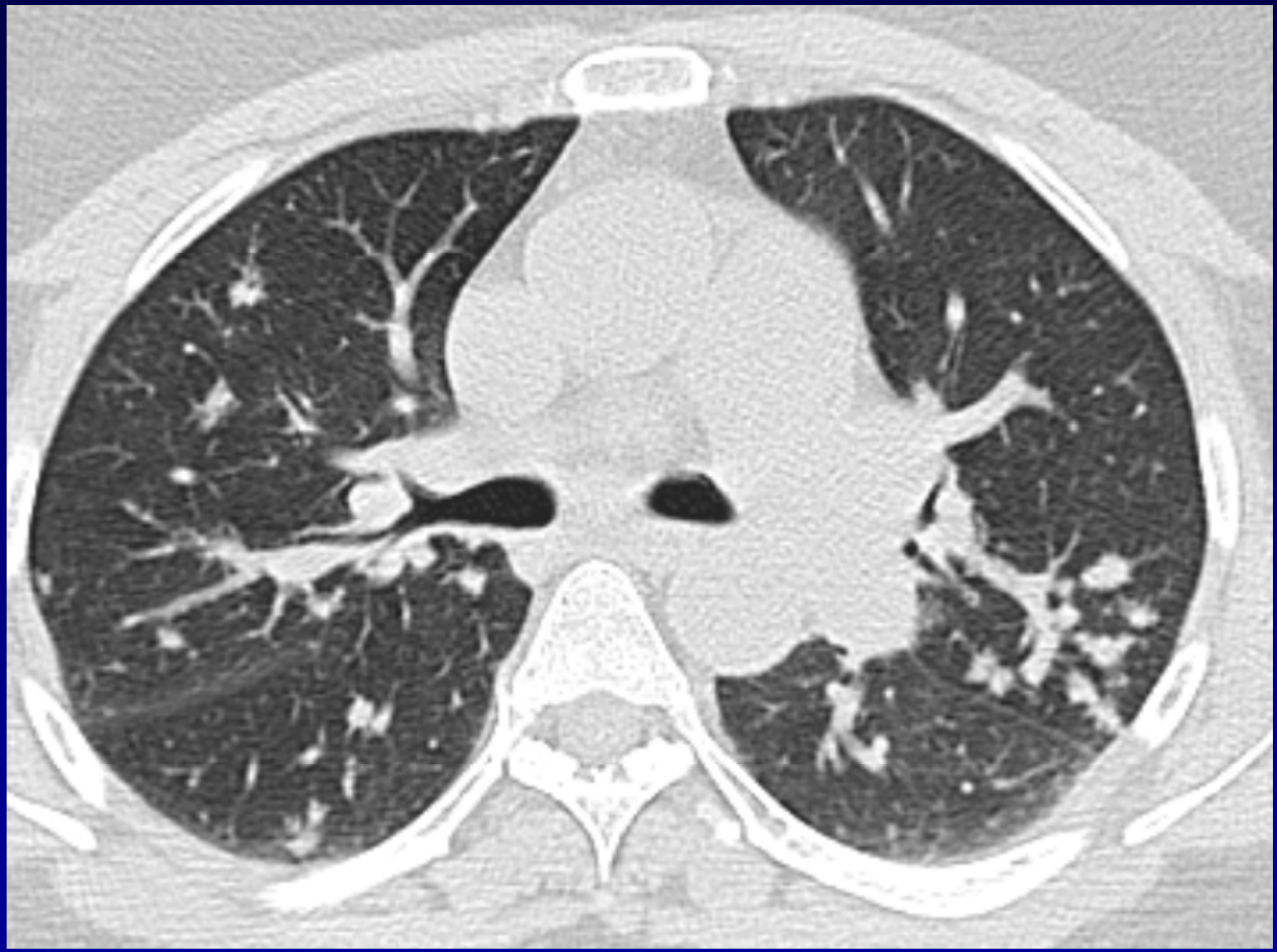
Should cryobiopsy have broad utilization?

- Well designed comparative trial awaits
- Complication rate should give pause
- Standardization of procedural technique
  - Intubation with bronchial blocker in place
  - Utilize 1.9 mm probe with fluoroscopy
  - Test freeze
  - 3-5 biopsies in different lobes or at least different segments
  - Post procedure chest x-ray

Hetzel et al, 2018 Respiration DOI 10.1159/000484055

Summary

- Ideal study to answer CBx role in well-designed comparative trial awaits
- Standardization of biopsy approach
- Educate patients about potential risks
- As a field we need to actively engage in 21st century technology clinical trials
  - Obviate need for any biopsy at all



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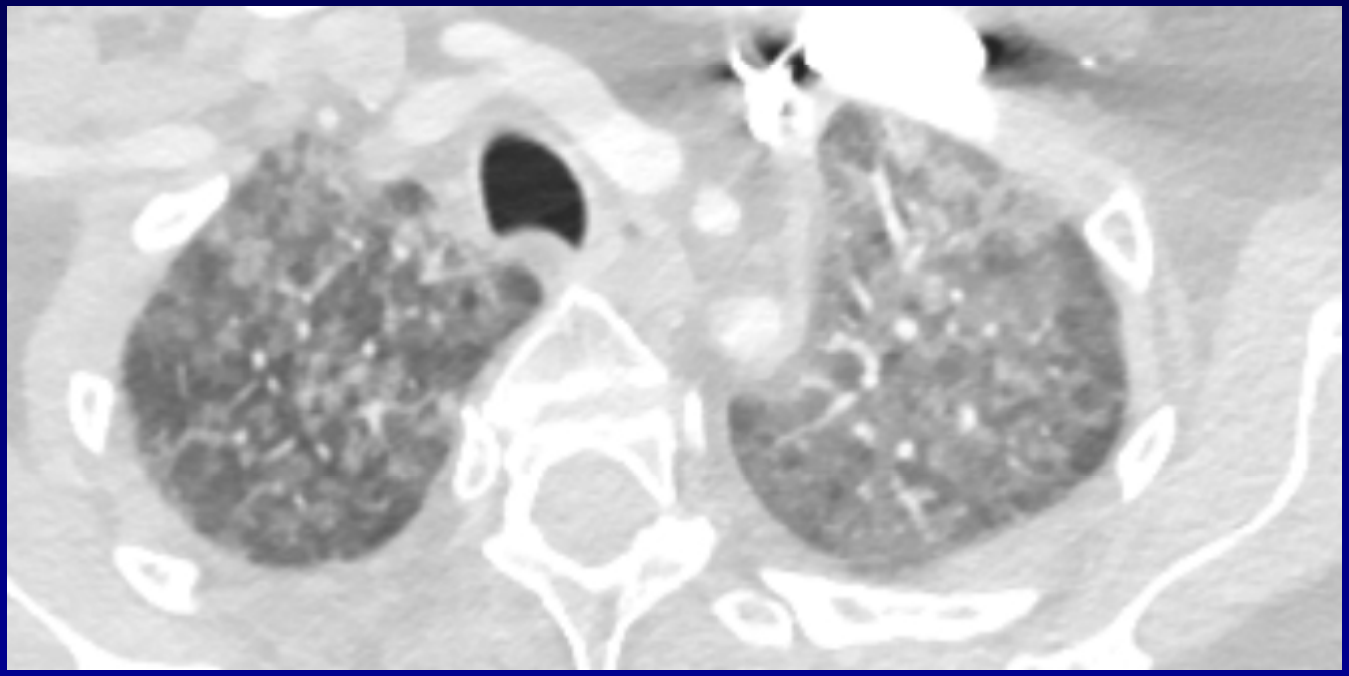
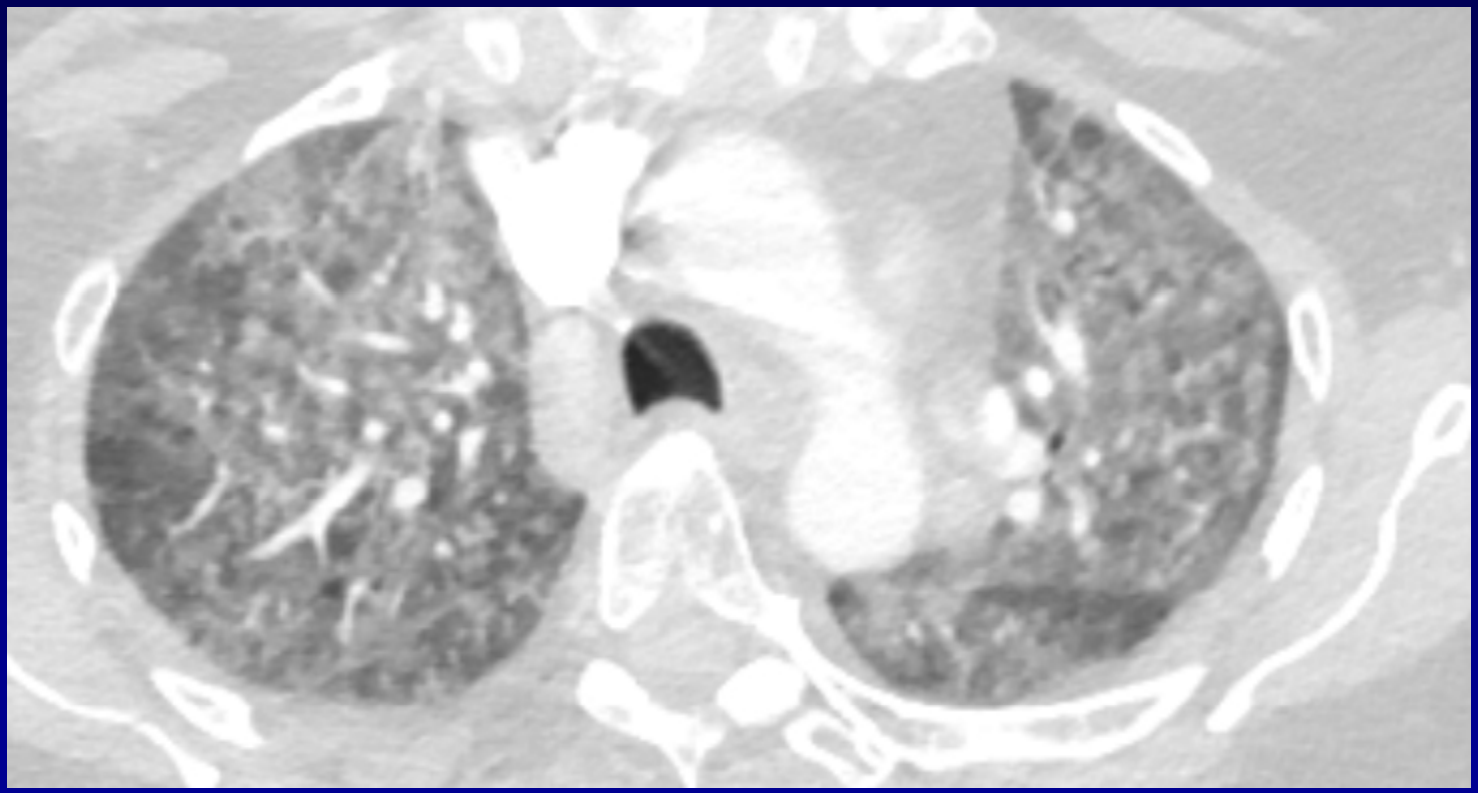
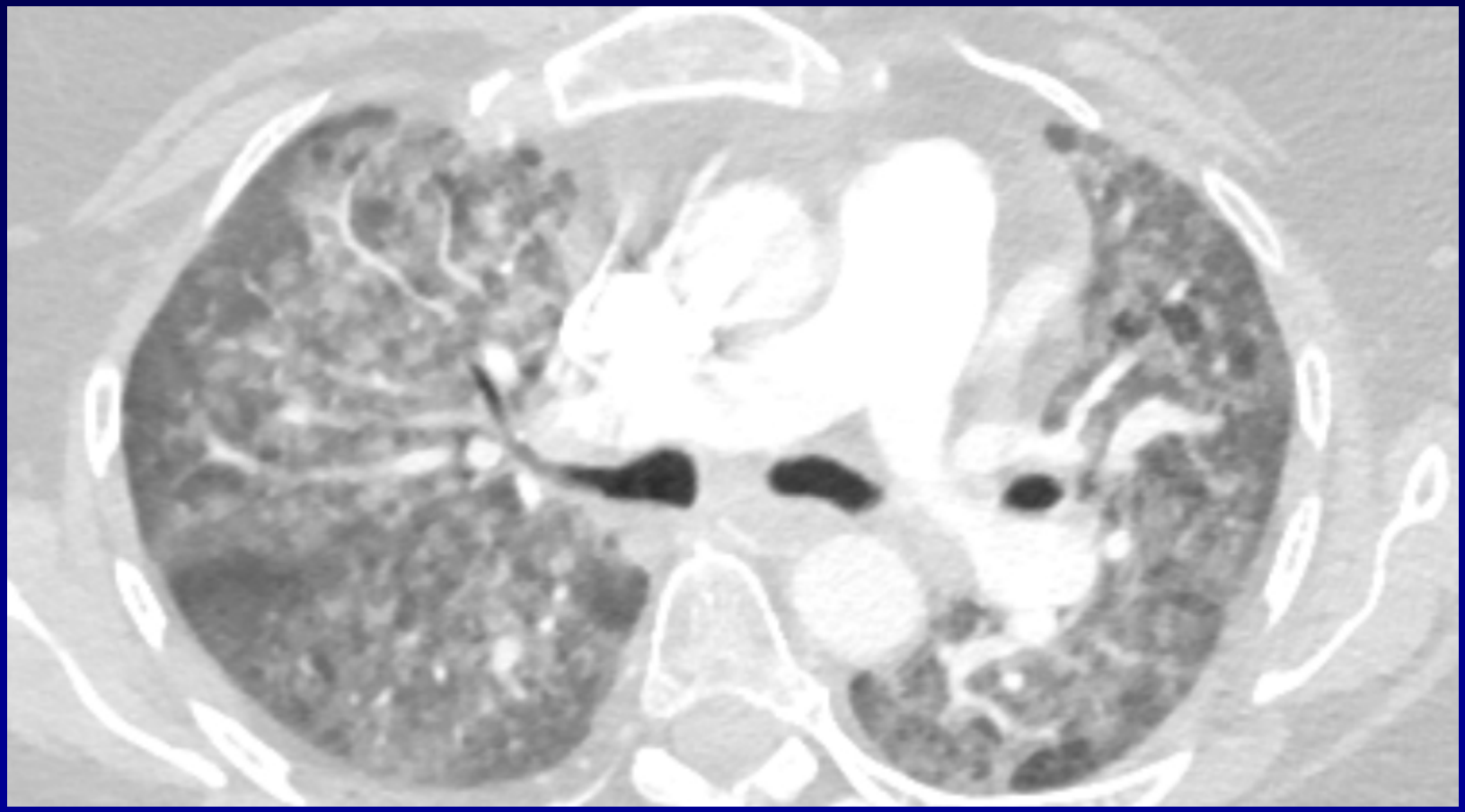
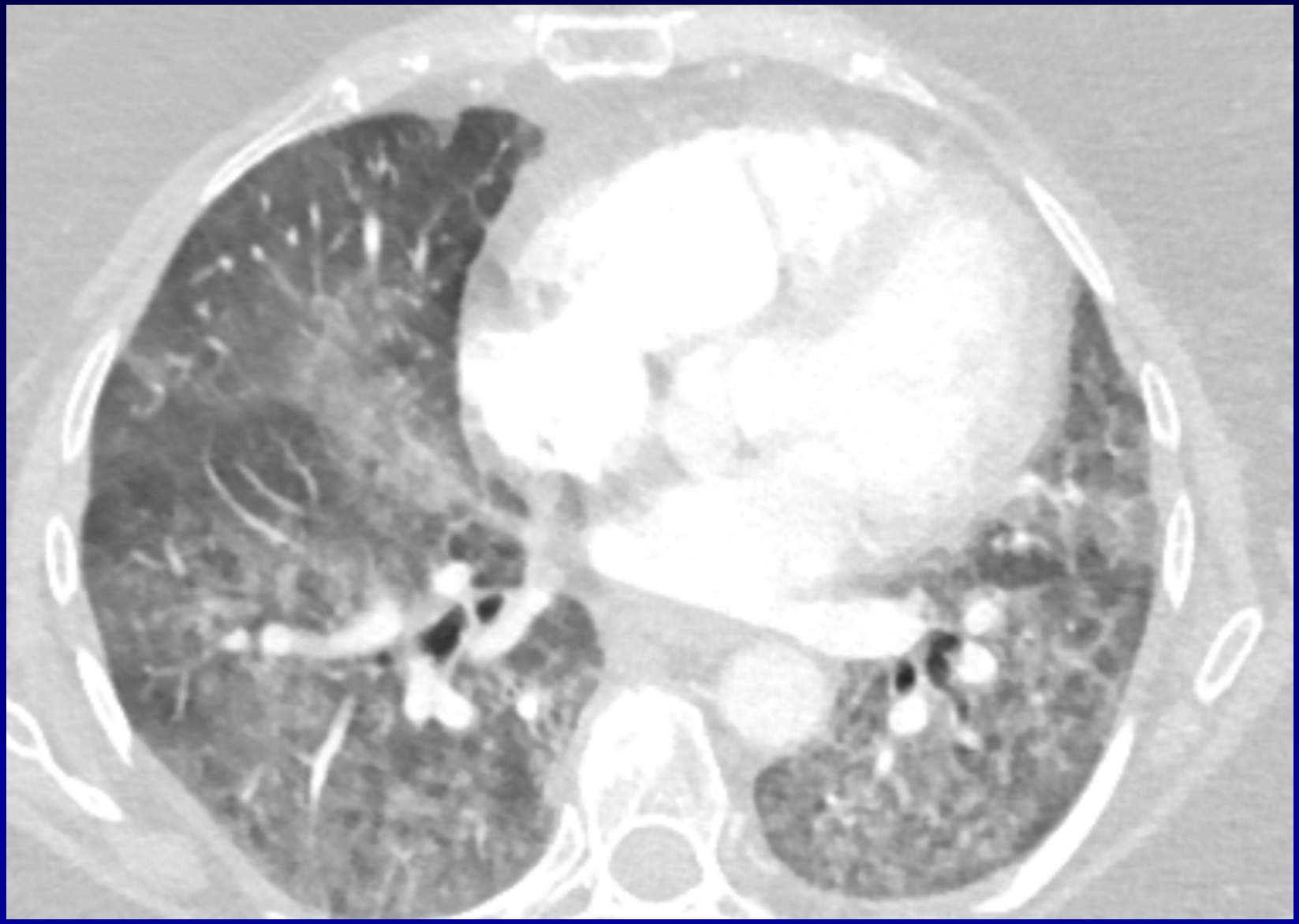
- D) HSP

- Diagnostic procedure:
- A) Transbronchial bx
- B) EBUS TBNA
- C) VATS/wedge
- D) Cryobiopsy









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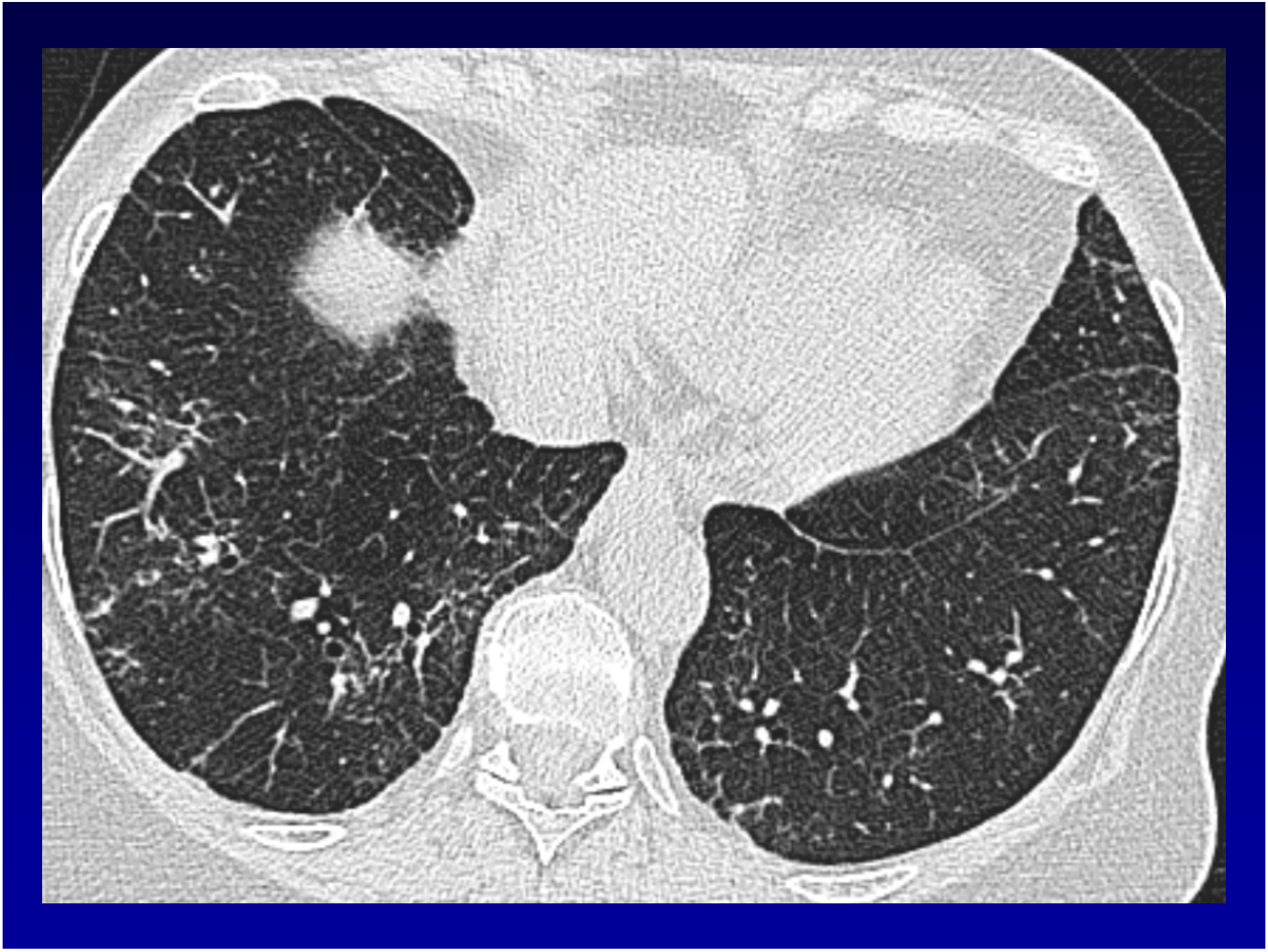
Final pathology

- Sections show lung parenchyma with an interstitial infiltrate composed predominantly of neutrophils, lymphocytes, and rare eosinophils. There are also intra-alveolar macrophages with neutrophils and focal fibrin deposition. No granulomatous inflammation to suggest hypersensitivity pneumonitis is identified. No viral inclusions are seen. The overall findings favor an acute pneumonia due to an infectious etiology, with some evidence of acute lung injury. Other considerations include eosinophilic pneumonia or drug reaction, although the eosinophils are not prominent. A Grocott stain is negative for fungal organisms, while AFB and Fite stains are negative for acid fast organisms. Correlation with microbiology studies is recommended.



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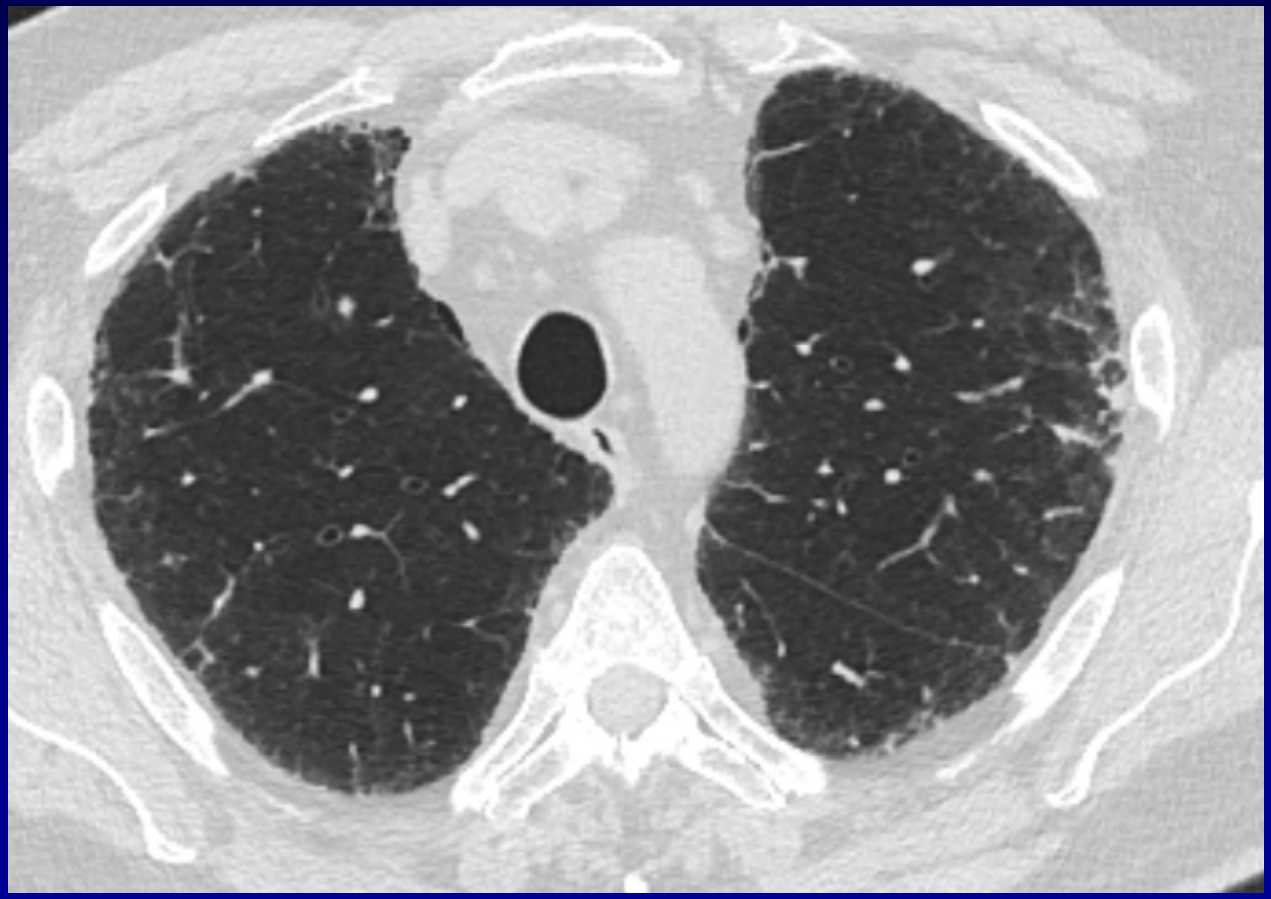

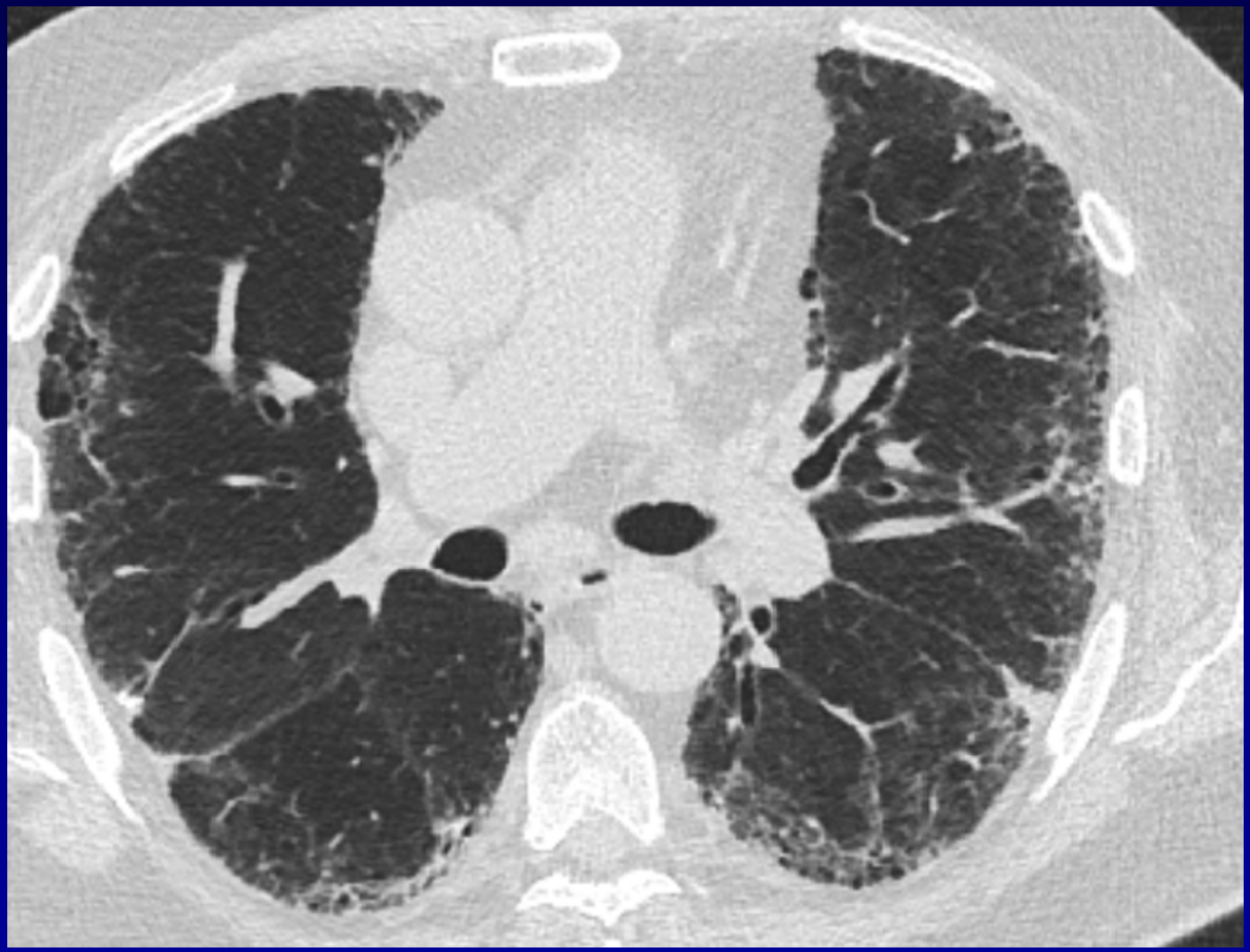

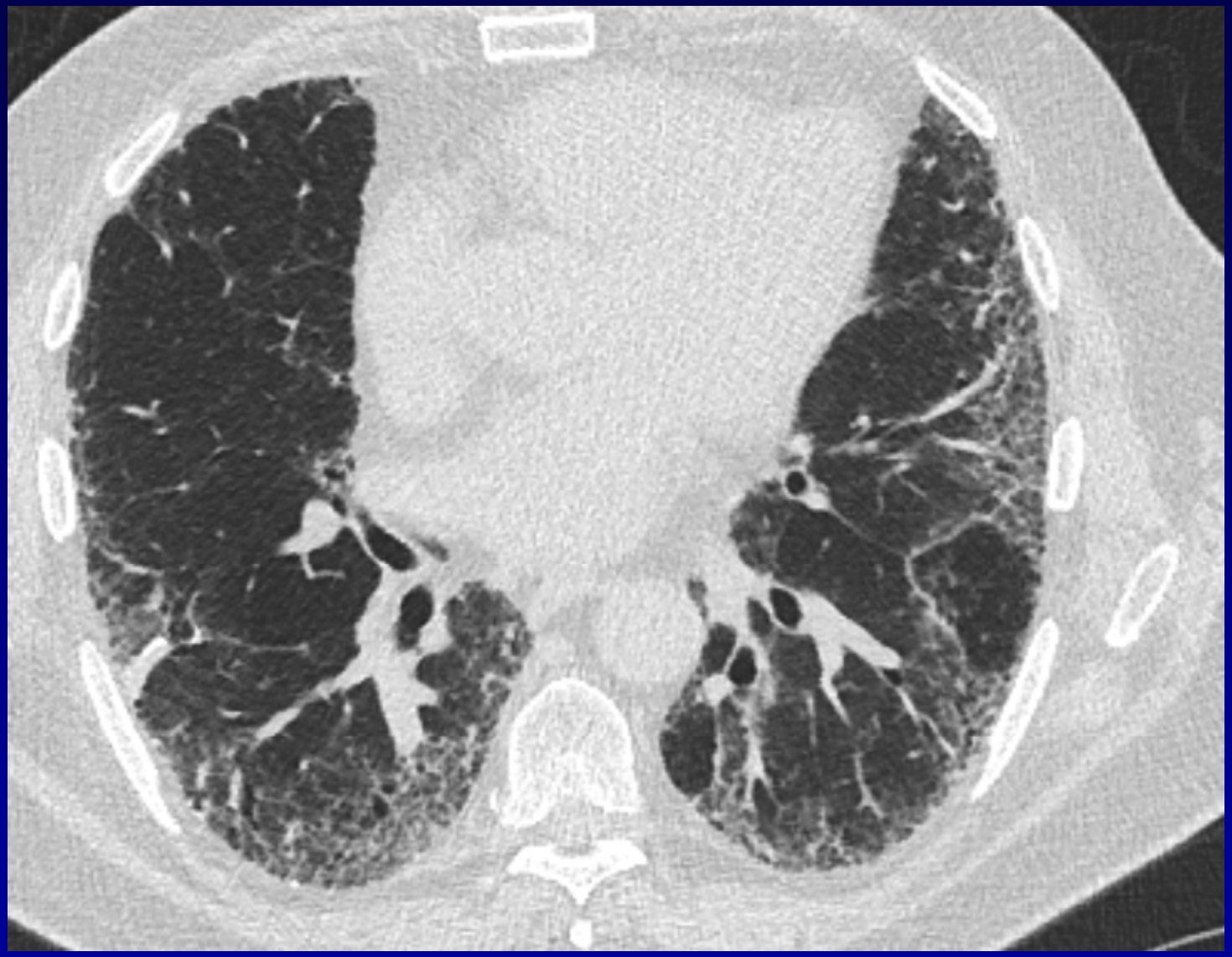

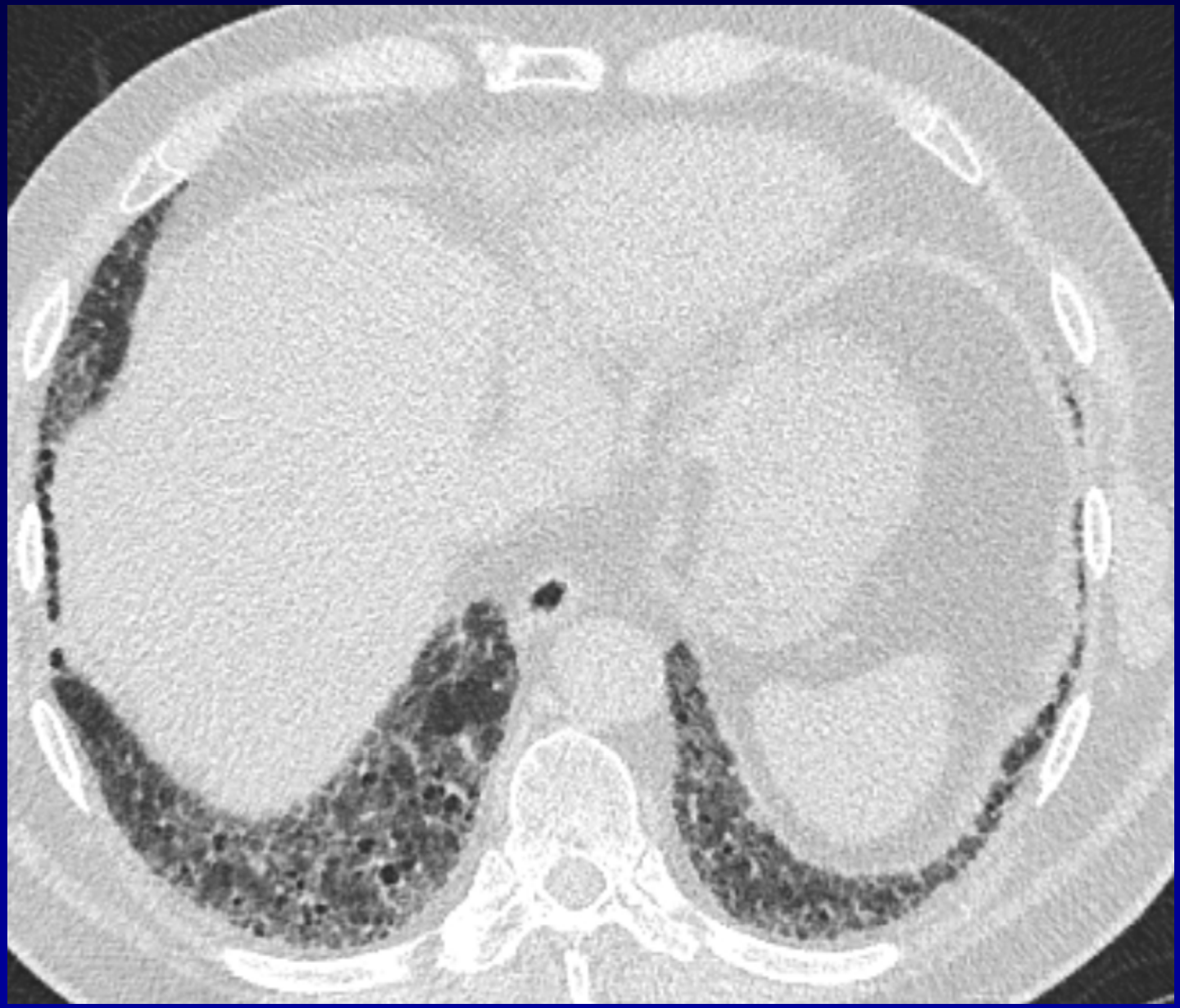

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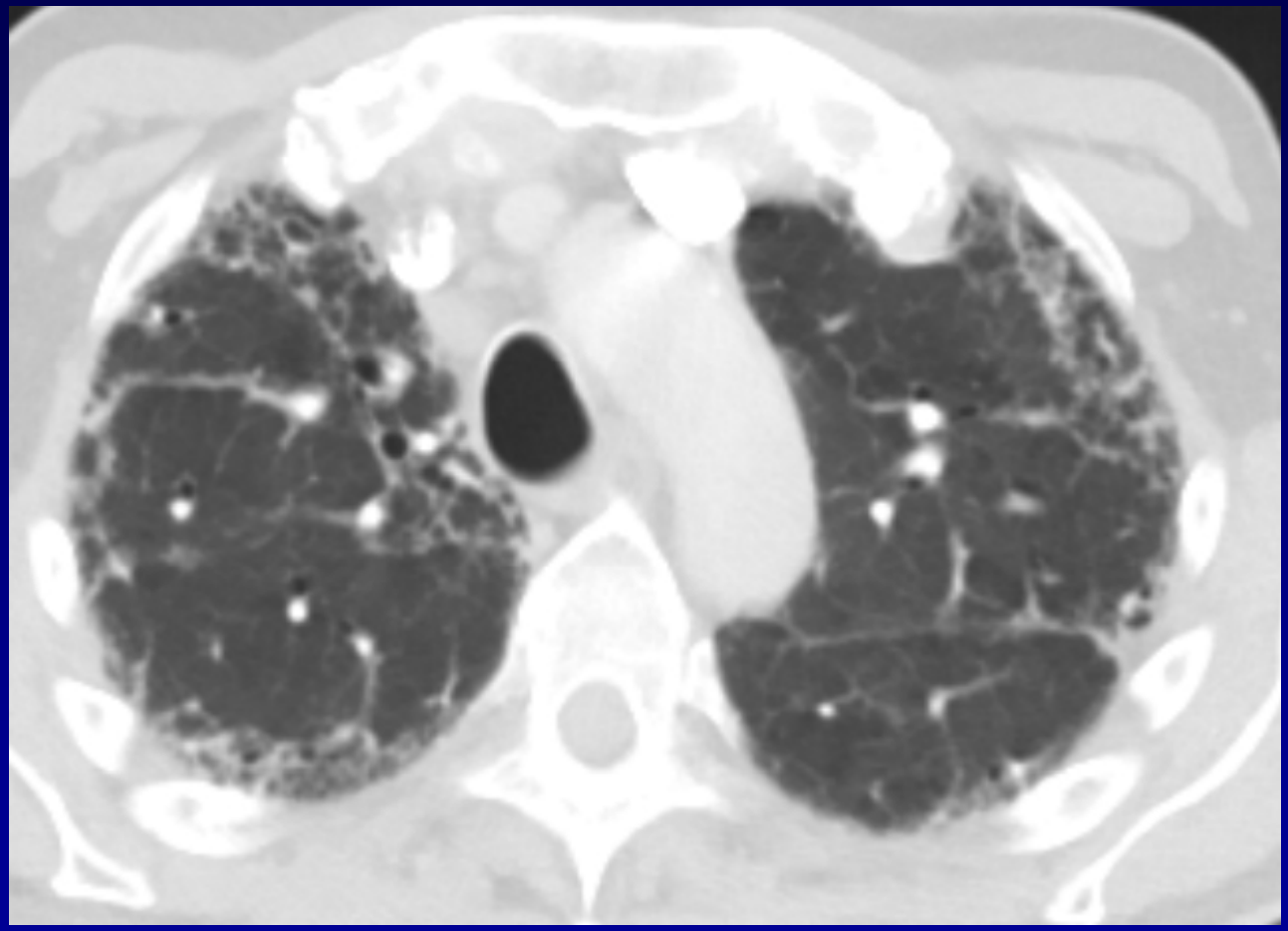

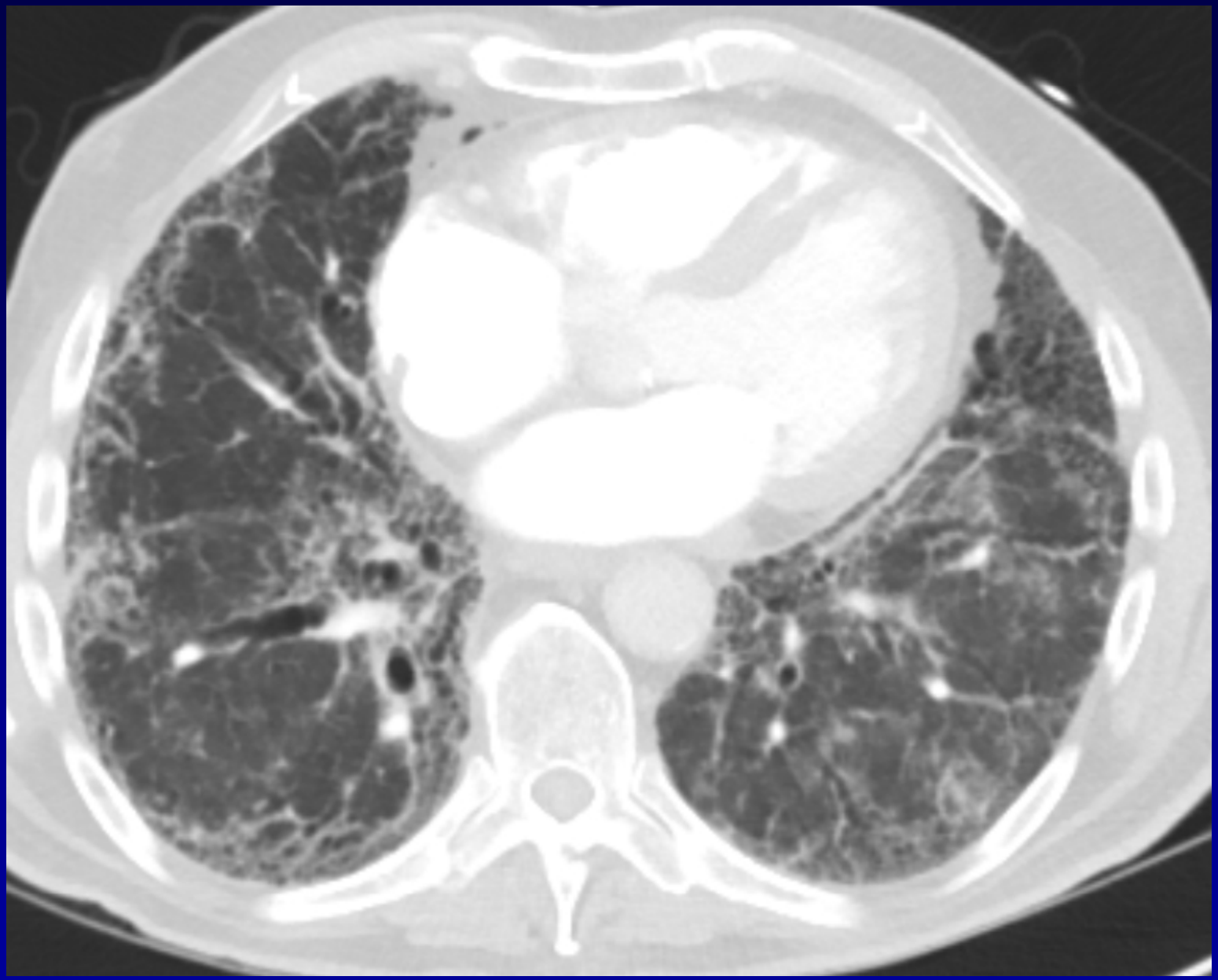

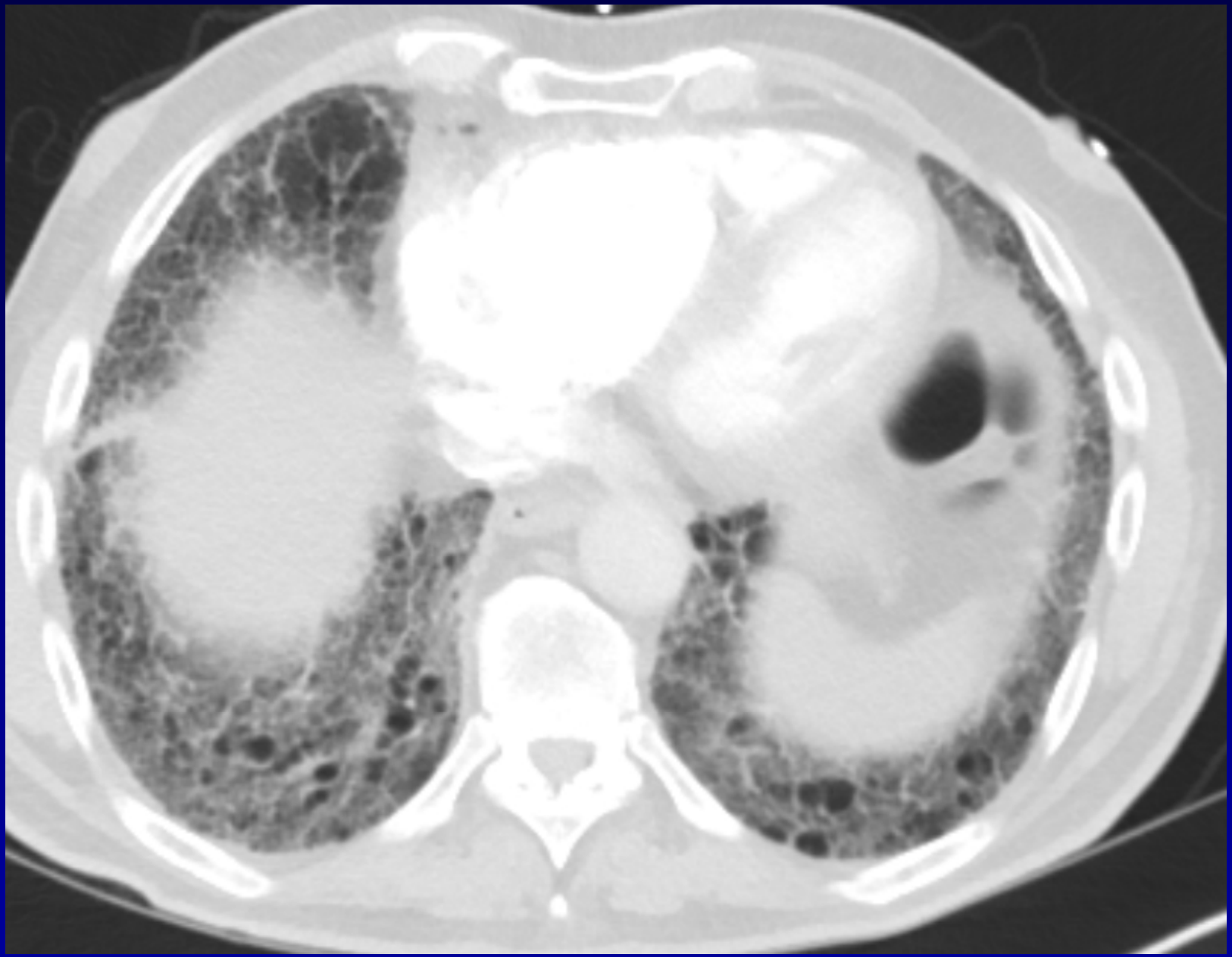

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