16:20-17:10 SALA MONTESSORI (Wk da 50 pax)

Workshop n. 2 - Nuove metodologie diagnostiche in ILD

Ruolo della pneumologia interventistica nella diagnosi differenziale – *M. Bonifazi, P. Lyberis, S. Tomassetti, F. Calabrese*

Fiorella Calabrese

Dipartimento di Scienze Cardiache, Toraciche, Vascolari e Sanità Pubblica

Università degli Studi di Padova

800 ANNI 1222·2022 — UNIVERSITÀ DEGLI STUDI DI PADOVA

Uomo caucasico, 58 anni

- **Storia di fumo**: ex-fumatore (dai 18 anni fino ai 47 anni 10 sigarette die, P/Y 11).
- **Allergie**: acari, muffe, aspergillus.
  Non allergie a farmaci.
- **Professione**: ex-coltivatore diretto con esposizione a fieno fino al 2007.
  Successivamente attività di amministrazione nell'azienda agricola di proprietà.

In anamnesi…

- Familiarità per asma bronchiale.
- Asma bronchiale noto fin dall'infanzia in terapia continuativa con ICS/LABA fino ad una decina di anni fa; attualmente SABA al bisogno.
- Non altri precedenti anamnestici.
- Terapia domiciliare: nessuna.

Anamnesi prossima

Maggio-Luglio 2018

- Episodi di tosse secca stizzosa, senso di costrizione toracica, respiro sibilante (1/sett); dispnea ingravescente (mMRC 1).
- Non variazioni dell'attività lavorativa o dell'ambiente domestico.

Luglio 2018

Prima valutazione pneumologica

(presso altra sede)

↓

Terapia steroidea orale a scalare
e terapia inalatoria con
budesonide/formoterolo 160/4.5

Paziente rivalutato a 20 giorni
con radiografia del torace

Si prescriveva TC del torace ad alta risoluzione e si inviava il paziente presso centro di terzo livello per il proseguimento dell'iter diagnostico-terapeutico.

Valutazione Pneumologica presso i nostri Ambulatori

Esame obiettivo (1)

Agosto 2018

- Eupnoico a riposo, dispnoico all'eloquio prolungato, non sofferente.
- **Cuore**: toni cardiaci validi, ritmici, non soffi né click, assenti III e IV tono.
- **Addome**: piano, trattabile, non dolente né dolorabile alla palpazione superficiale e profonda, peristalsi presente e valida, fegato e milza non palpabili.

Esame obiettivo (2)

Agosto 2018

- **Torace**: alla percussione suono chiaro polmonare, basi polmonari mobili e simmetriche, MV ridotto su tutto l'ambito polmonare, qualche sibilo e gemito espiratorio sparso, crepitii a velcro bibasali.
- **Arti inferiori**: non edemi declivi, polsi periferici validi e simmetrici.
- EO neurologico: ndp.

Emogasanalisi arteriosa

Agosto 2018

pH	**7,45**
pCO2	**34 mmHg**
pO2	**68 mmHg**
HCO3-	**22 mmol/L**
BE	**1 mmo/L**
SatO2	**92%**

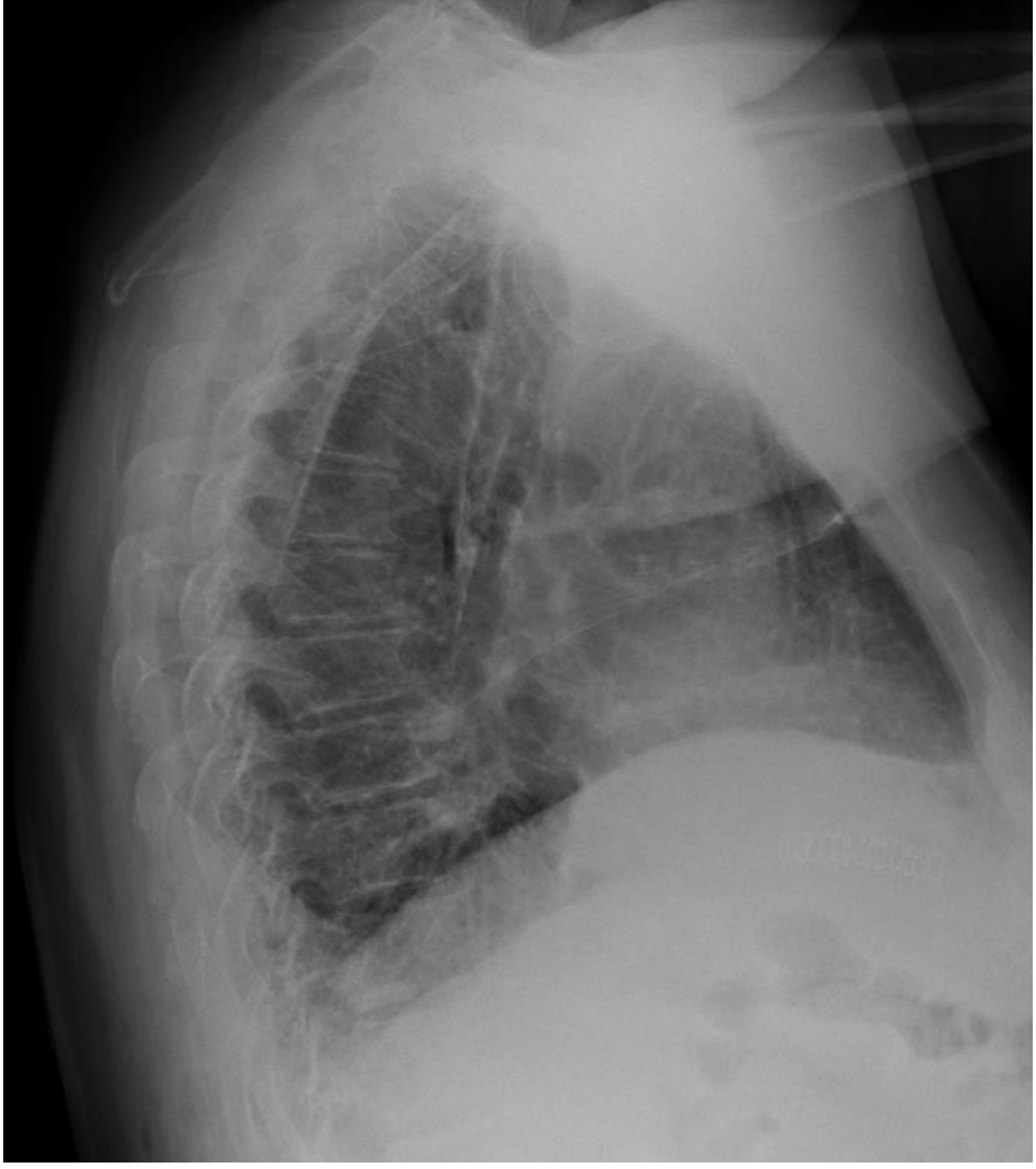
PAO2 – PaO2 = 107 – 68 = 39 mmHg

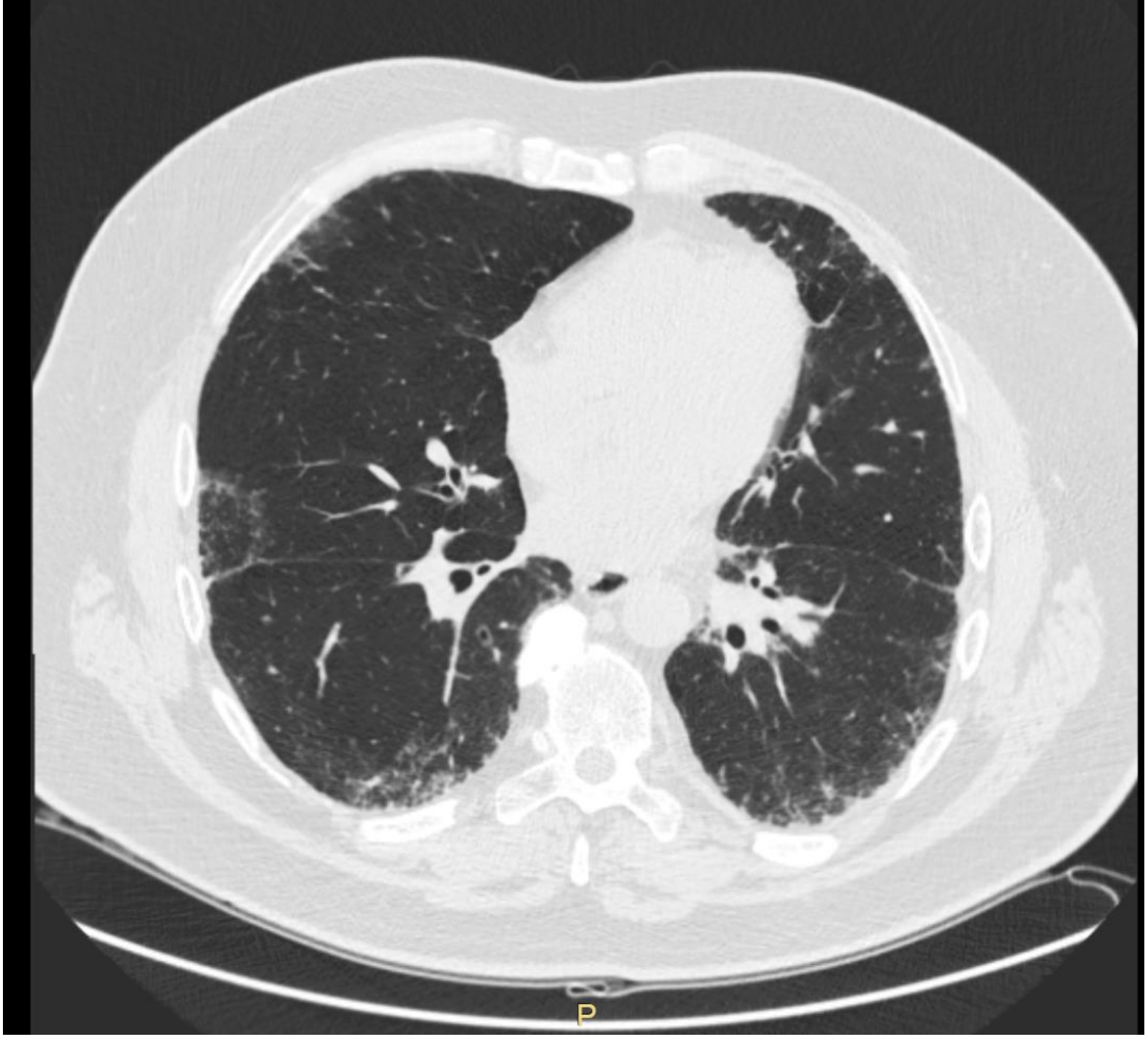
Spirometria

Agosto 2018

FEV1	3,94 L (86%)
FVC	3,23 L (89%)
FEV1/FVC	82%
TLC	6,16 L (84%)
DLCO	58%

From R. Polverosi: esiti di versamento pleurico a destro, minimo ipessimento reticolare basale soprattutto in sede retrocardiaca sn

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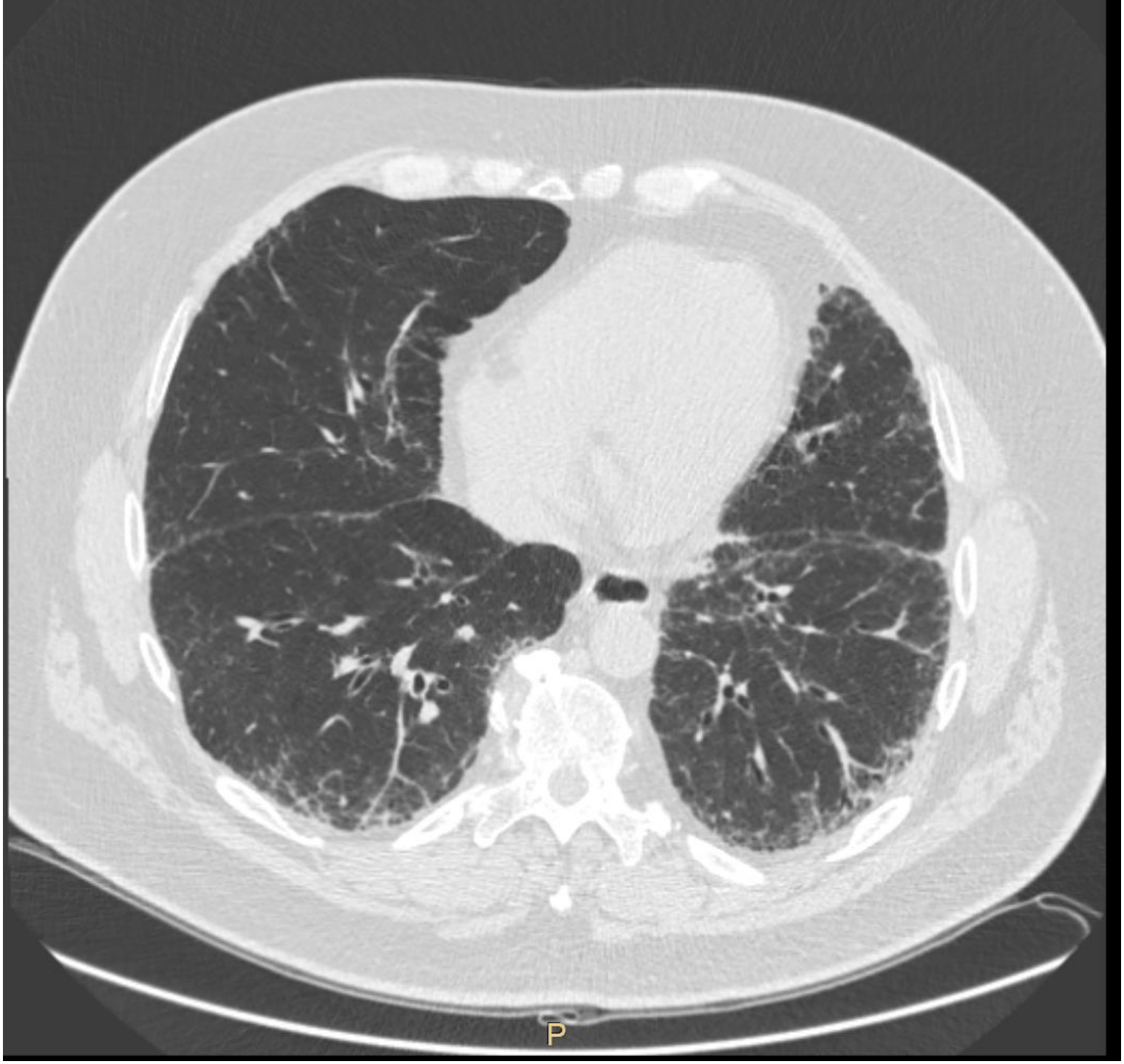
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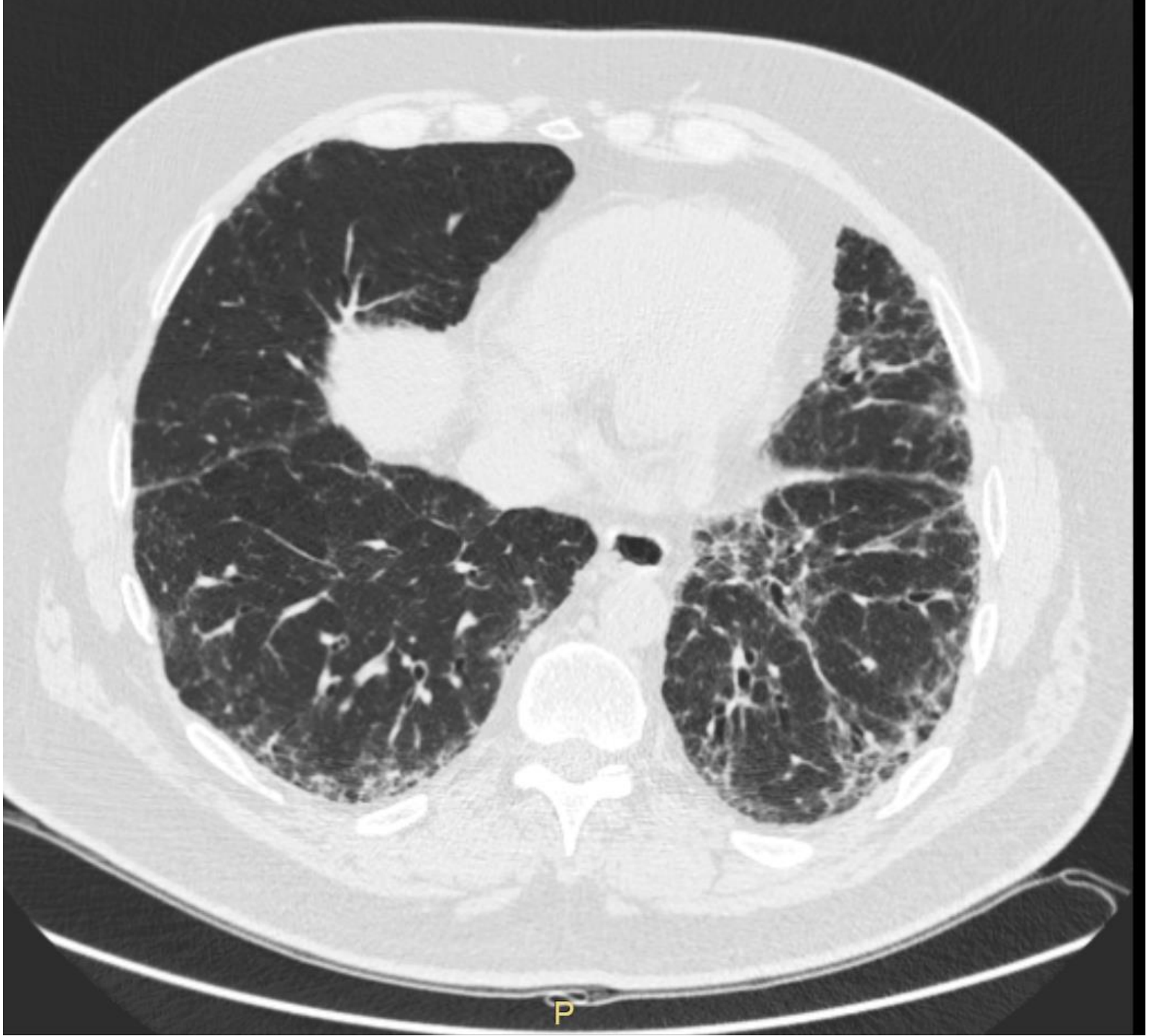
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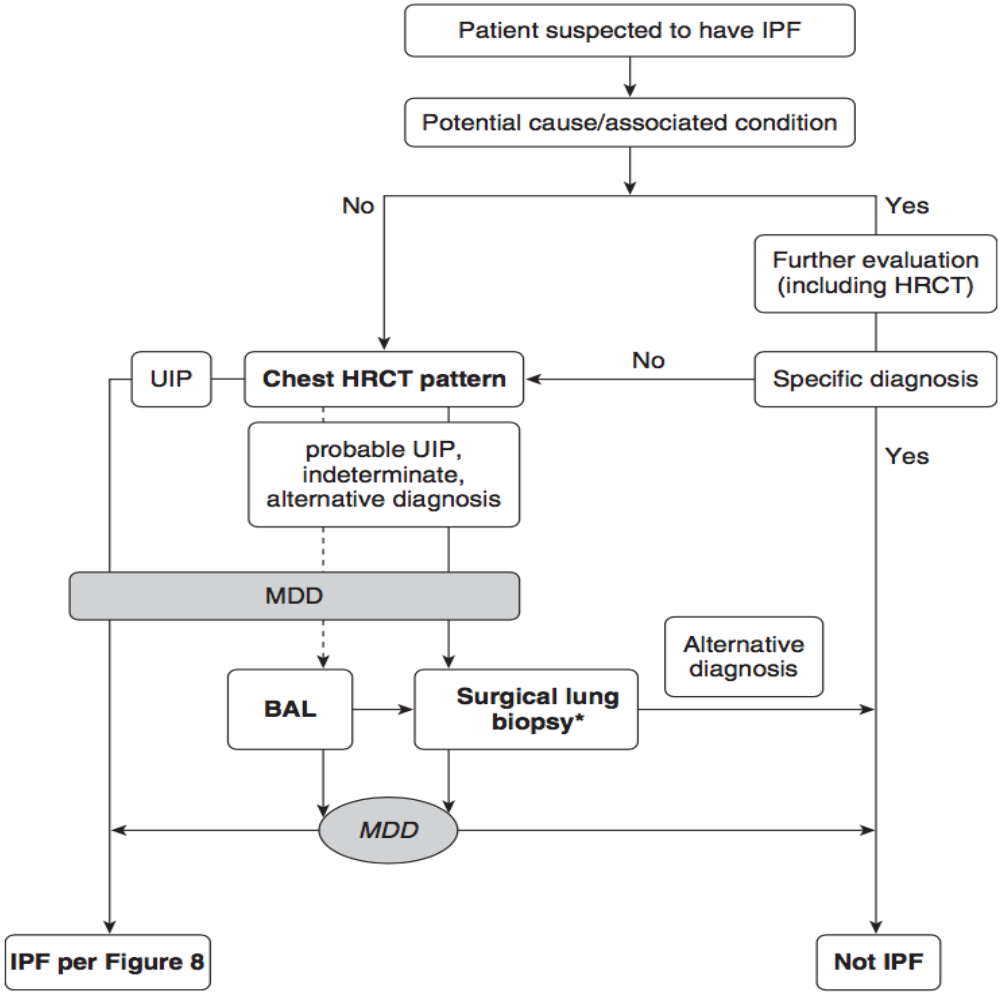
Dott. R. Polverosi :Ispessimento irregolare dei + bronchiettasie/bronchiolectasie da trazione. No honey.
Più esteso a sin , con **pattern UIP probable**

AMERICAN THORACIC SOCIETY DOCUMENTS



For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis:

- We suggest cellular analysis of their BAL fluid (*conditional recommendation, very low quality of evidence*).
- We suggest surgical lung biopsy (SLB) (*conditional recommendation, very low quality of evidence*).
- The panel made no recommendation for or against transbronchial lung biopsy (TBBx).

- The panel made no recommendation for or against lung cryobiopsy.

Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

Come procedere?

Accesso presso il Day Hospital

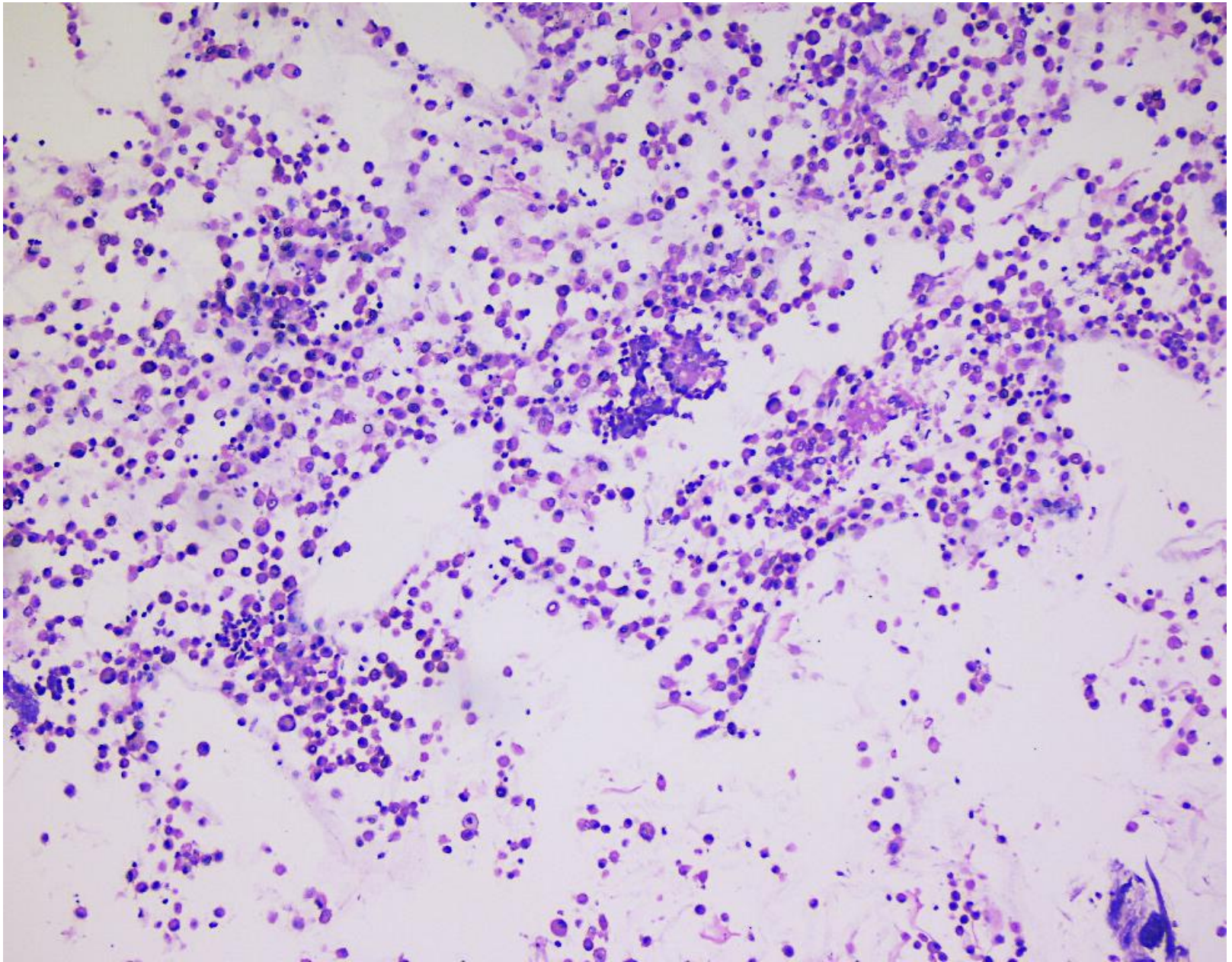
Settembre 2018

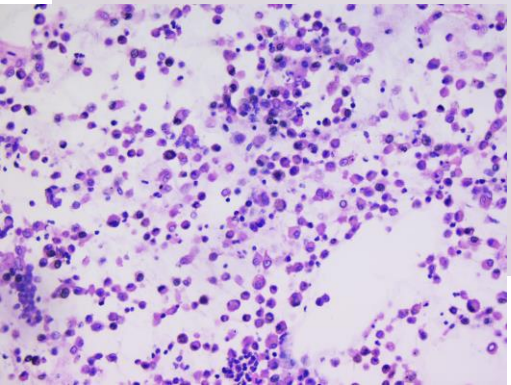
- Si programma esecuzione di broncoscopia con BAL e biopsia tranbronchiale, oltre che esami ematochimici di autoimmunità.

Broncoscopia

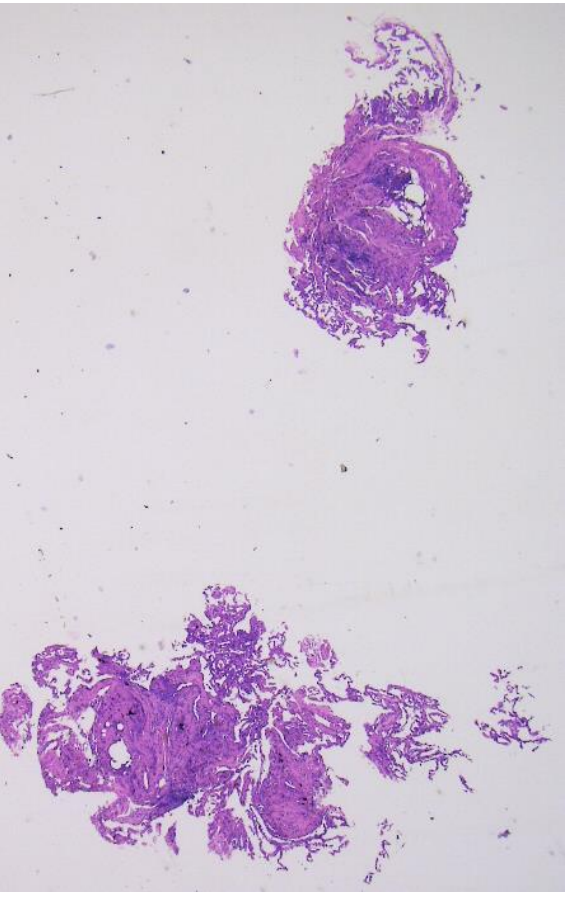
“Trachea e bronchi pervi nel settore esplorabile. Carena e speroni sottili, mobili. Segue BAL nel medio e multiple TLB ai segmentari basali di sinistra. Aspirato per citologia, microbiologia, B.K.”

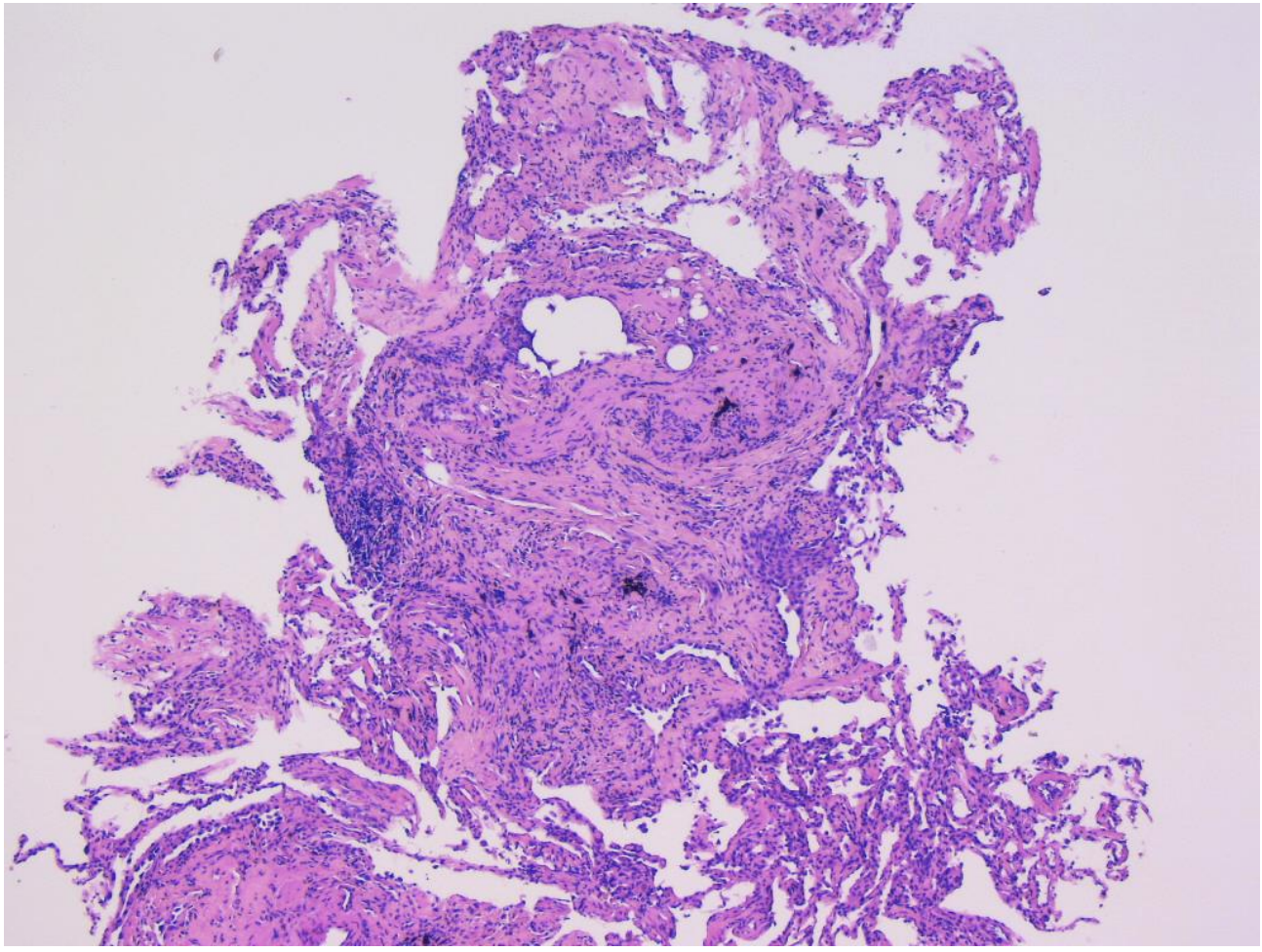
TBB

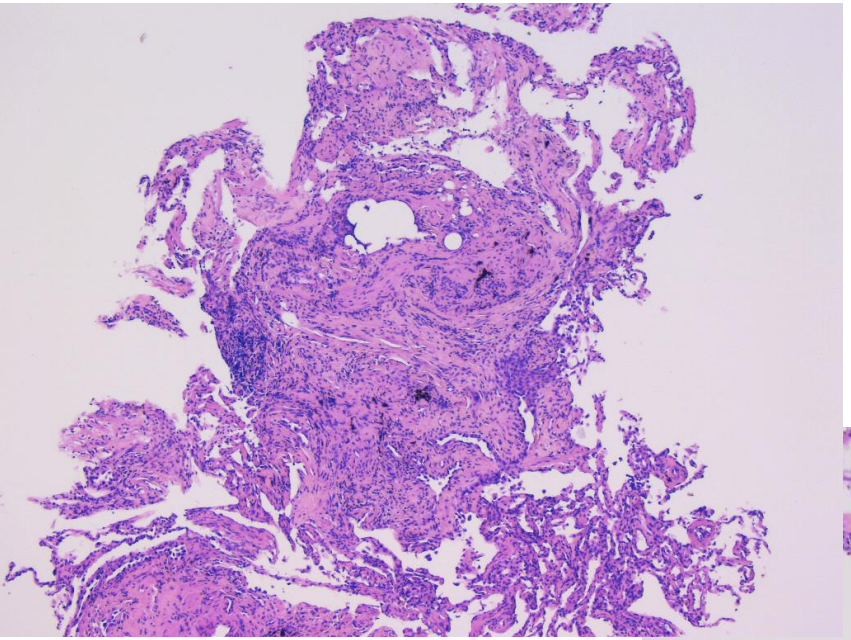


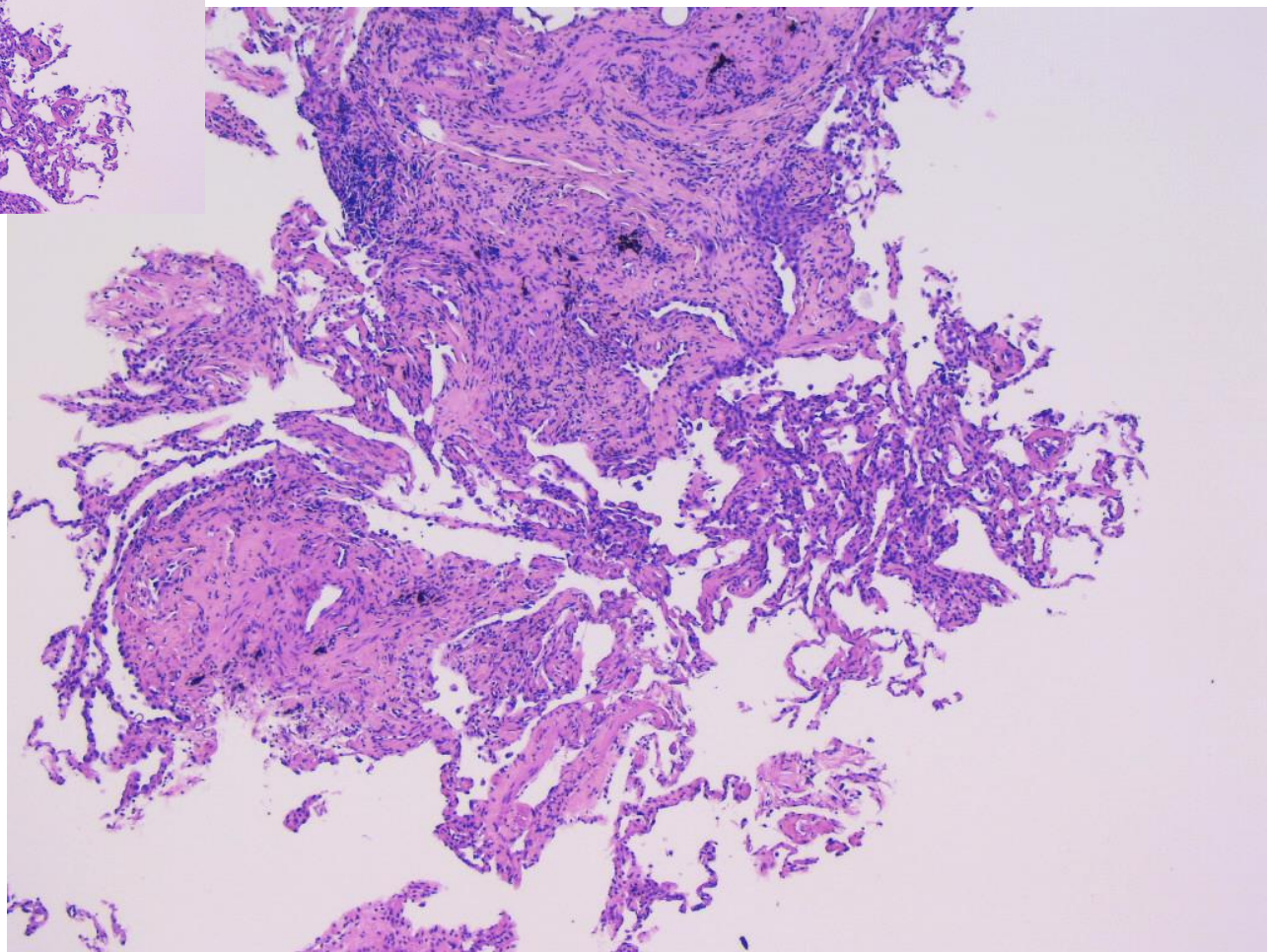


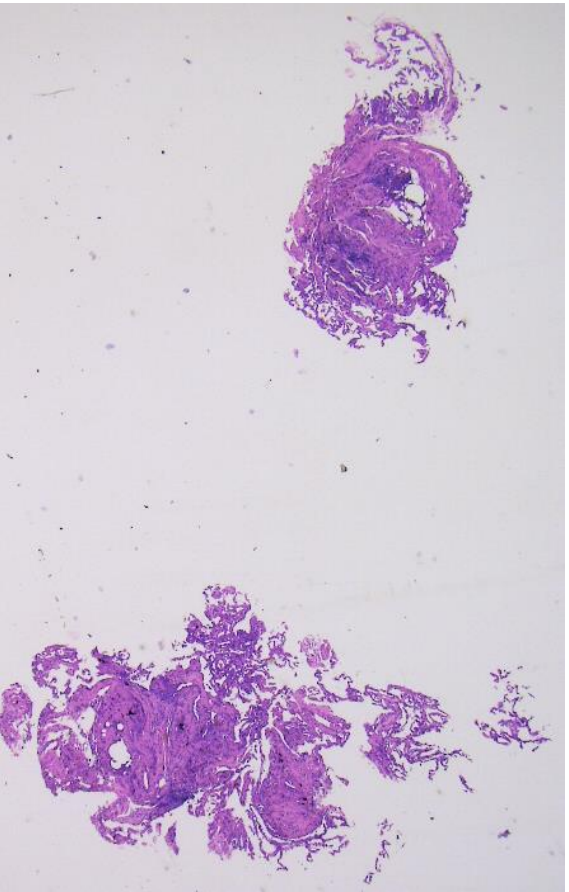
TBB

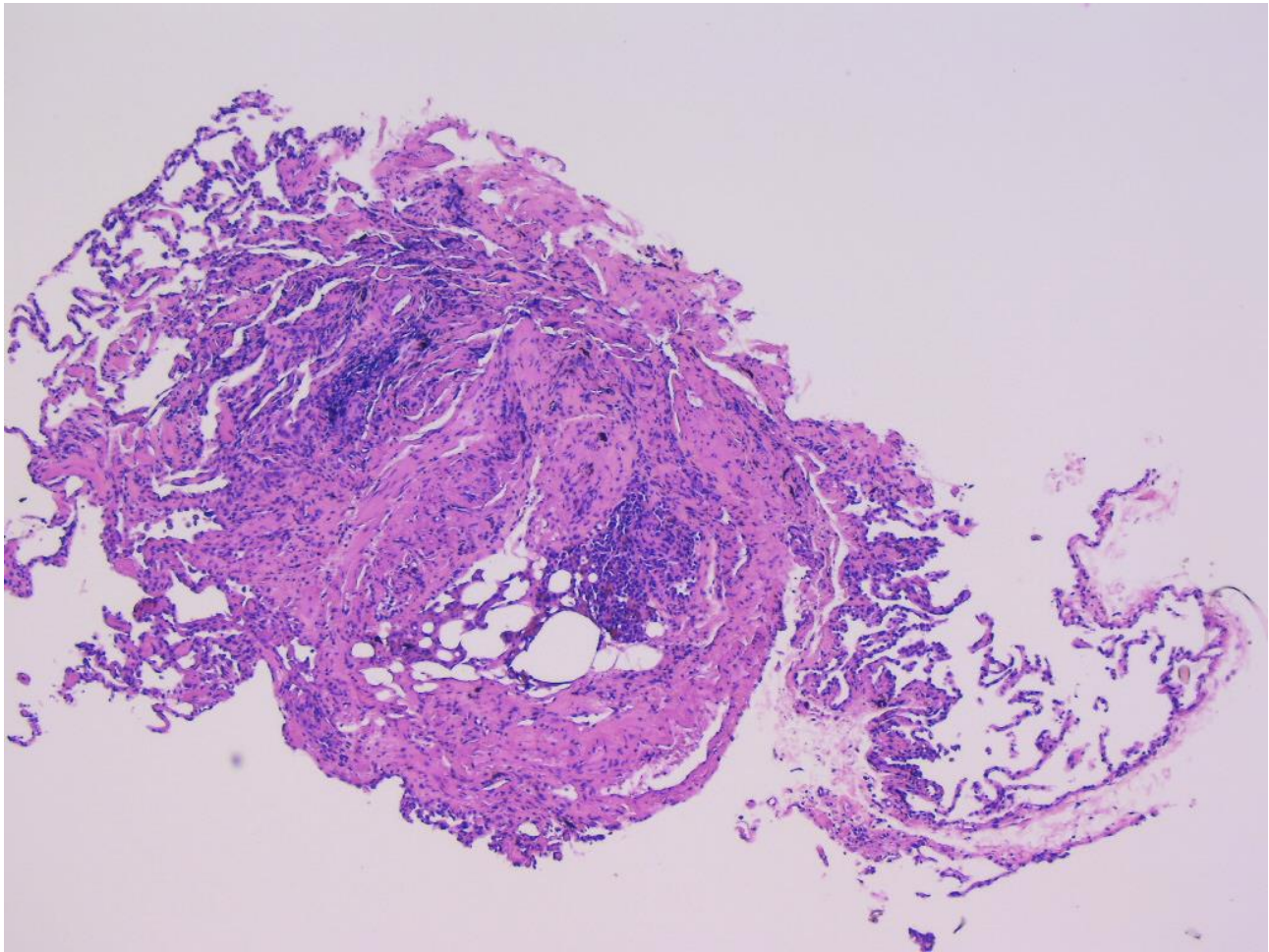


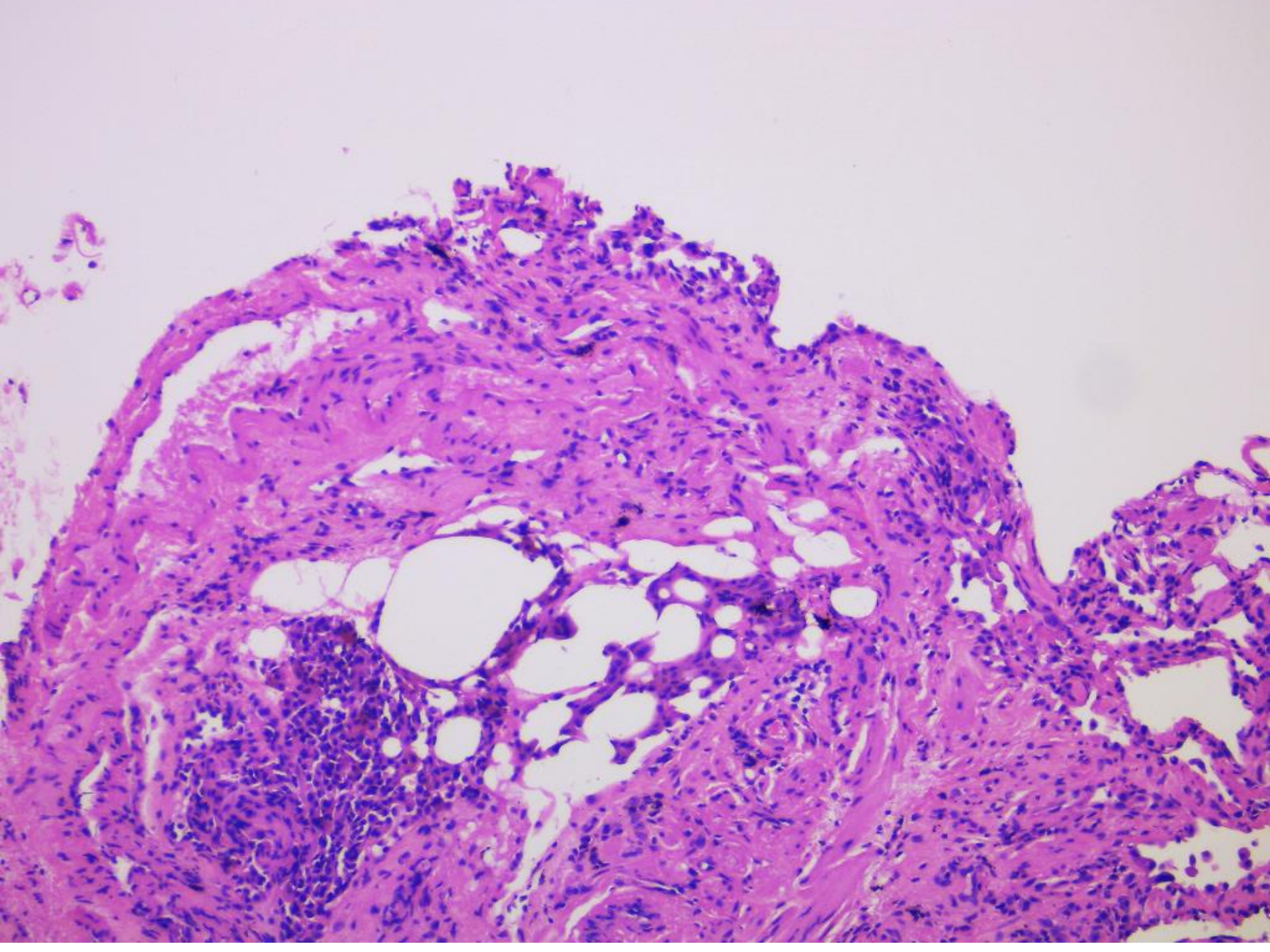


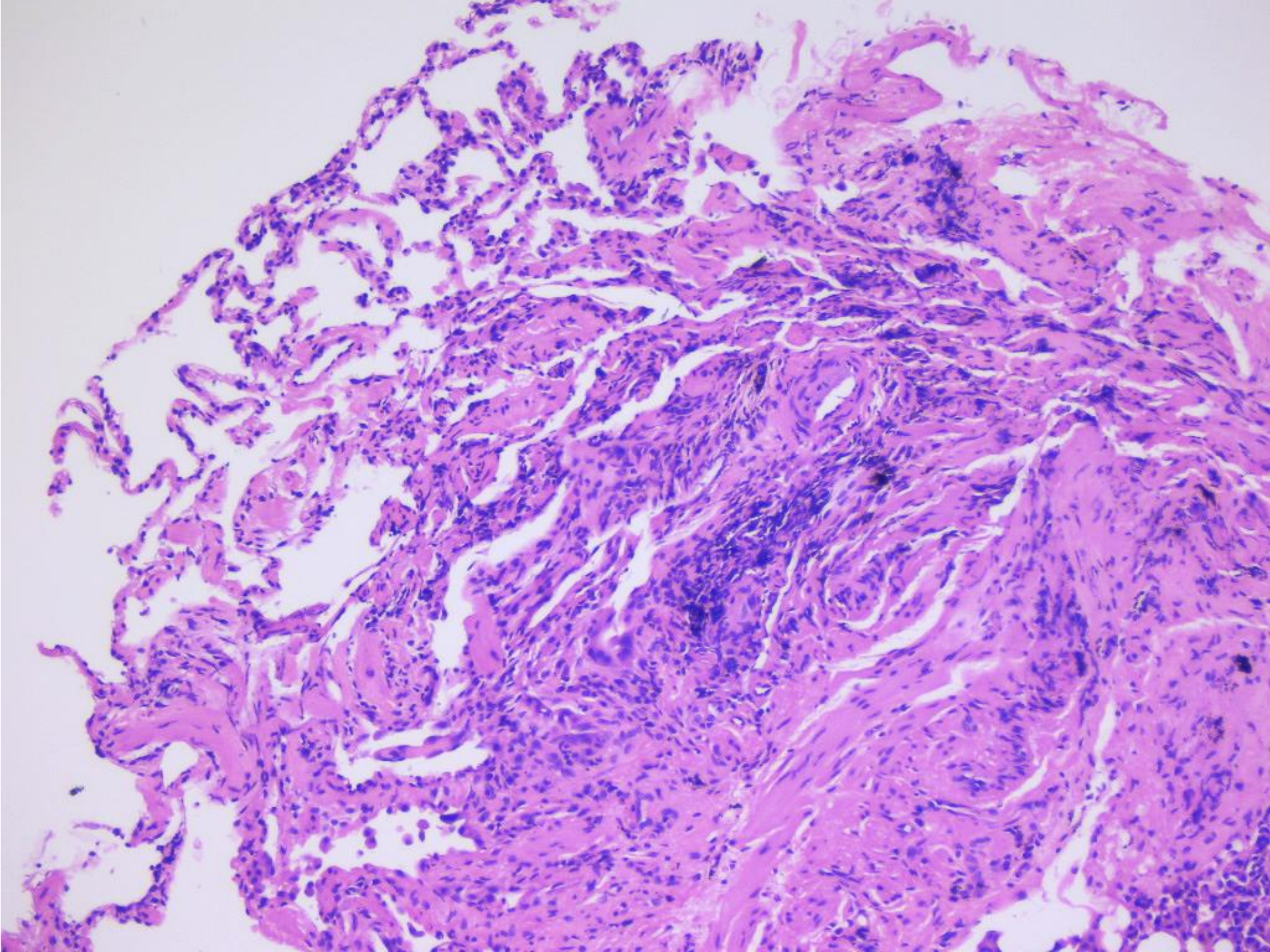


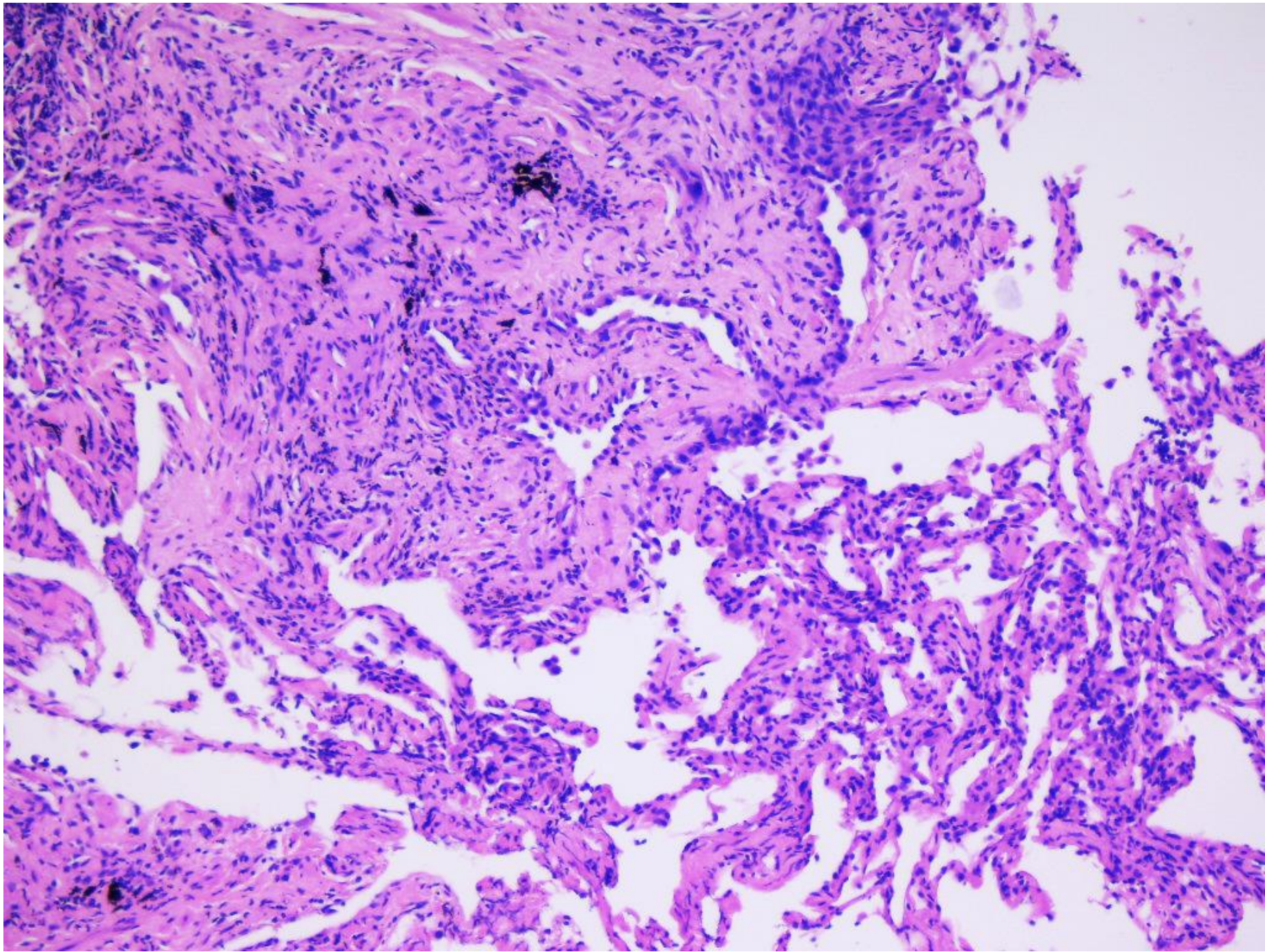


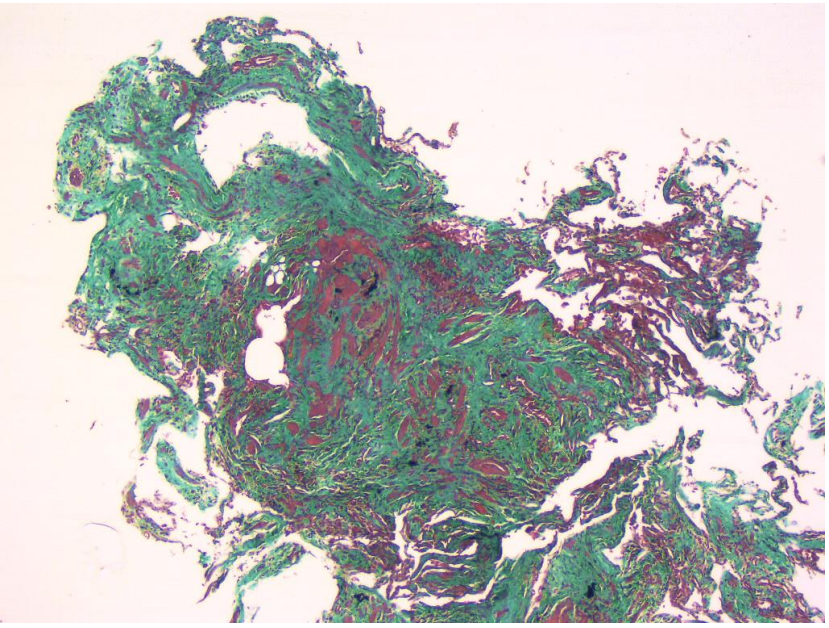


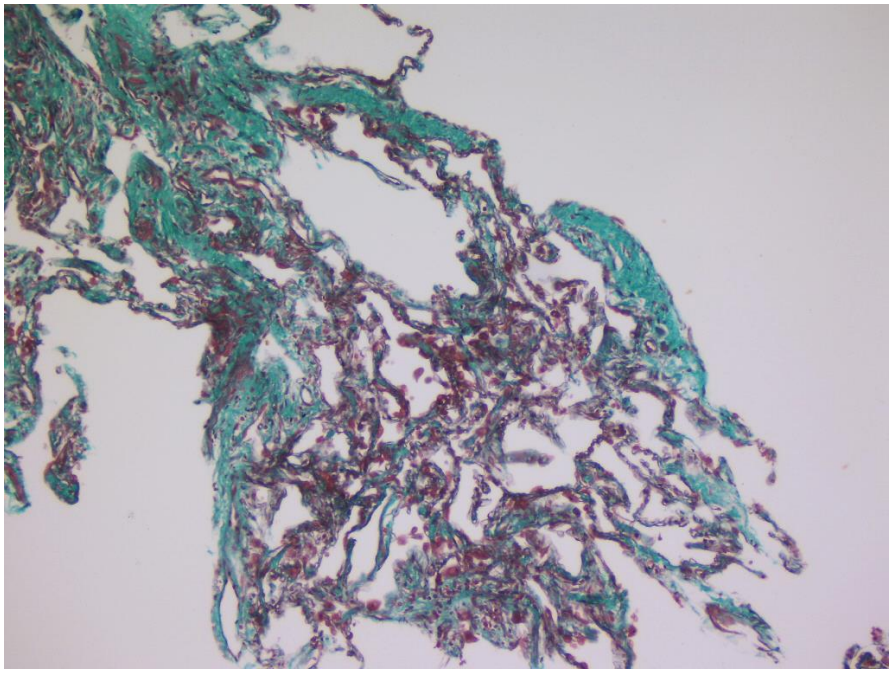


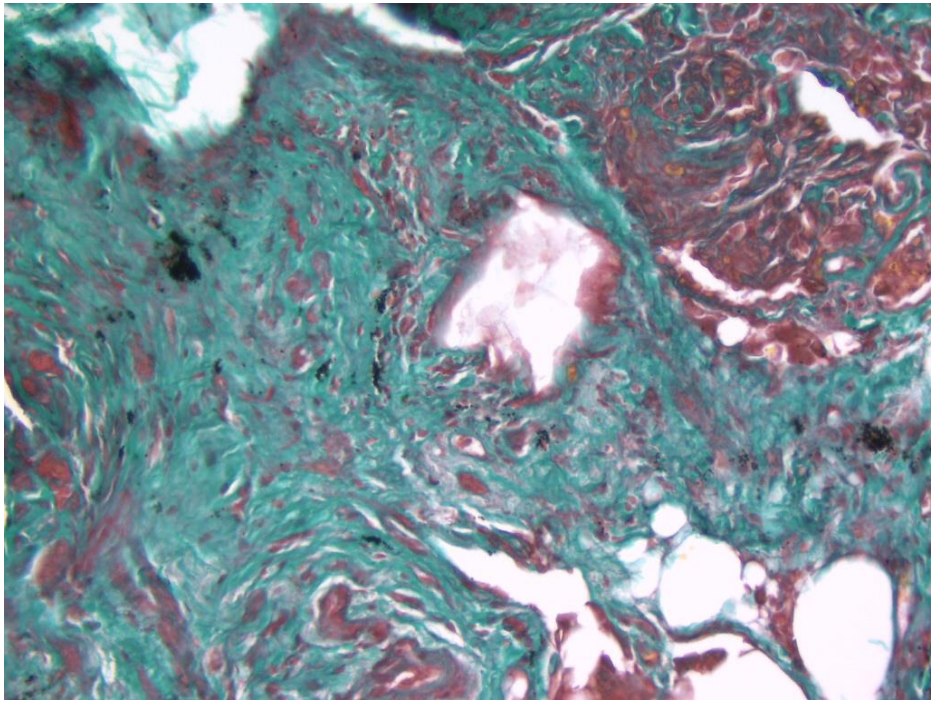












Esame istologico e citologico su BAL

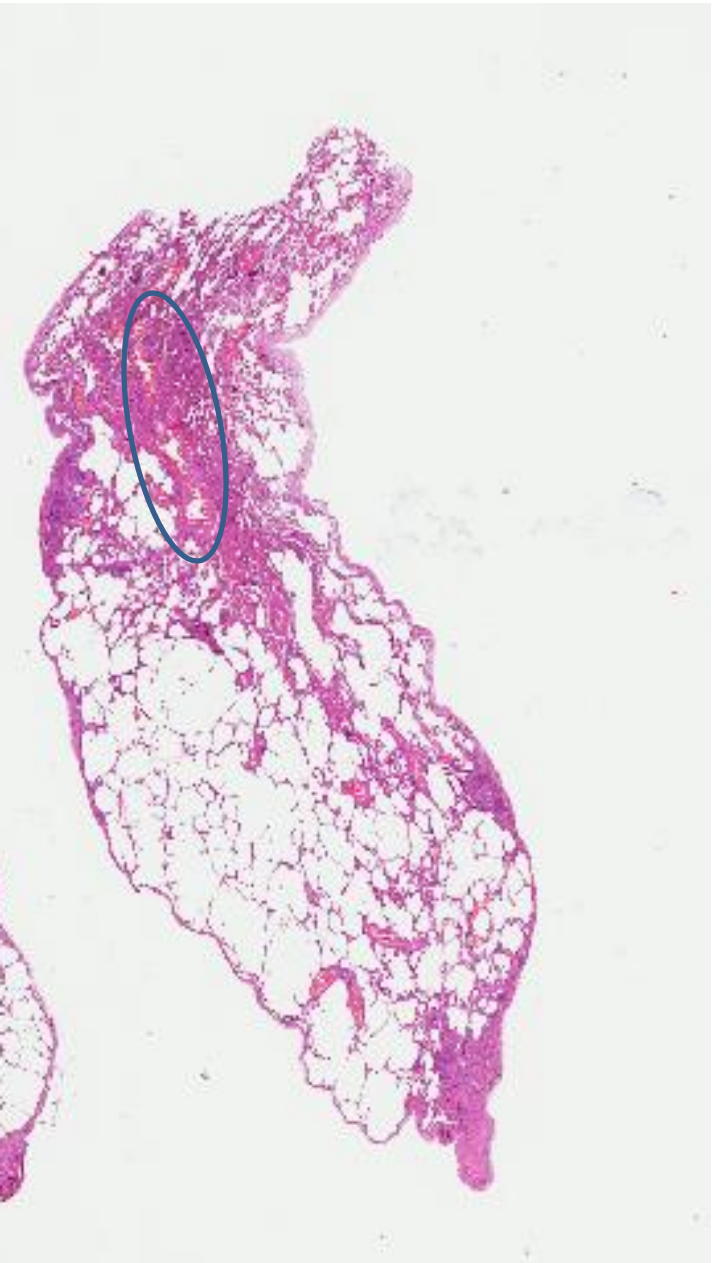
- “Citoincluso di BAL comprendente macrofagi (85%), linfociti (15%)
- “Frustoli di parenchima alveolare con eterogenità temporale di lesioni, fibrosi interstiziale e trasformazione tipo "micro-honeycomb". Non si rivengono strutture riferibili a vie aeree.
- **Diagnosi conclusiva:** Il quadro morfologico potrebbe deporre per una pneumopatia cronica fibrosante con pattern UIP probable” ma l’assenza delle vie aeree non consente una precisa categorizzazione. BAL con modica linfocitosi: suggestivo ma non indicativo di patologia cronica non IPF.

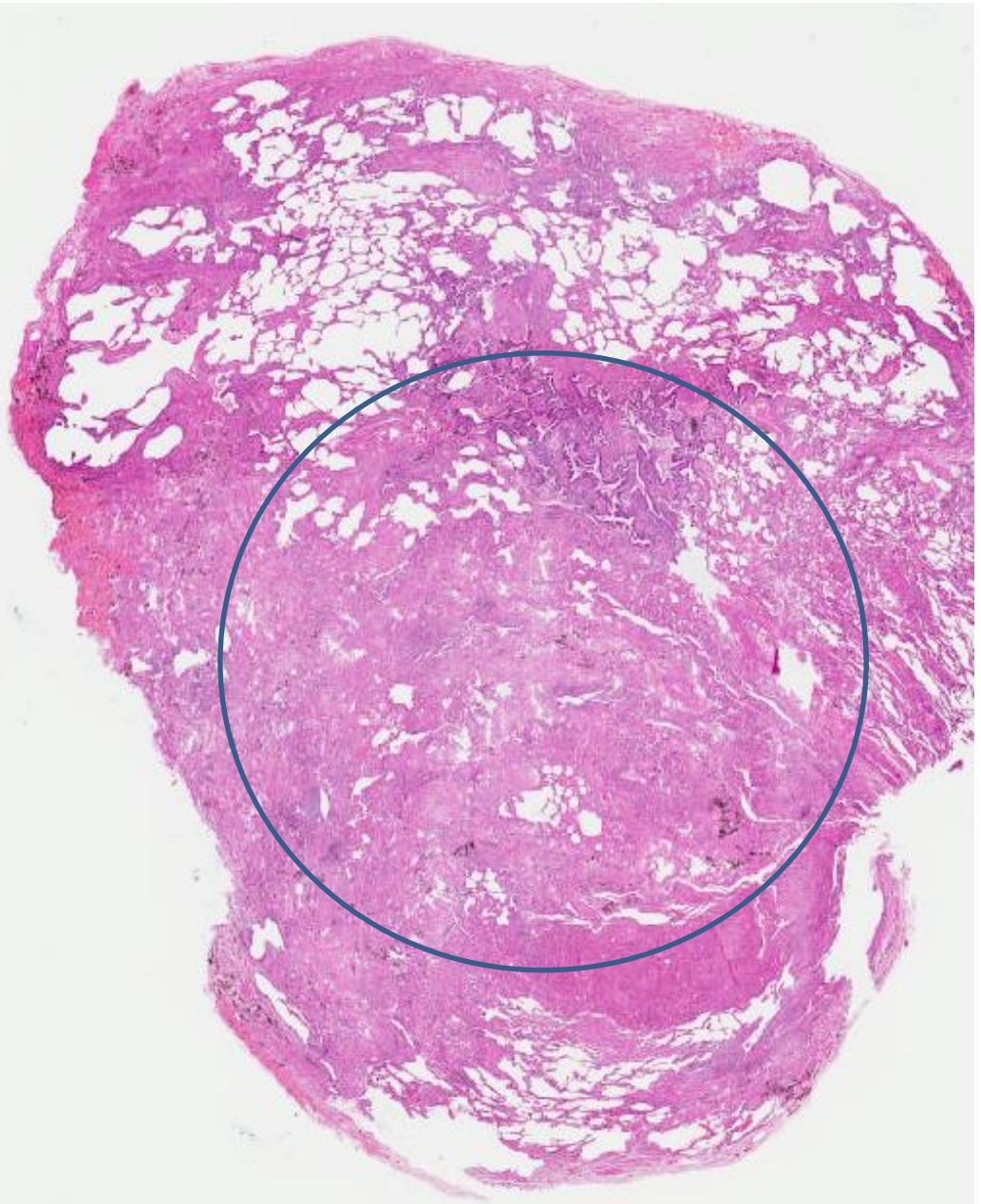
Discussione multidisciplinare

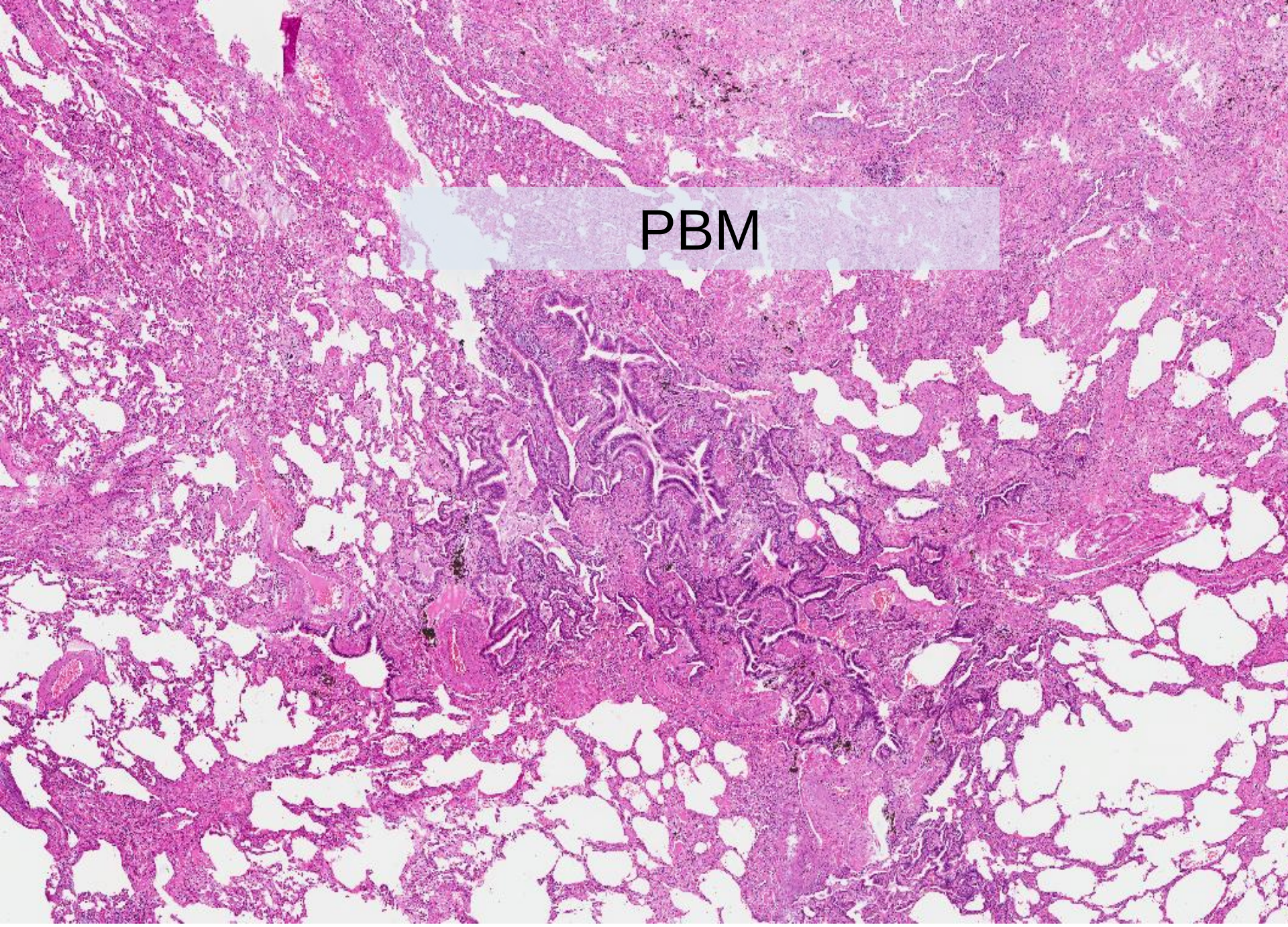
- TC torace → UIP *probable*
- Esame istologico → UIP *probable ???*
- Clinica...???

E quindi…?

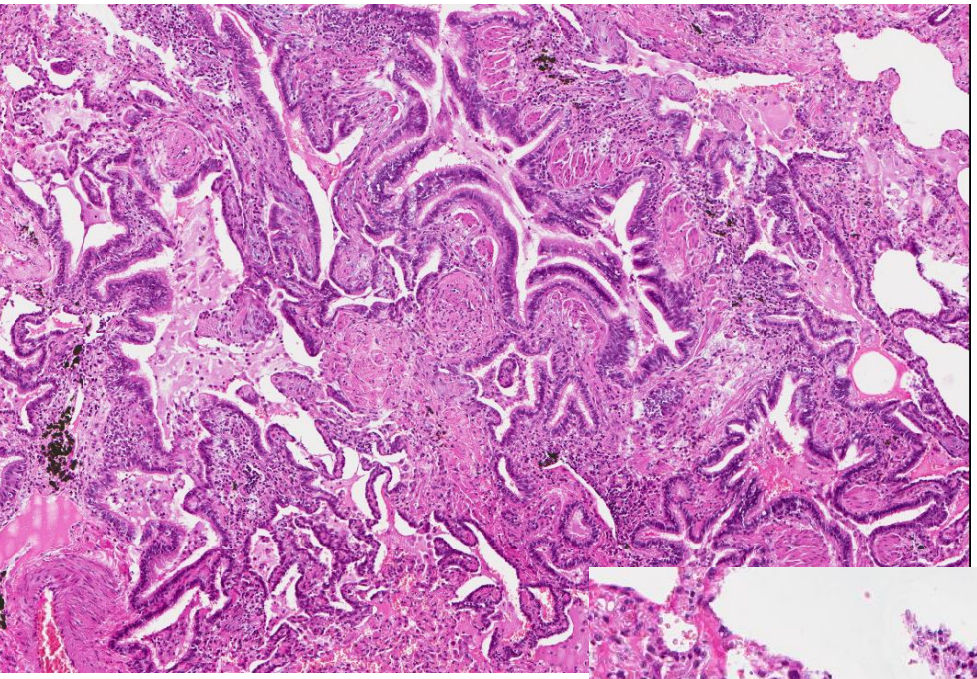
Patologia focale ? SI; Eterogenea ?: Si; DISTRUBUZIONE ?

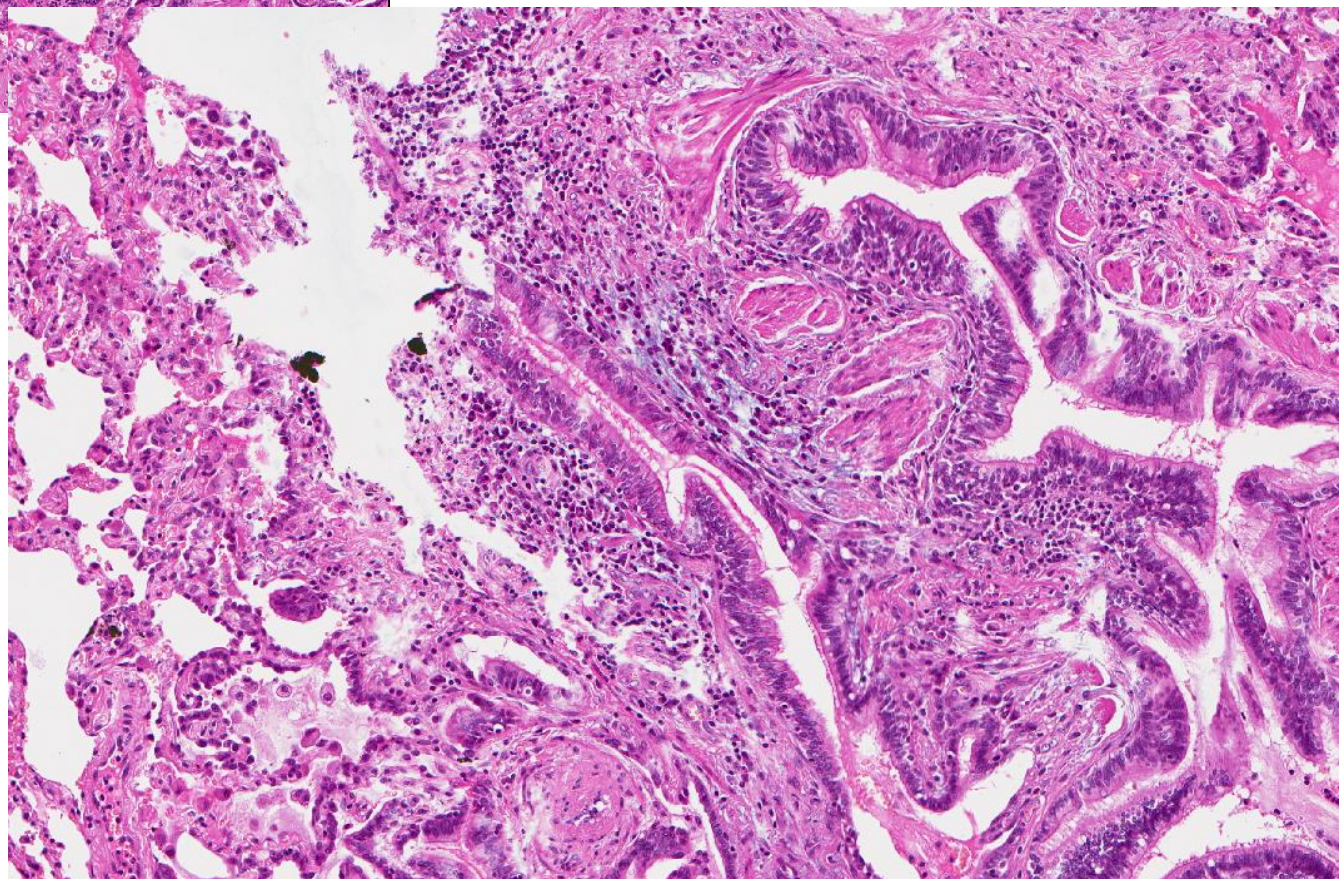




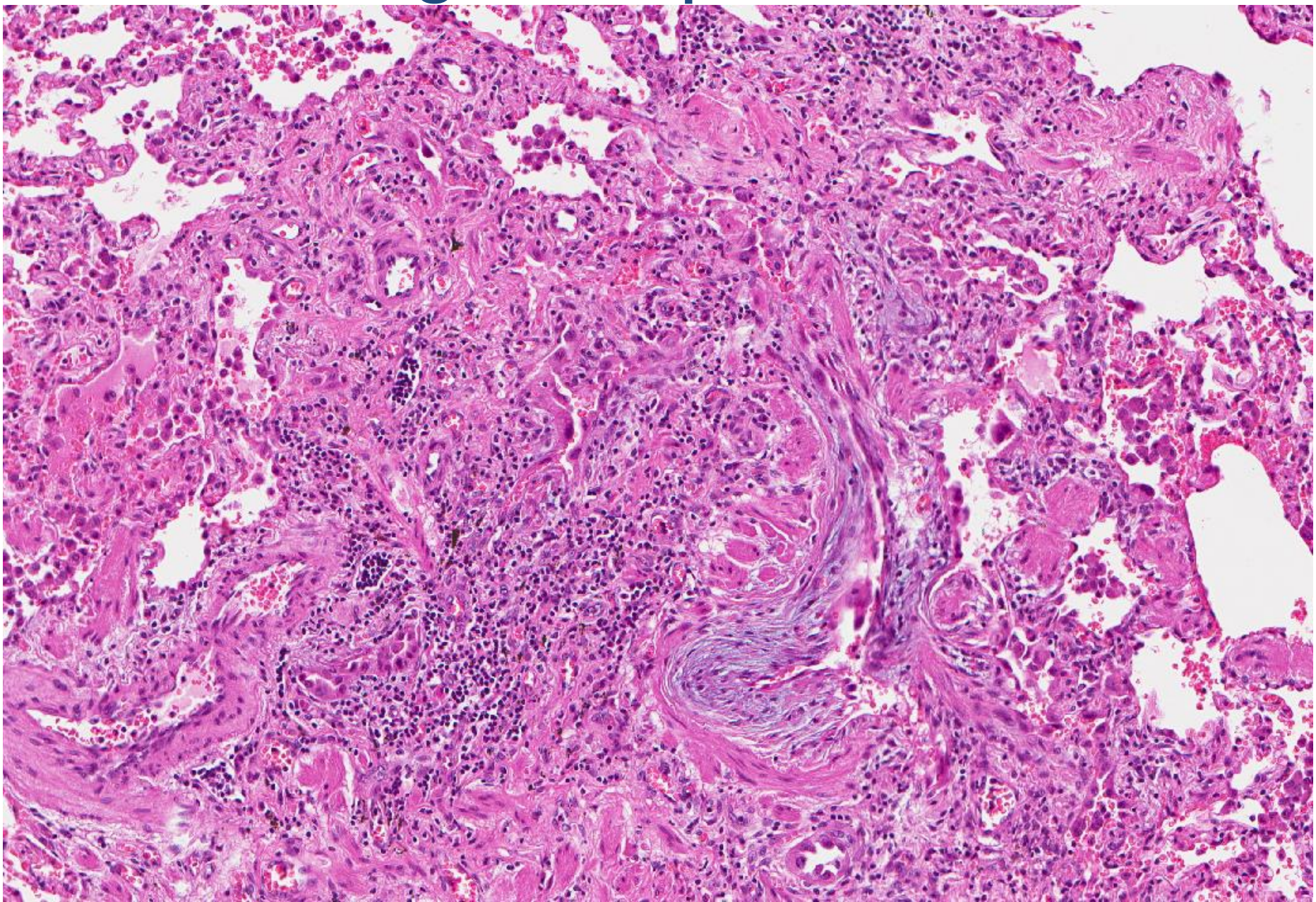

PBM

Flogosi
Neofibrogenesi

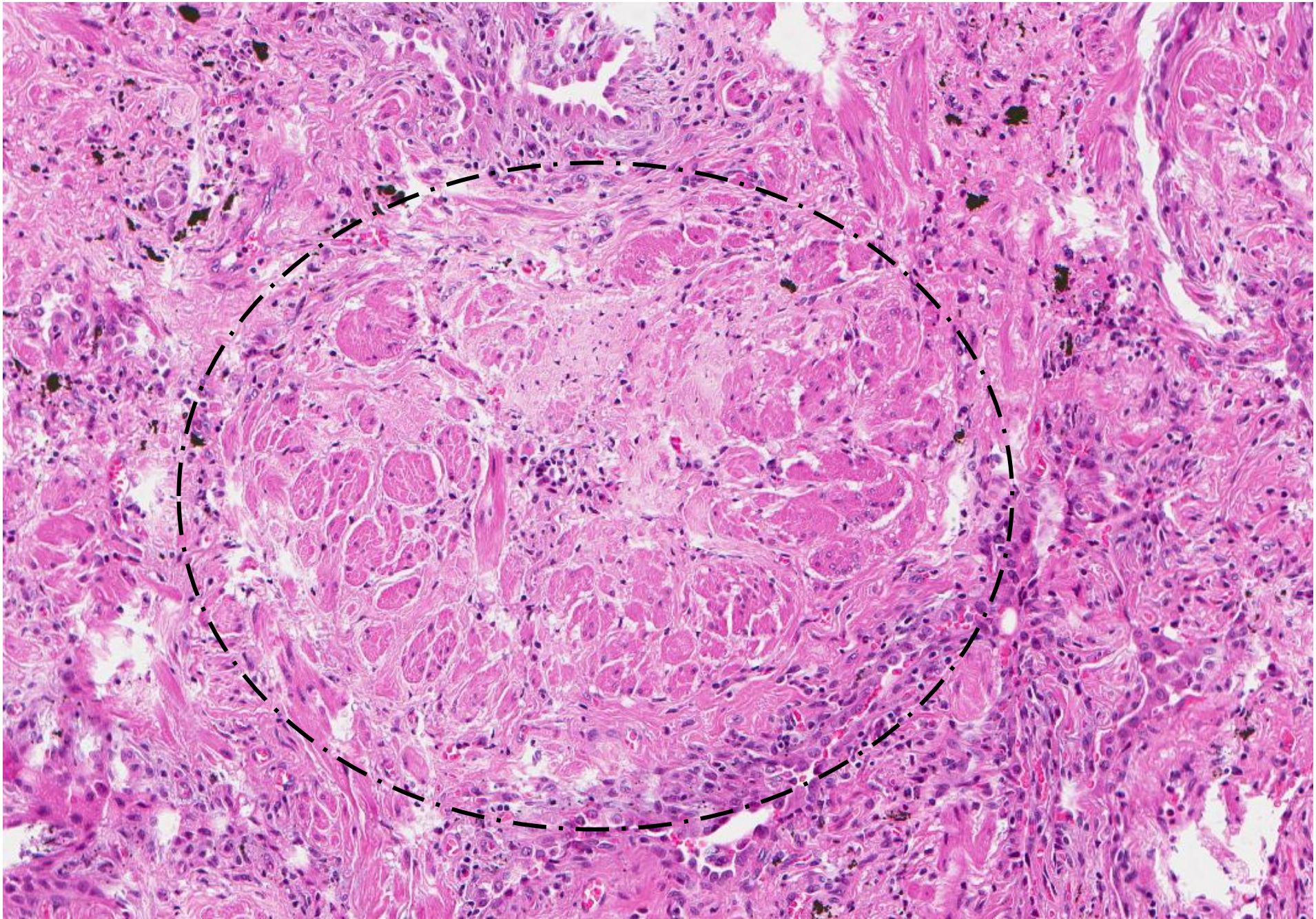




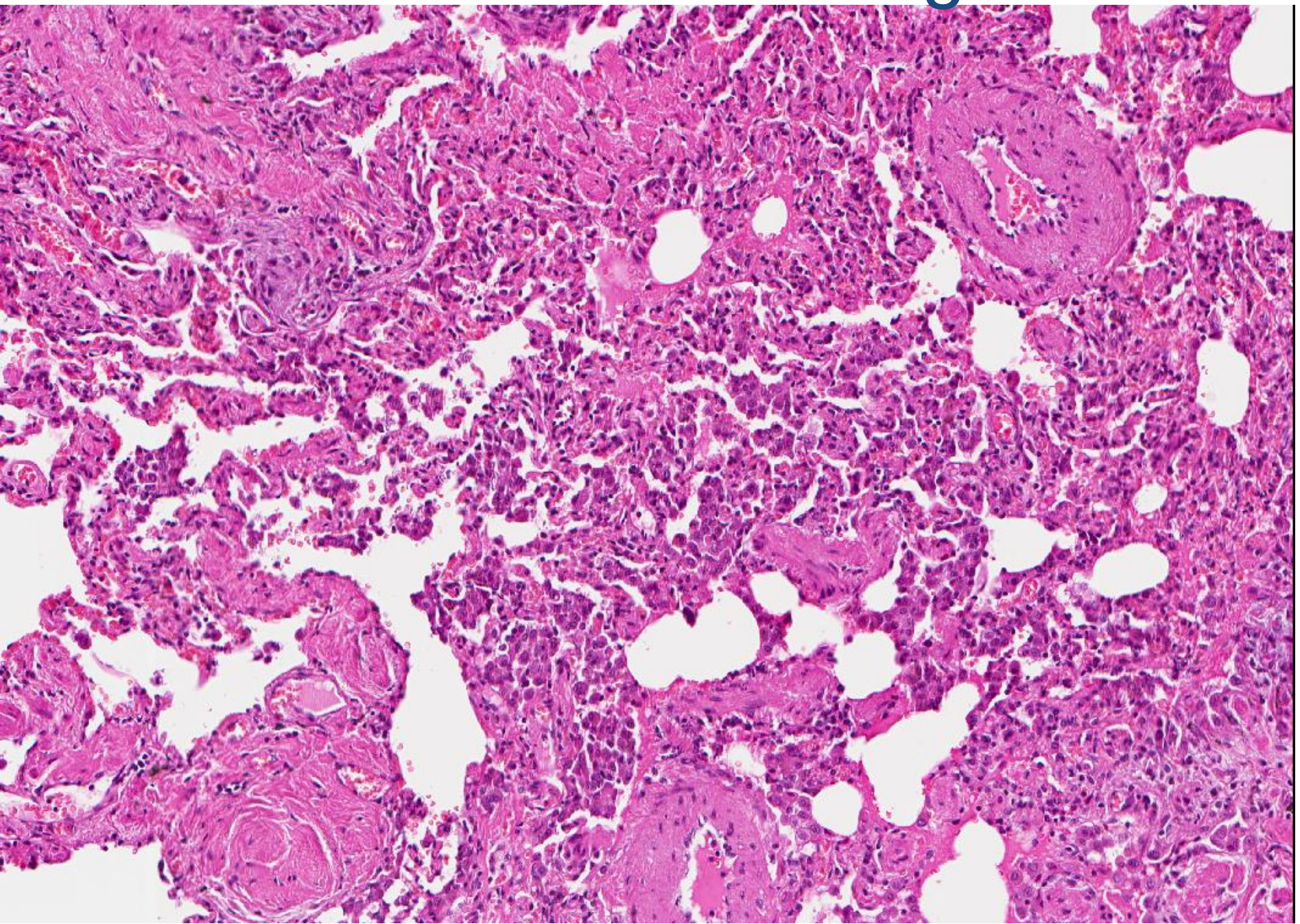
Neofibrogenesi peribronchiolare



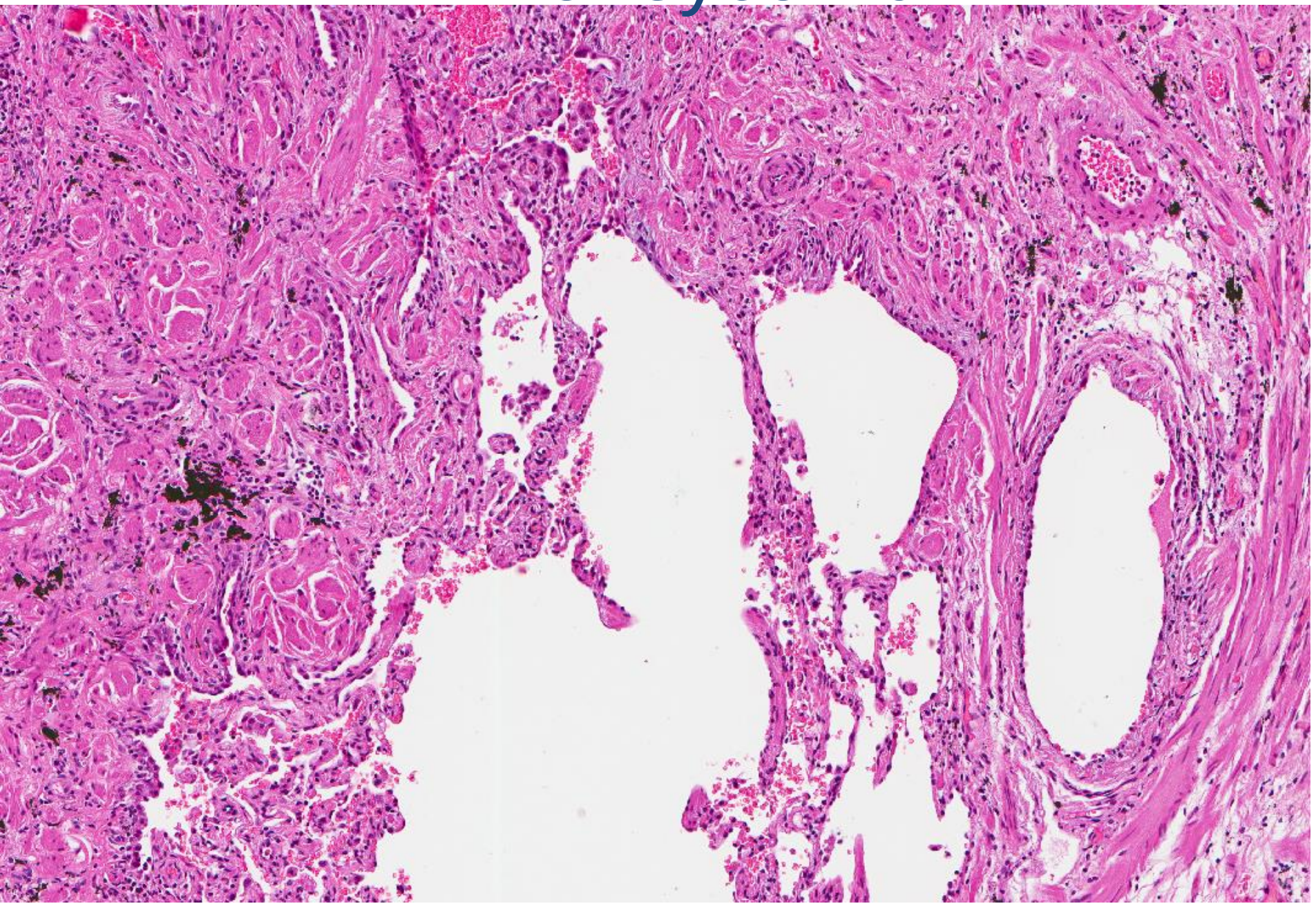
Bronchiolite obliterante



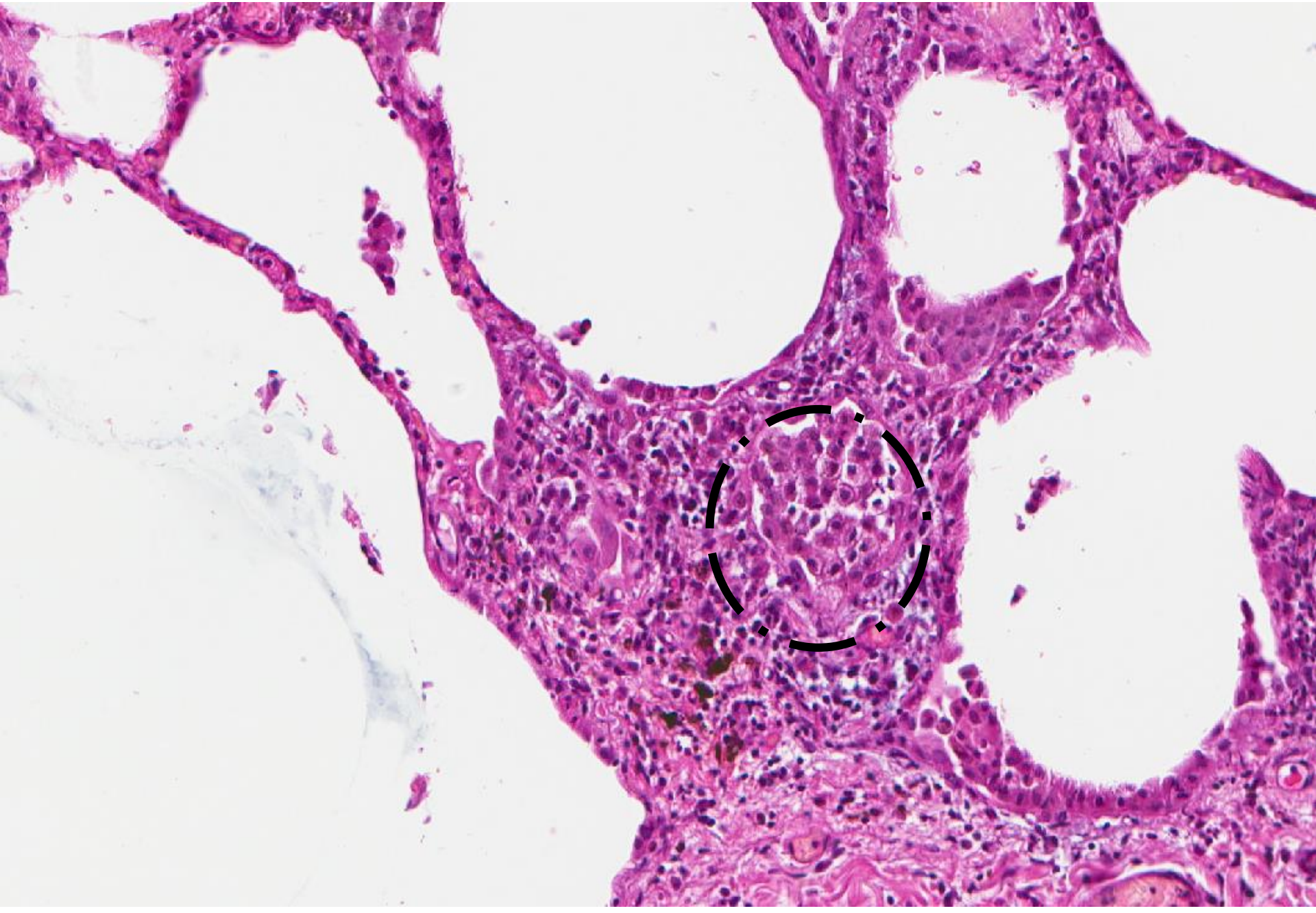
Alveolite macrofagica

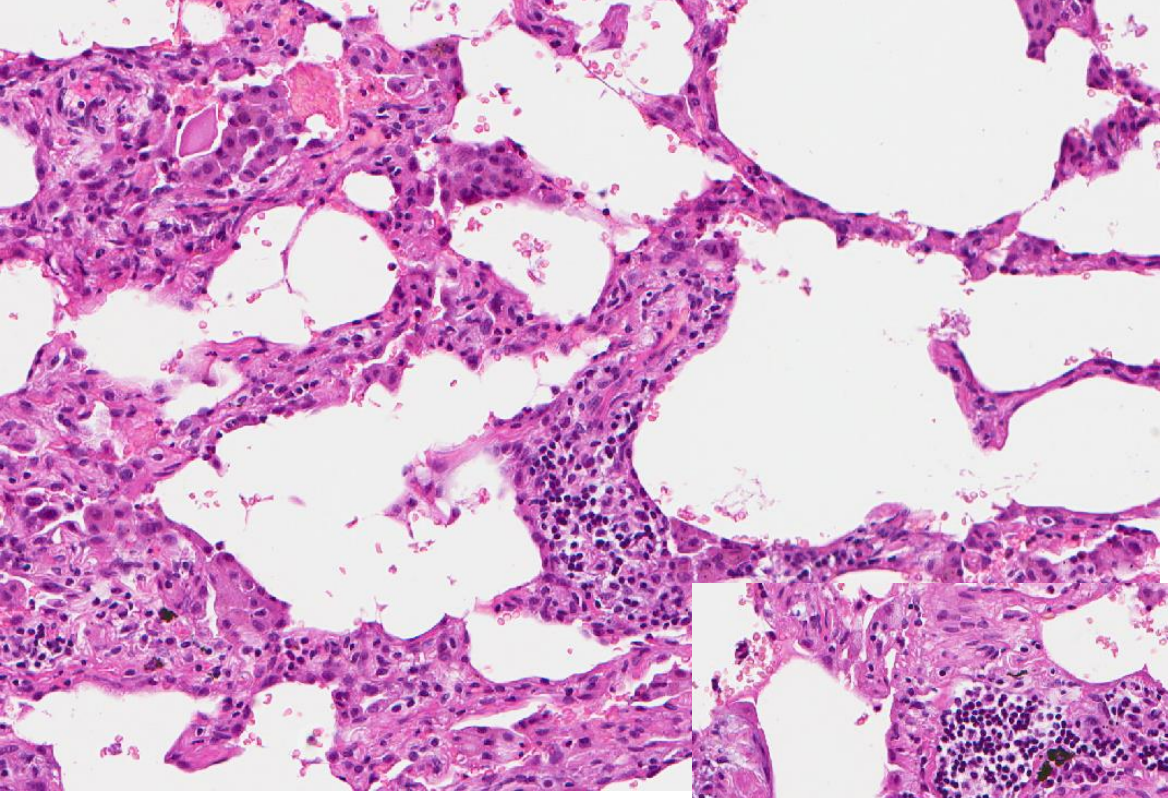


Honeycomb



Aggregato macrofagico (abortive granuloma ??)

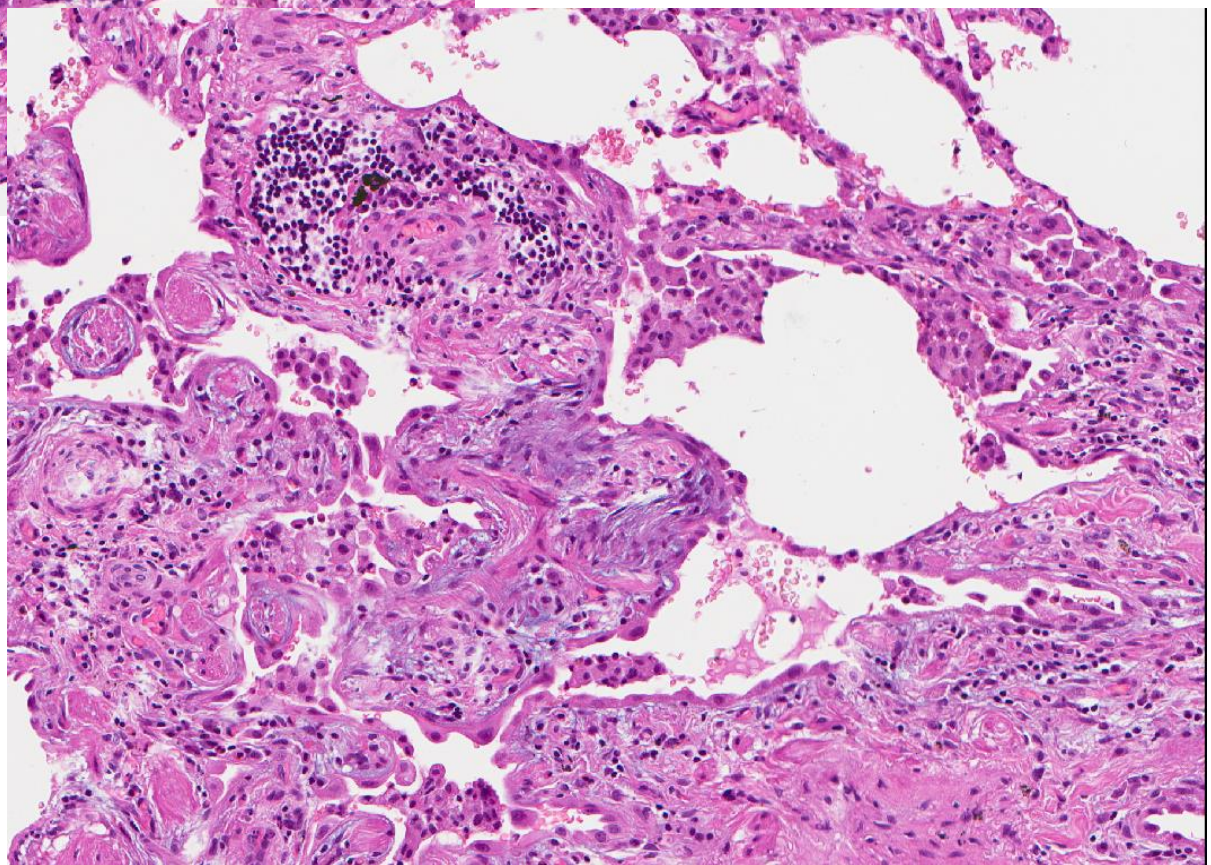




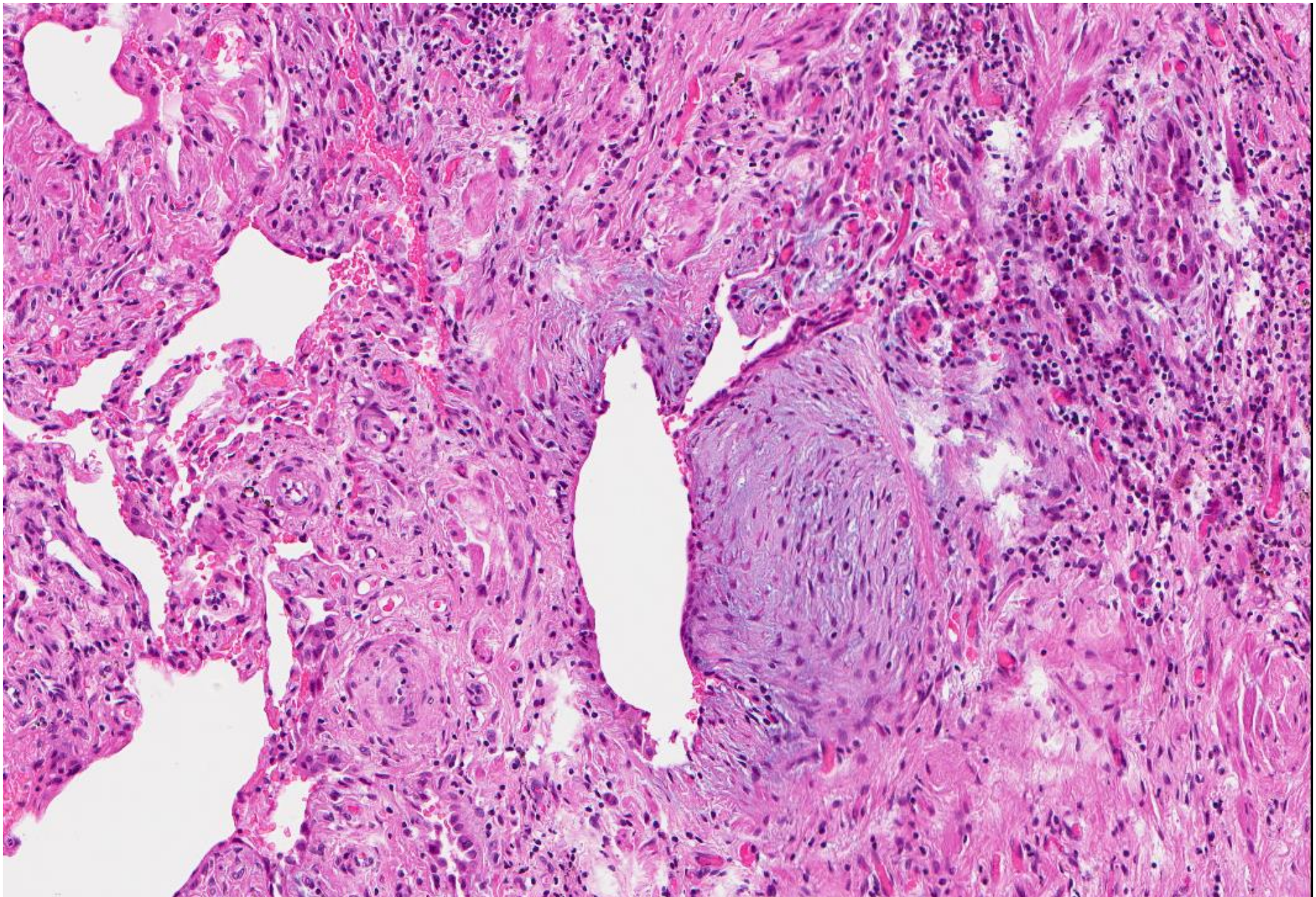
Organizing pneumonia

+

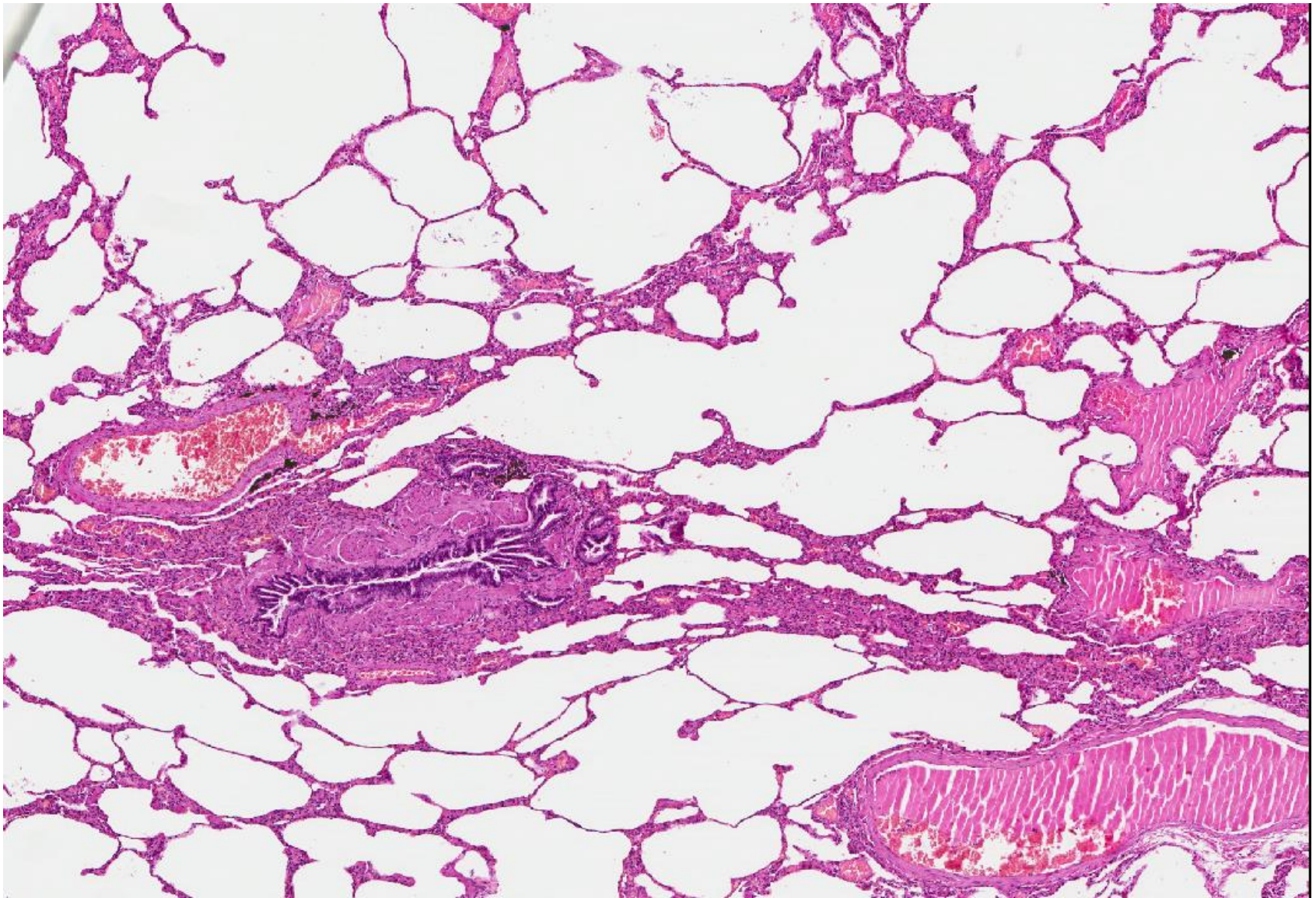
Inflammation



Fibroblastic Foci



LOBO SUPERIORE



Istologico su biopsia polmonare

“I reperti depongono per una pneumopatia fibrosante/infiammatoria a pattern UIP ("UIP indeterminate") con associati aspetti da polmonite da ipersensibilità (pattern UIP secondario).”.

TBB/BAL : AVEVA SUPPOSTO LA DIAGNOSI

Diagnosi differenziale del pattern UIP

- Interstiziopatia polmonare associata a connettivopatie.
- HP cronica.
- Pneumoconiosi (asbestosi, talcosi, berilliosi, caolinosi).
- Sarcoidosi fibrosante (prevalente ai lobi superiori).
- Fibrosi polmonare idiopatica.

Lynch D. A. ***Lancet Resp Med*** **2018 6: 138-53**

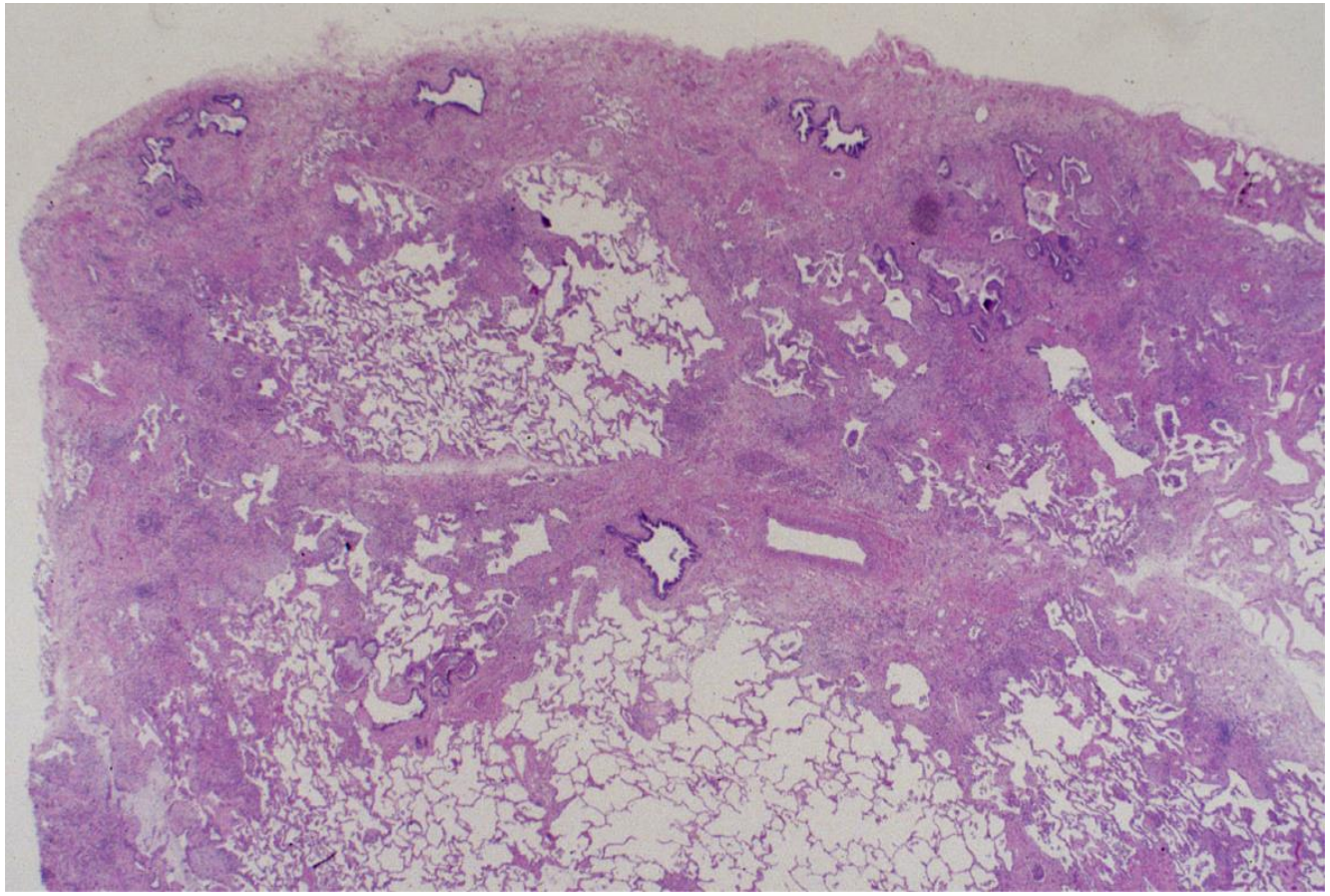
2 “Hot Topics”

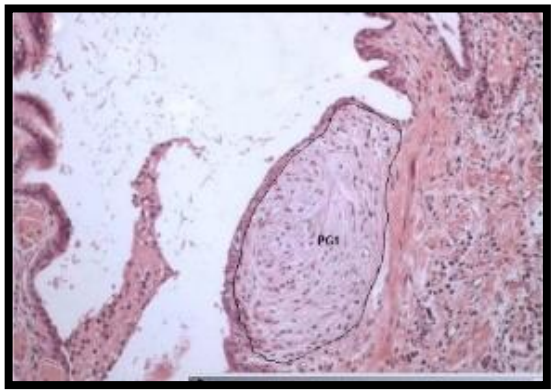
L’utilizzo della TBB/BAL come strumento diagnostico di primo livello nell’approccio iniziale

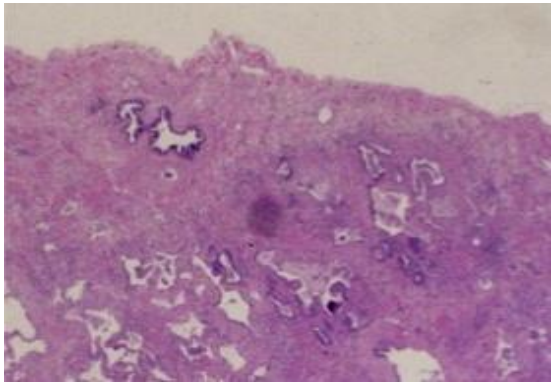
L’utilizzo della TBB/BAL in “end stage”

UIP/IPF: patologia ad interessamento **multifocale, periferico ed eterogeneo**

COME POSSIAMO DOCUMENTARLA CON UNA TBB ??





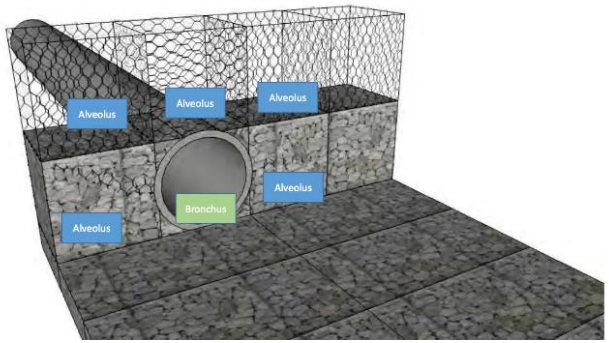


UTILIZZO DELLA TBB

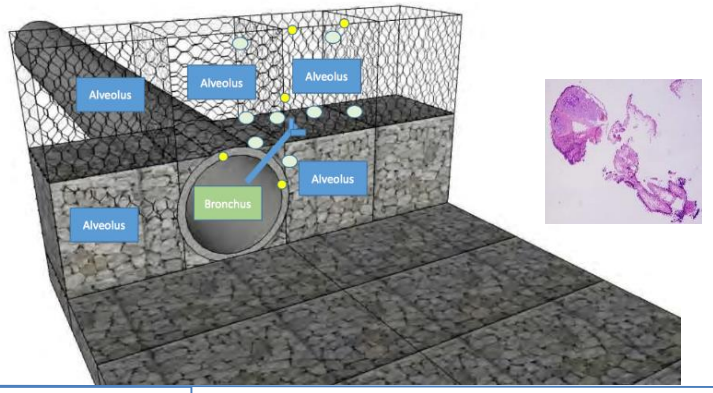
Anche il rigetto acuto parenchimale è una patologia multifocale **eppure la TBB è considerata il gold standard** per la diagnosi di monitoraggio dei pazienti trapiantati

YOU CAN SAMPLE SECONDARY LOBULE!!!

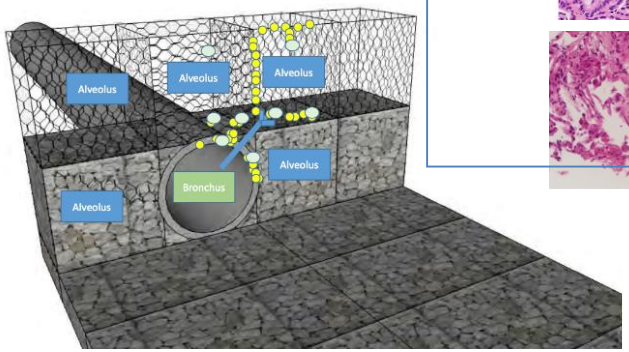
Transbronchial biopsy: basics

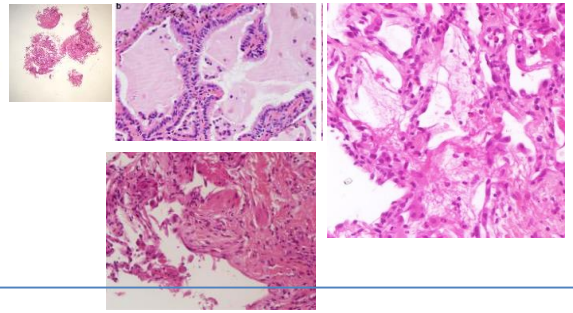


Sampling error

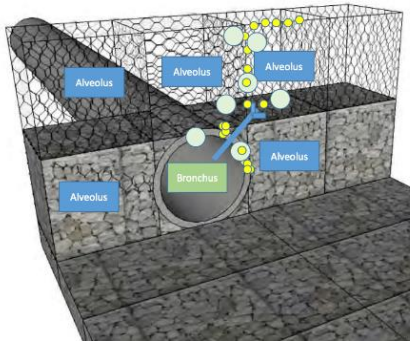


Best case scenario



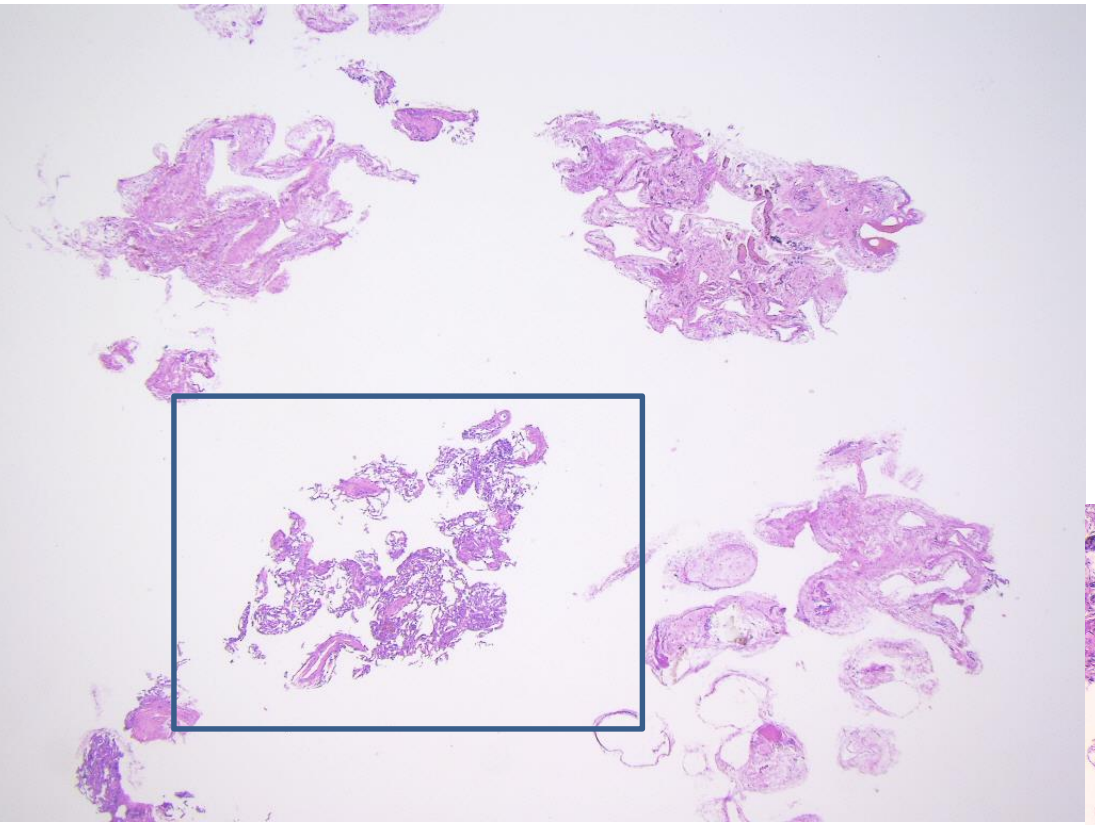


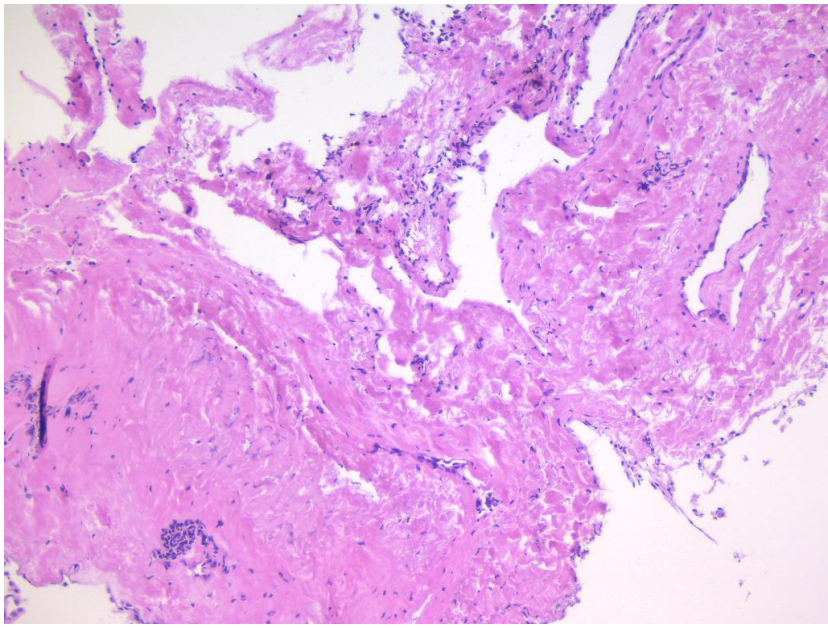
Transbronchial cryobiopsy

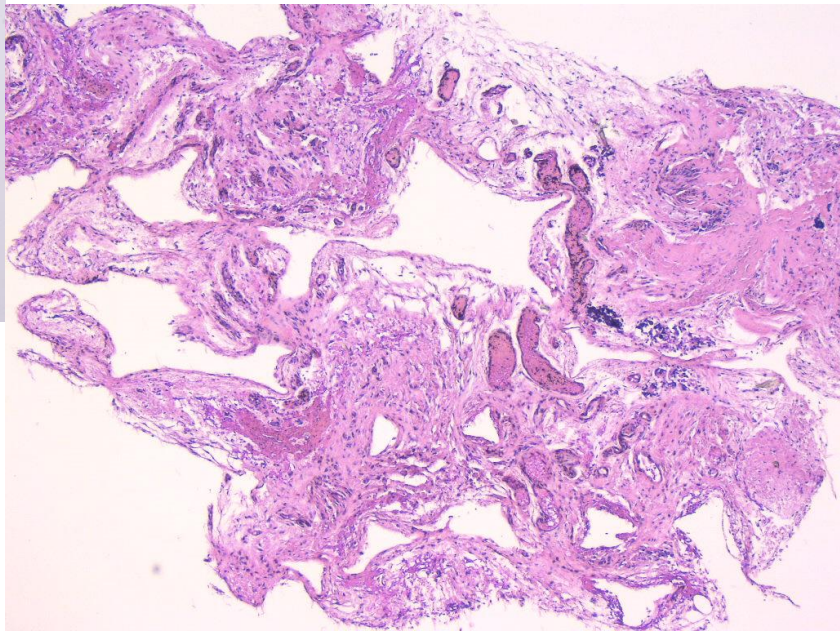


Of course bigger is better!

ESPERIENZA QUOTIDIANA







Utility of Transbronchial vs Surgical Lung Biopsy in the Diagnosis of Suspected Fibrotic Interstitial Lung Disease

Jamie S. Sheth, MD; John A. Belperio, MD; Michael C. Fishbein, MD; Ella A. Kazerooni, MD; Amir Lagstein, MD; Susan Murray, ScD; Jeff L. Myers, MD; Richard H. Simon, MD; Thomas H. Sisson, MD; Baskaran Sundaram, MD; Eric S. White, MD; Meng Xia, MS; David Zisman, MD; and Kevin R. Flaherty, MD

CHEST 2017; 151(2):389-399

- Only 18% of TBB specimens were inadequate, consisting of bronchial wall, pleura or debris, which is a similar percentage compared to older TBB studies.

- When clinical and HRCT data are suggestive but not diagnostic of UIP, clinician confidence in IPF diagnosis is increased when a TBB specimen contains the characteristic histologic features of UIP.

- Information from TBB, when combined with clinical and HRCT data, may provide enough information to make a confident and accurate diagnosis in approximately 20-30% of patients with ILD.

From PPS 2017

Use of transbronchial biopsies and core needle biopsies for diagnosing non-neoplastic diseases

Sanjay Mukhopadhyay, MD
Staff Pathologist
Cleveland Clinic

PPS Pulmonary Pathology Society

Pulmonary Langerhans cell histiocytosis can be diagnosed in core needle biopsies

UIP can (rarely) be diagnosed in transbronchial biopsies

Sensitivity about 36%

thelancet.com/respiratory Published online April 1, 2019

Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study

Ganesh Raghu, Kevin R Flaherty, David J Lederer, David A Lynch, Thomas V Colby, Jeffrey L Myers, Steve D Groshong, Brandon T Larsen, Jonathan H Chung, Mark P Steele, Sadia Benzaquen, Karel Calero, Amy H Case, Gerard J Criner, Steven D Nathan, Navdeep S Rai, Murali Ramaswamy, Lars Hagmeyer, J Russell Davis, Umair A Gauhar, Daniel G Pankratz, Yoonha Choi, Jing Huang, P Sean Walsh, Hannah Neville, Lori R Lofaro, Neil M Barth, Giulia C Kennedy, Kevin K Brown, Fernando J Martinez

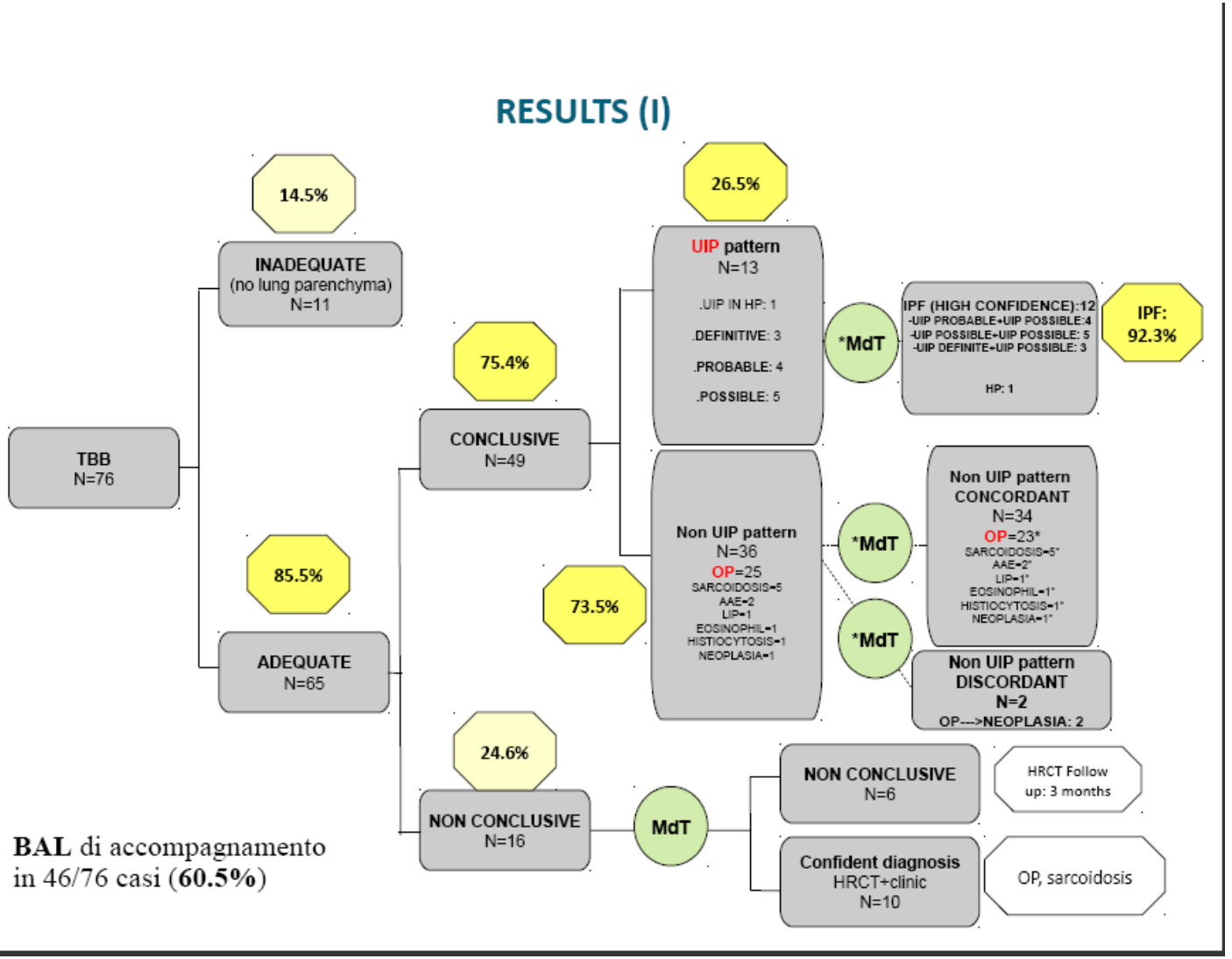
Molecular analysis is a fantastic ancillary tools but cannot replace the histology

WHY ???

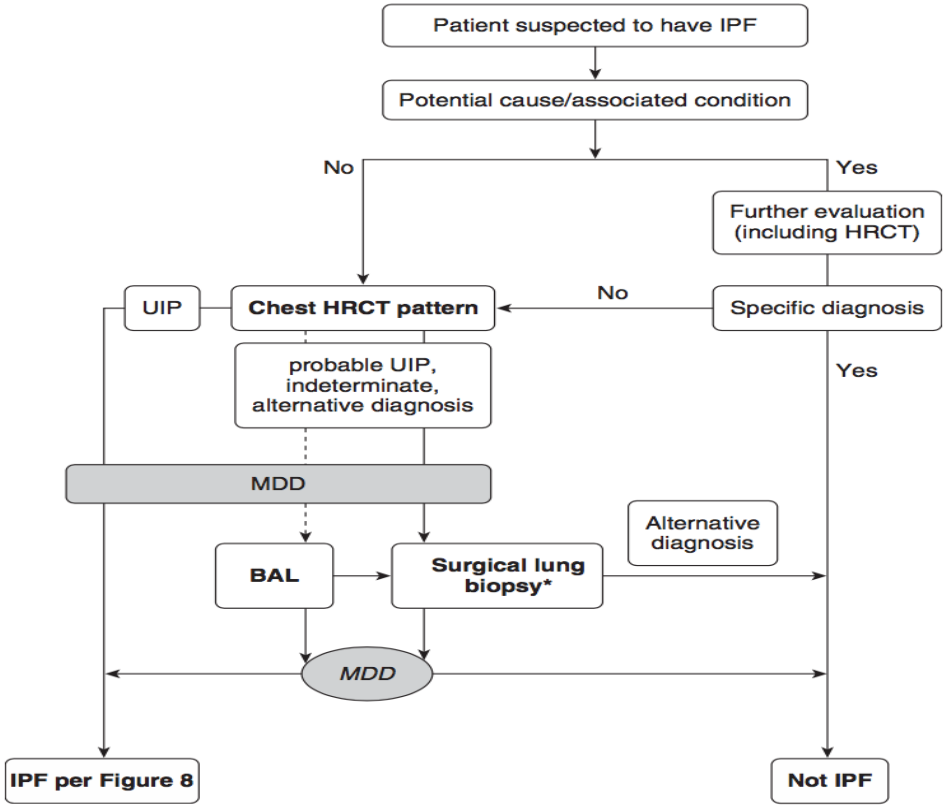
- ✓ Several molecular markers are found in different diseases
- ✓ Molecular markers is sensitively influenced by the disease timing (early, late ?)
- ✓ To date: no standardization of Omic tecnologies (no precise cut-off)
- ✓ Etc…

We may glimpse our future by recalling our past. Indeed, we should be mindful of Morgagni's teaching:" to admire [...] and to follow not the ancient, not the modern, not the traditional, but always and **only the truth"**

Padova Experience Transbronchial Biopsy: ILDs



AMERICAN THORACIC SOCIETY DOCUMENTS



What is the sensitivity of TBB + BAL ??

Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

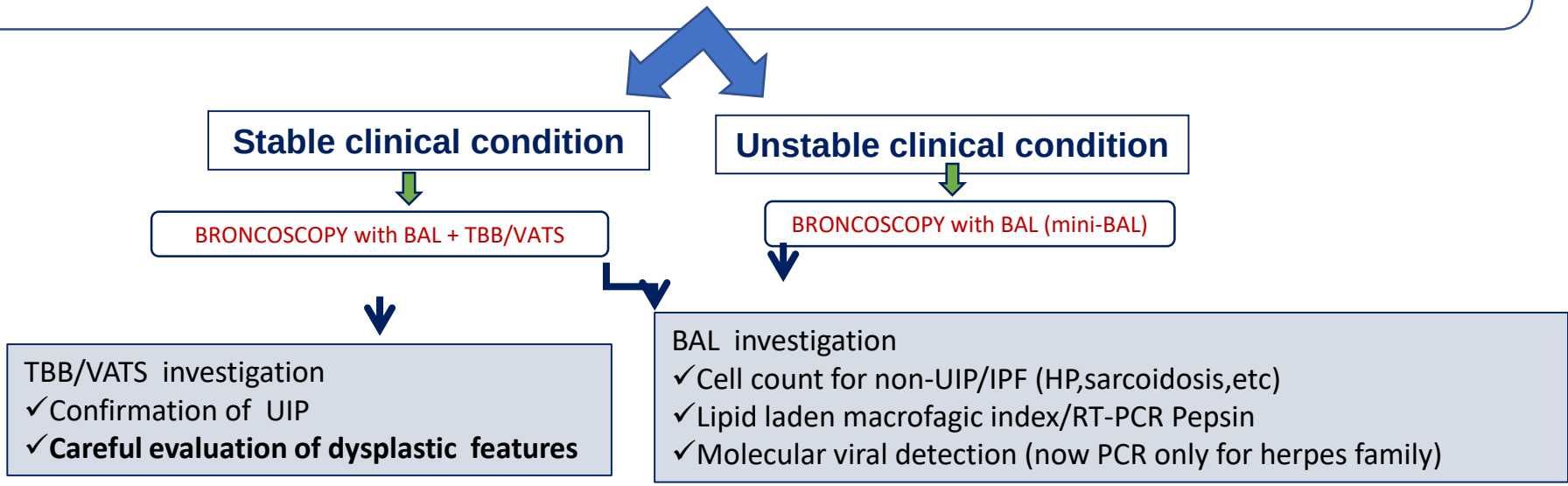
2 “Hot Topics”

- L’utilizzo della TBB/BAL come strumento diagnostico di primo livello nell’approccio iniziale

- L’utilizzo della TBB/BAL in “end stage”

Pre-transplant Management IPF/non IPF ILDS

Clinical/radiological suspicious of IPF- MDD-: Biopsy
For pts coming from other centres:
1) revision of biopsy 2) new biopsy in case of UIP probable, indeterminate and alternative

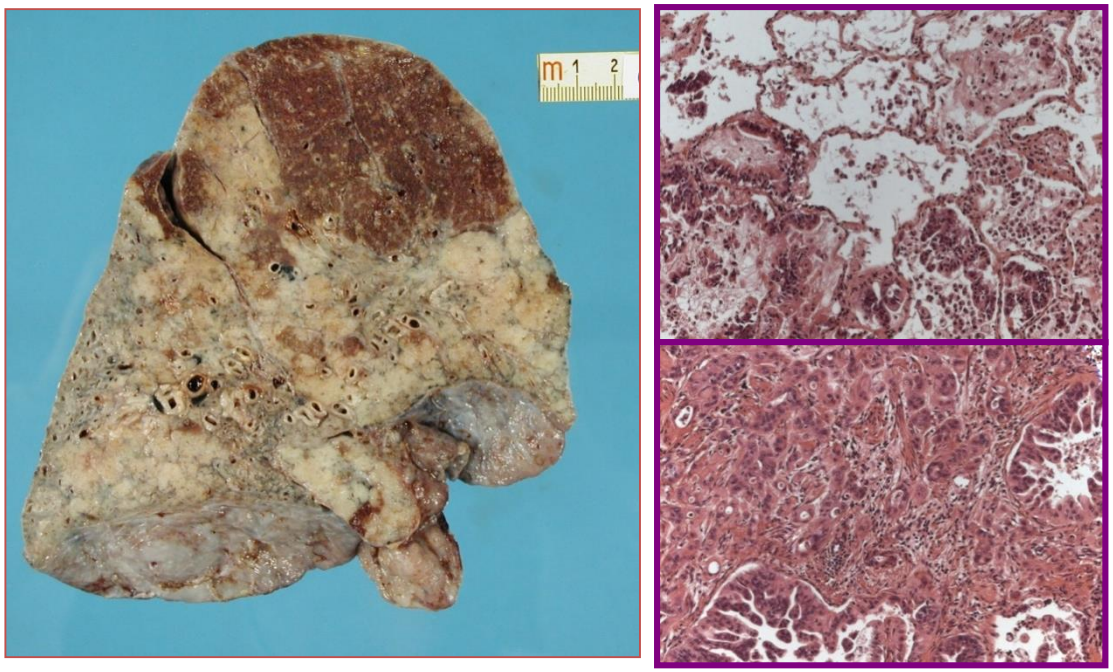


IPF/LC and Lung Transplantation

- No indication rather it is a contraindications !!
- Unfortunately this may sometimes occurs ….
- And when it is:

- a tremendous failure for the LT staff !!!!

Lung Transplant: January **2006** (N°141) Unknown lung cancer before LT



DISASTER !!!: The patient died 6 months after LT

Comparison Between Referral Diagnosis of Patients Requiring Transplantation and Pathologic Diagnosis of Native Lungs

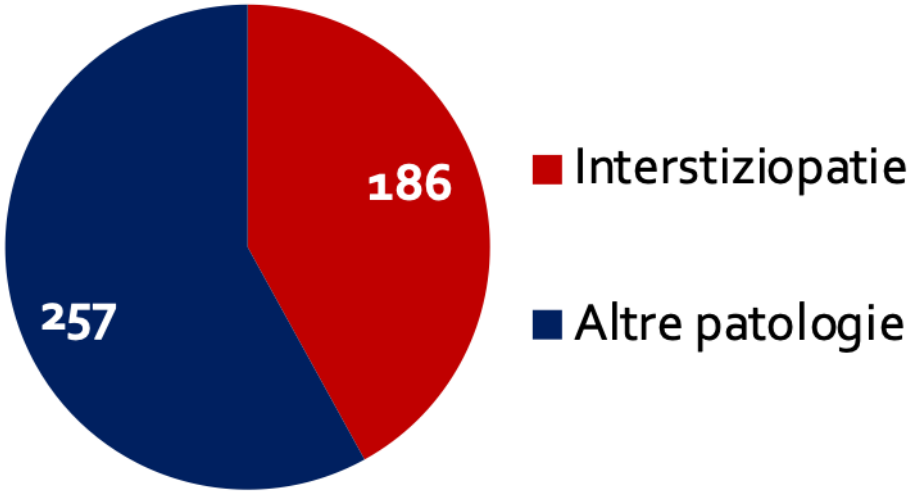
Fiorella Calabrese, MD,[a] Lara Alessandrini, MD,[a] Monica Loy, MD,[b] Giuseppe Marulli, MD,[b] Elisabetta Balestro, MD,[b] Egle Perissinotto, ScD,[c] Marialuisa Valente, MD,[a] and Federico Rea, MD[b]

J HEART LUNG TRANSPLANT 2009;28:1135-40

Table 1. Referral and Confirmed Diagnoses in 175 Lung Transplant Recipients

In conclusion, a relatively high rate of discrepancies has persisted between pre- and post-transplant diagnoses over the last decade. Most *major* or *minor* discrepancies are recorded among DPLDs, emphasizing the difficulties in the diagnosis of these entities. Short-term survival is significantly lower in patients with discrepancies. A careful multidisciplinary revision of these diseases should be performed by all transplant specialists and 6-month check-ups should be planned for waiting list patients.

Lung Cancer in LT 1995-2018 → 443 LT



11/186 **(6%): in all case the diagnosis was performed after a careful sampling of explant lungs**

From 2009: 7 cases !!

8 Adenocarcinoma
1 Combined (NSCLC + SCLC)
1 Carcinoid (AT)
1 Tumorlet

Our thoracic surgeon : Dott.ssa Monica Loy

And last year ……

Another bad surprise ……
let me tell you the story

Case J. E. 48 yrs-old male,
Former smoker (3-4 cigarettes / day from 20 to 44 years)

Previous occupational exposure (iron) and currently (pesticides; he is working as gardener)

December 2014: cough with sputum, dyspnea and fever

Spirometry: Restrictive pattern FVC 2.19 L 43%, FEV1 2.11 L 50%

Chest x-ray: thickening of the pulmonary interstitium, mainly at the bases

December 2015: slight deterioration, admitted to Pulmonology department (Padova hospital)

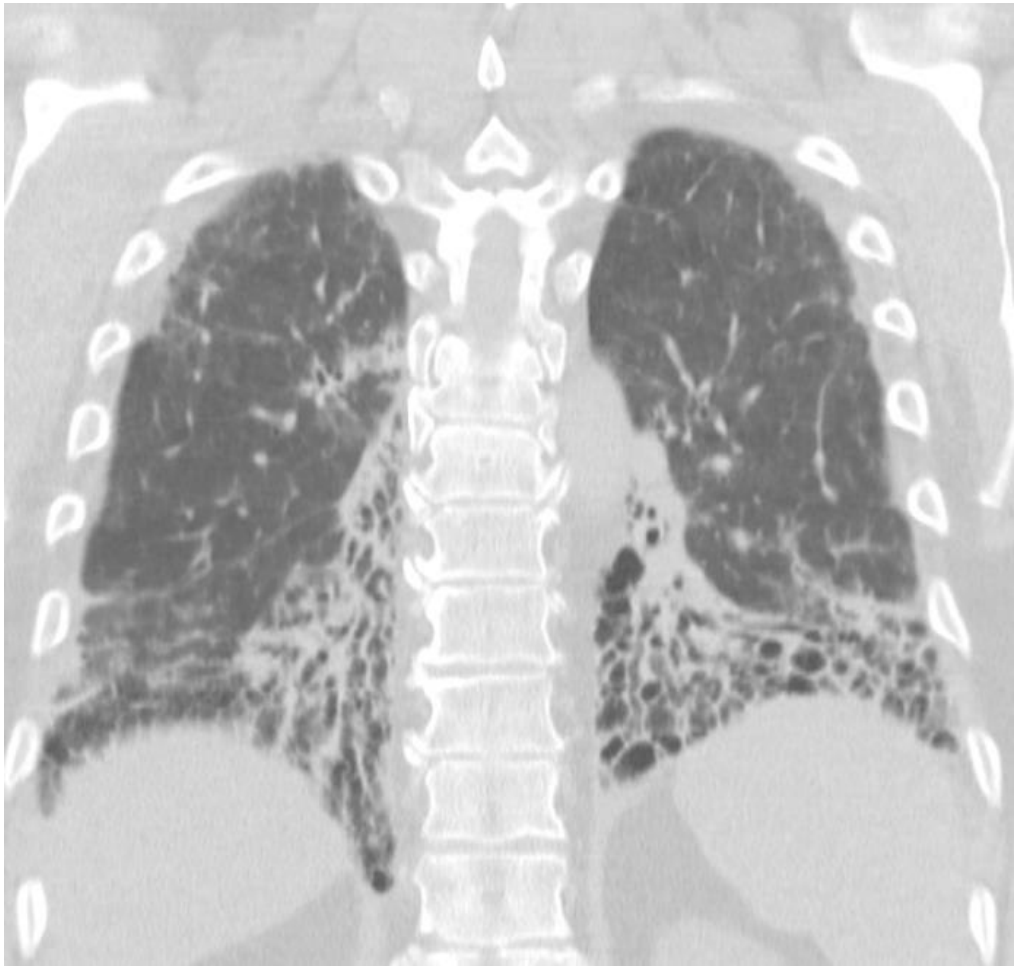
November 2017: progressive respiratory dysfunction; waiting list evaluation

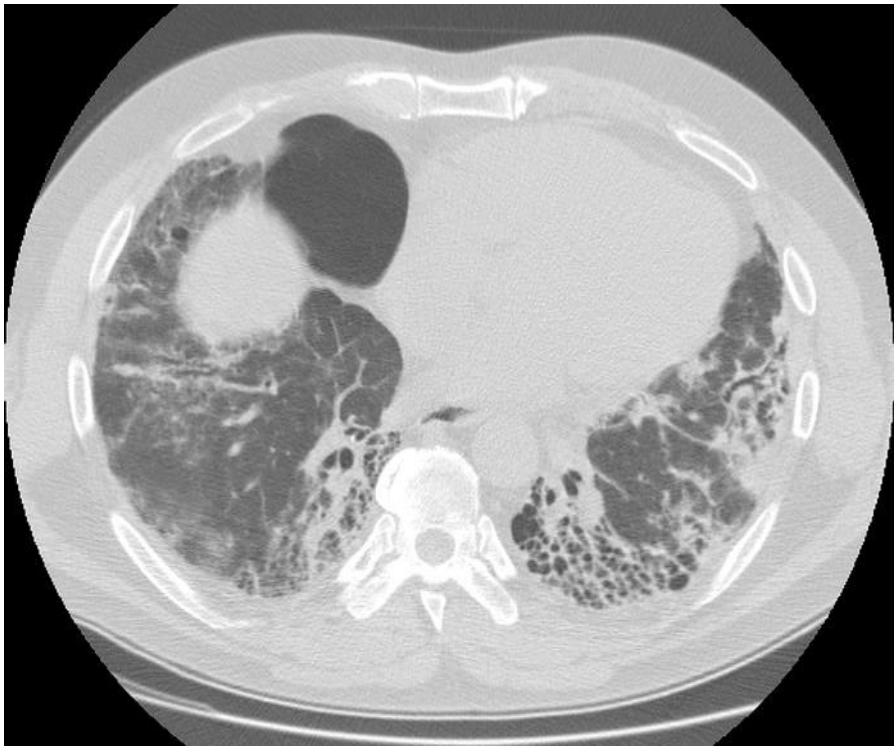
Case J. E. 48 yrs-old male,

Waiting list evaluation:

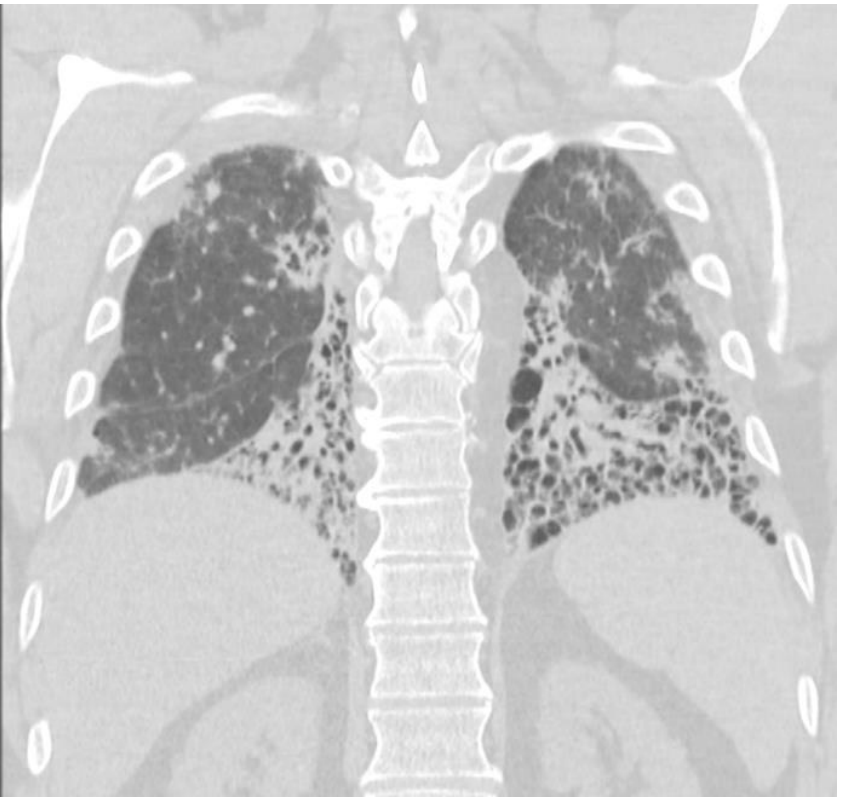
- Cardiac function: no altered parameters
- Infective screening: no infections
- Psicological evaluation: highly motivated
- HRCT: severe IPF with foci of AE

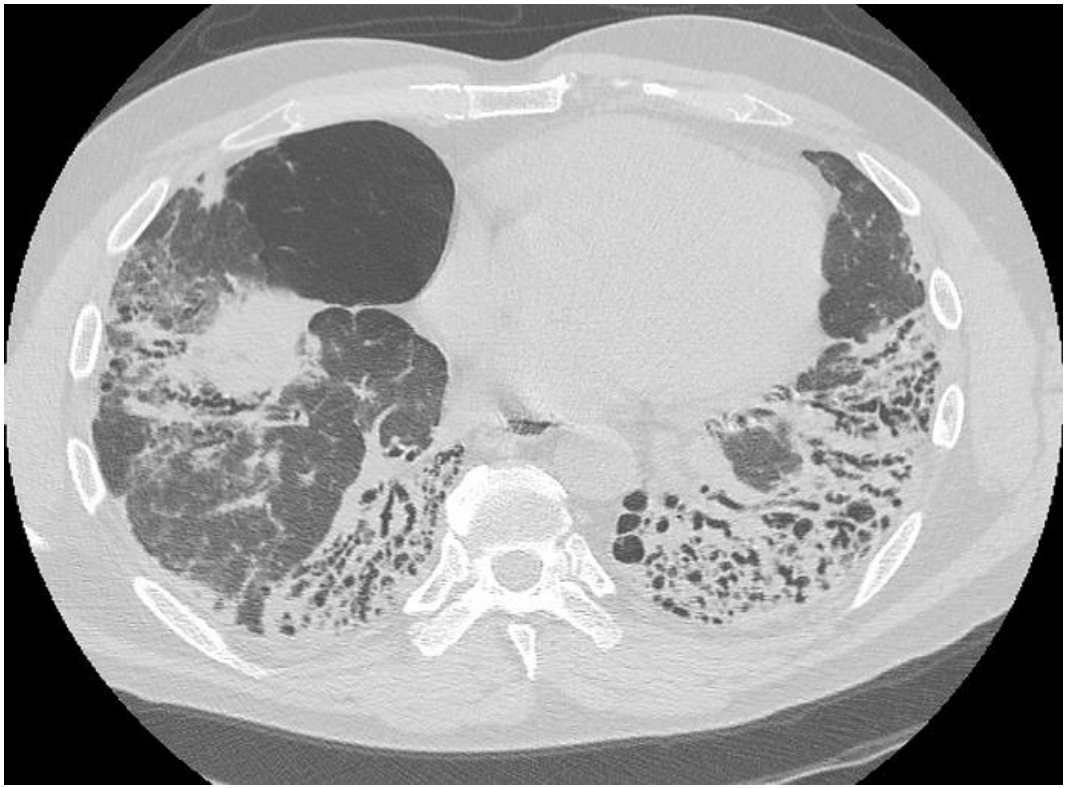
Case J. E. 48 yrs-old male, 1rst MDT evaluation





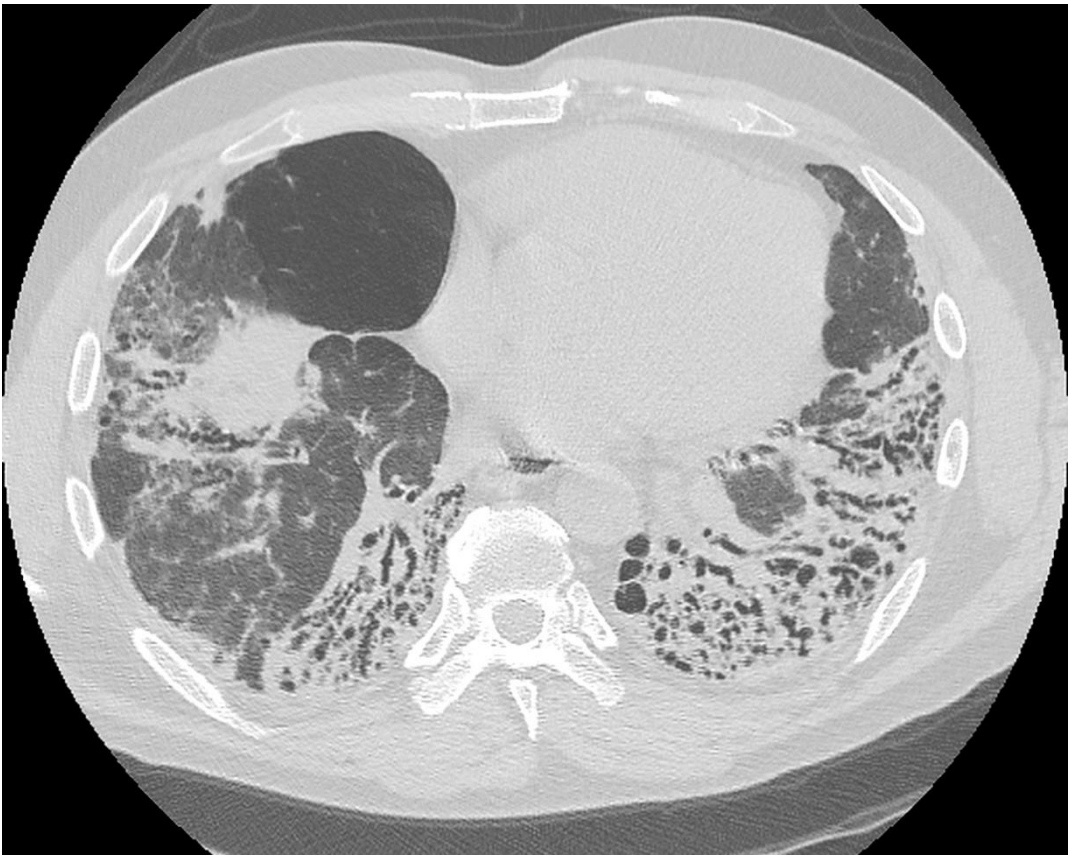
Case J. E. 48 yrs-old male, 1rst MDT evaluation

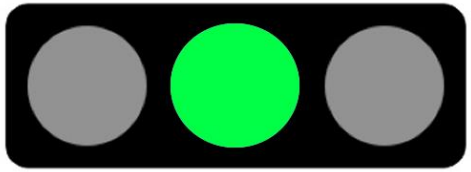




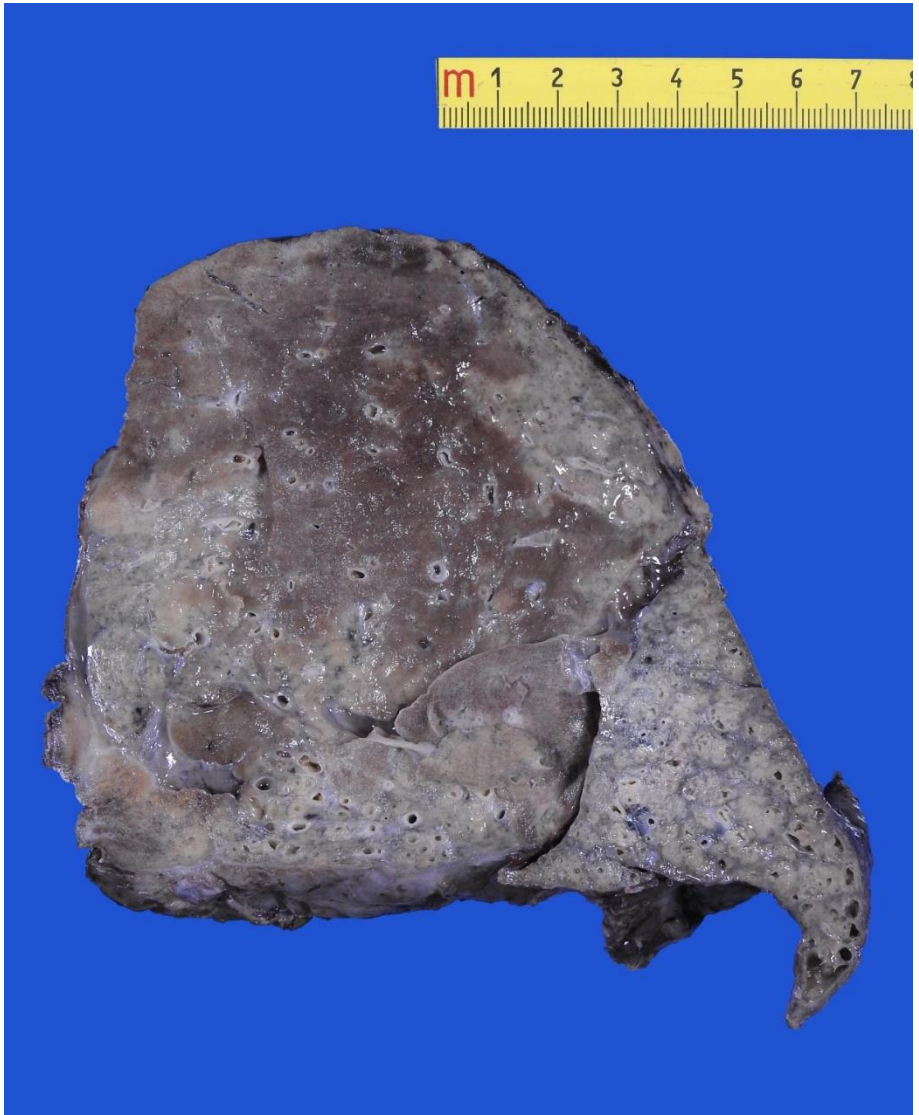
The case was discussed in several MDT

At last MDT (…..) : final diagnosis carried out by dedicated thoracic radiologists was **IPF + AE**

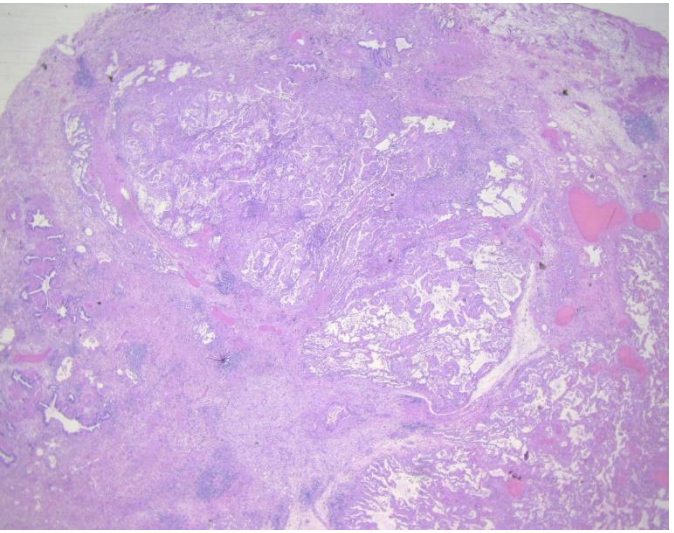


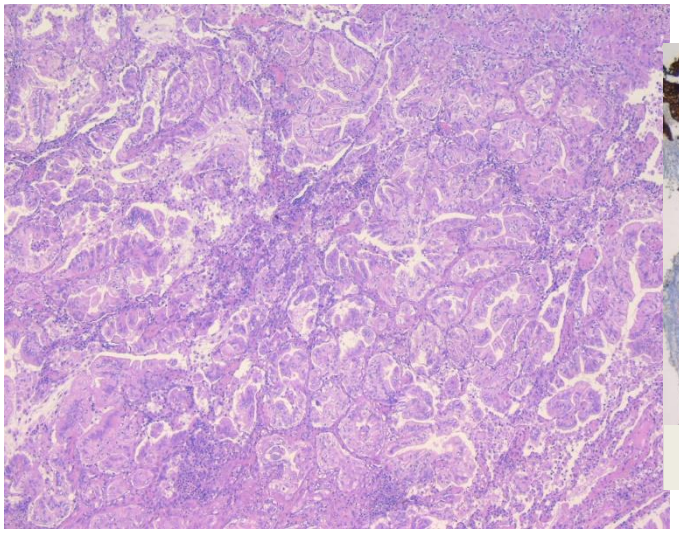


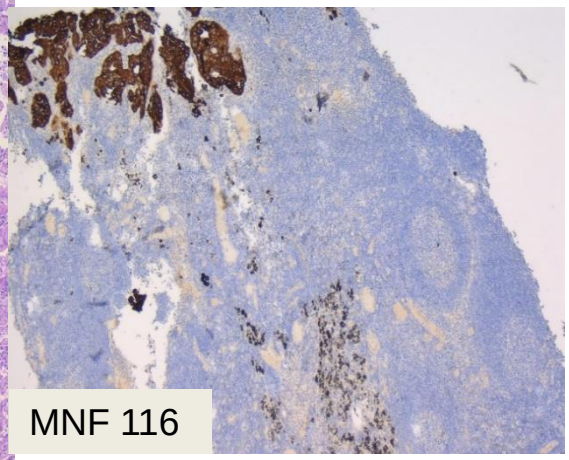
Lung transplant Octomber 2018 (N° 435)

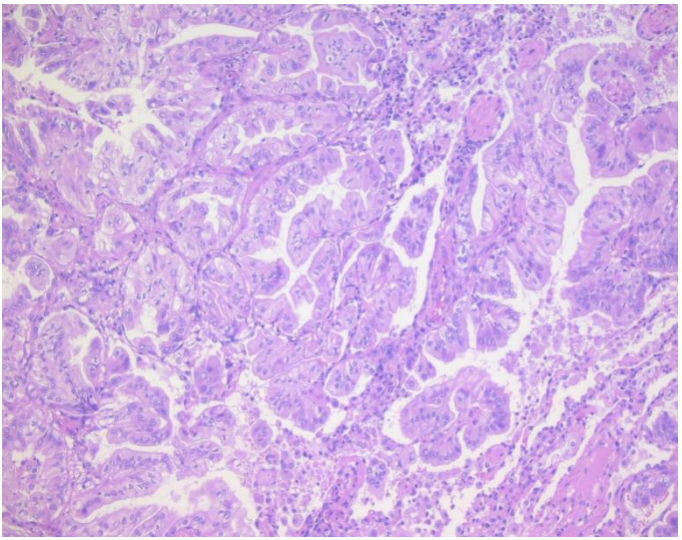


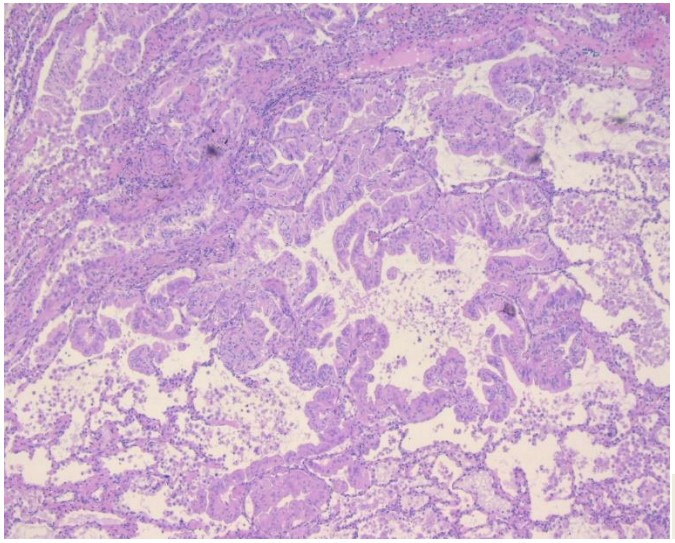
Lung transplant Octomber 2018 (N° 435)

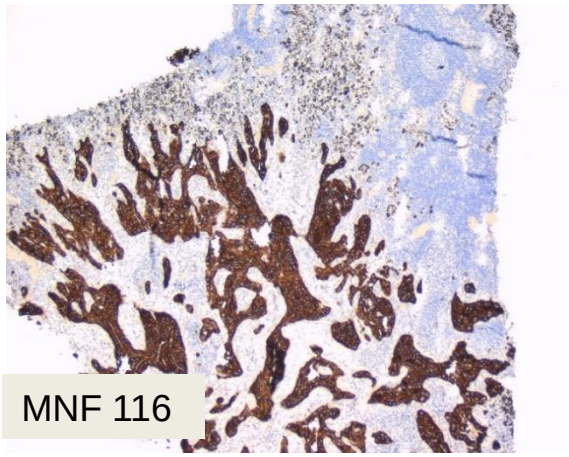












but at that time the reaction was truly explosive !!!!!!

Diagnosis: UIP and adenocarcinoma with prevalent features of papillary, solid pattern (foci of mucinous aspects)

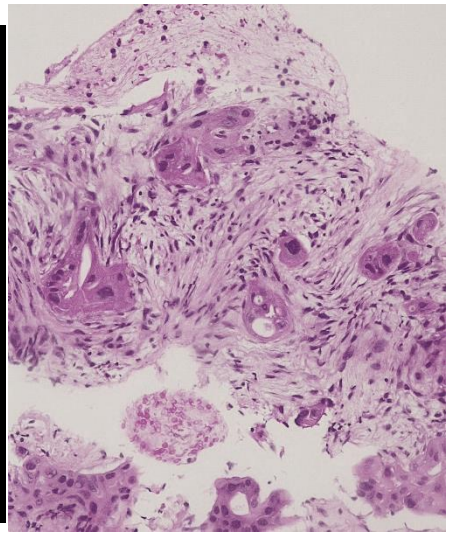
EGFR: no mutation in exons 18, 19, 20, 21

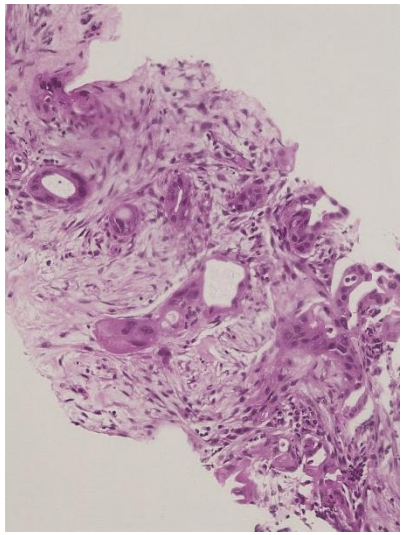
Biomakers	Details	Results
PD-L1	PD-L1 (LDT*; Clone E1L3N; cell signaling technology; 1:200; Bond III immunostainer; Bond polymer refine detection kit)	NEGATIVE
TPS**	TPS<1% (negative); 1-49% (intermediate); >50% (high)	<1%
Positive control	Placent	POSITIVE
ALK	ALK (LDT; clone D5F3, cell signaling technology, 1:150; Bond III immunostainer; Bond polymer refine detection kit	NEGATIVE
Score	Score 0 (negative); Score 1 (mild); Score 2 (moderate); Score 3 (high)	0
Positive control	Neoplastic sample (IHC +/FISH+)	POSITIVE
ROS1	ROS1 (LDT; Clone D4D6, cell signaling technology, 1:150; Bond III immunostainer; Bond polymer refine detection kit)	NEGATIVE
Score	Score 0 (negative); Score 1 (mild); Score 2 (moderate); Score 3 (high)	0
Posutive control	Neoplastic sample (IHC +/FISH+)	POSITIVE
EQA***	2018 ESP Lung EQA	Received June 2019

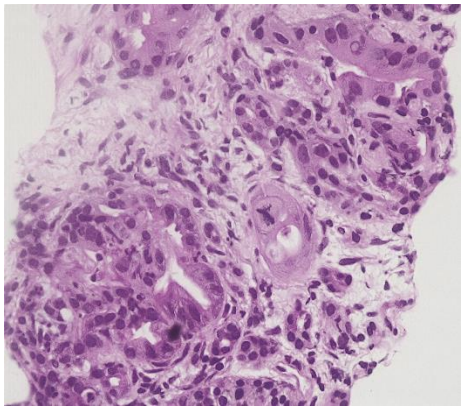
*LDT: Laboratory Developed Test
**TPS Tumor Proportion Score
*** EQA: External Quality Assessment

Case J. E. 48 yrs-old male, 1rst MDT evaluation

9 months after LT:
TAC total body: abdominal metastasis (pancreas); adrenal, bone

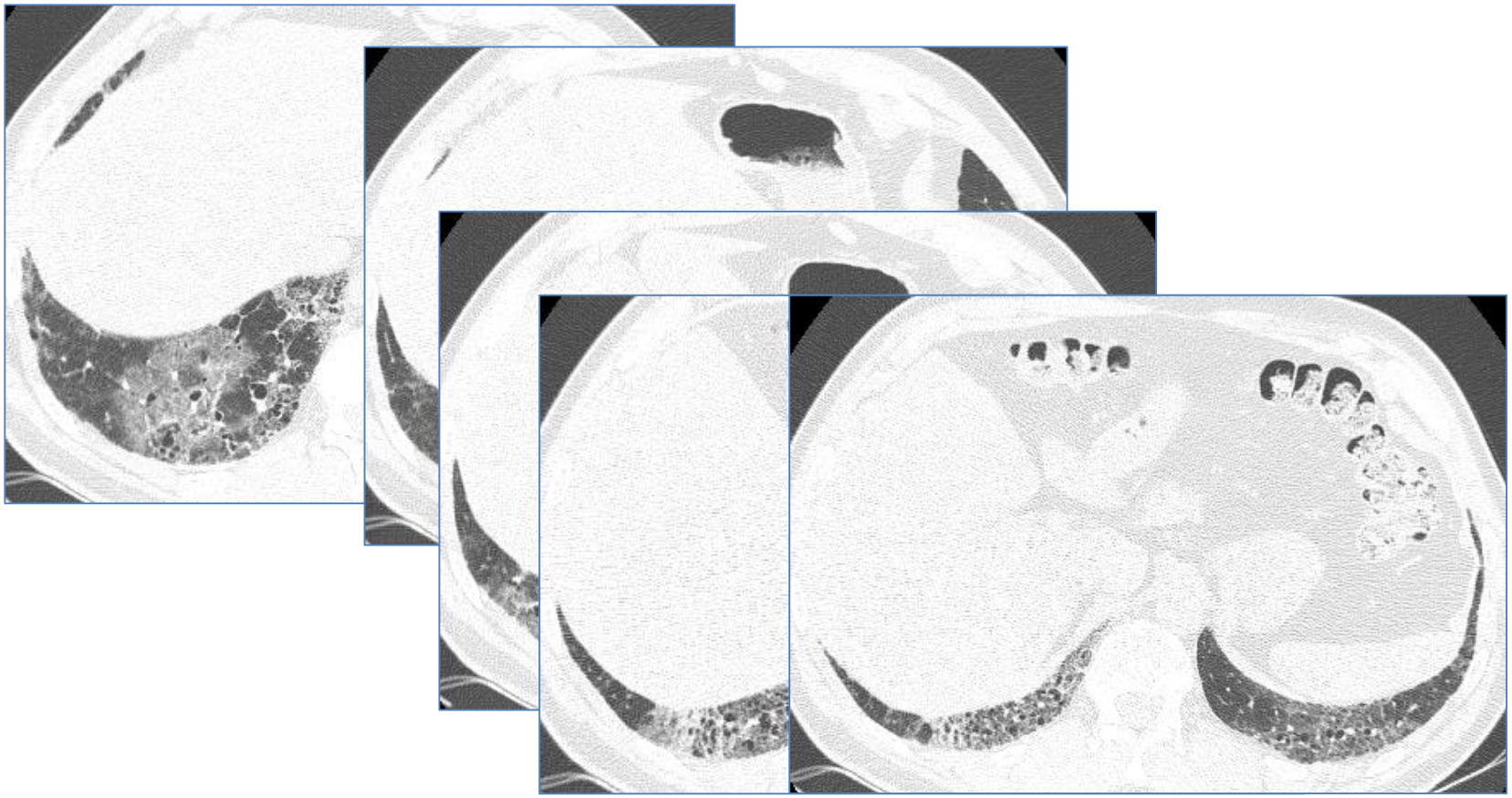






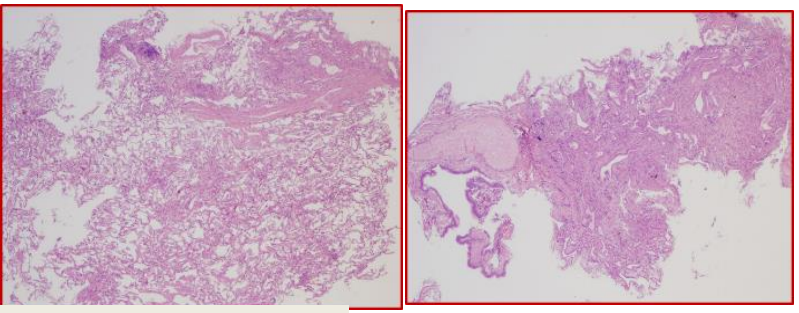
Follow-up 12 after LT: under oncological screening; palliative treatment

Male, 56 years old, in the last three years (2014-2015), progressive dyspnea: clinic/radiological diagnosis probable UIP /IPF. Referred to our center Referred to our LTX program for inclusion in waiting list

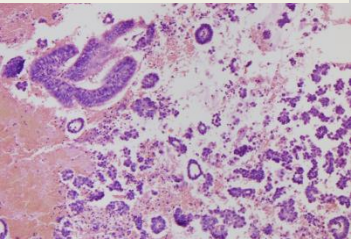


Due to the presence of multiple GGO and clinical conditions not so bad a TBB and BAL was carried out

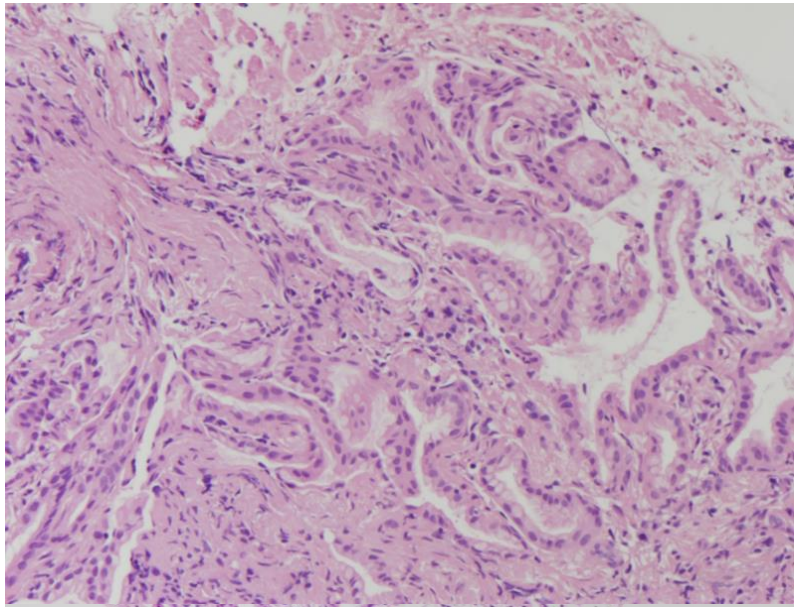
TBB



BAL



Final diagnosis:
NSCLC (in favor of adenok) in UIP



FINAL DECISION :
NO LONGER CONSIDERED CANDIDATE

when possible biopsy (even TBB/BAL) should be performed

IPF and Cancer

- What we know from pathological point of view ??

Primary Pulmonary Carcinoma in Patients With Idiopathic Pulmonary Fibrosis

Mayo Clin Proc. 2002;77:763-770

MARIE-CHRISTINE AUBRY, MD; JEFFREY L. MYERS, MD; WILLIAM W. DOUGLAS, MD; HENRY D. TAZELAAR, MD; TANYA L. WASHINGTON STEPHENS, MD; THOMAS E. HARTMAN, MD; CLAUDE DESCHAMPS, MD; AND V. SHANE PANKRATZ, PHD

- **24** pts with UIP/IPF/LC
- **63** pts with only UIP/IPF
- **532** pts with only LC

Analysis of several Clinical/demografical parameters: (including morphological features)

Table 1. Summary of Clinical Findings in 24 Patients With Idiopathic Pulmonary Fibrosis and Lung Carcinoma*

Characteristics	Result	Characteristics	Result
Sex, No. (%) (N=24)		Surgery, No. (%)	22 (92)
Male	21 (88)	Lobectomy	13
Female	3 (12)	Wedge or segmentectomies	5
Age (y) (n=23)		Bilobectomy	1
Median	72.8	Pneumonectomy	1
Mean ± SD	72.3±9.1	Combined wall resection and lung resection	2
Range	50-89	Adjuvant therapy, No. (%)	2 (8)
Smoking status (N=24)		No treatment, No. (%)	1 (4)
Current	2 (8)	Postoperative complications,† No. (%) (n=23)	9 (38)
Past	20 (83)	Acute respiratory failure	3
Never	2 (8)	Prolonged mechanical ventilation	2
Pack-years (N=24)		Bronchopleural fistula	1
Median	51	Gastrointestinal hemorrhage	1
Mean ± SD	53.5±26.8	Persistent pneumothorax	1
Range	10-105	Chest tube leak	1
PFT pattern, No. (%) (n=23)		Multiple pulmonary embolisms	1
Normal	3 (13)	Cerebrovascular accident	1
Restriction	9 (39)	Postoperative mortality, No. (%)	3 (12)
Obstruction	4 (17)	Outcome, No. (%) (N=24)	
Mixed	7 (30)	Alive	7 (29)
DLCO (% predicted) (n=22)		Mean (range) duration of follow-up from diagnosis of IPF (y)	2.2 (0.2-10.0)
Median	48.5	Mean (range) duration of follow-up from diagnosis of carcinoma (y)	1.2 (0.1-3.8)
Mean ± SD	51.3±20.1	Dead	16 (67)
Range	27-99	Mean (range) survival from diagnosis of IPF (y)	2.3 (0.02-7.7)
Sao_2 at rest (%) (n=20)		Mean (range) survival from diagnosis of carcinoma (y)	1.6 (0.02-6.1)
Median	95	Lost to follow-up	1 (4)
Mean ± SD	94±2.2	Recurrence or metastases	8 (33)
Range	87-97	Time to recurrence (y)	1.7 (0.2-6.1)
Sao_2 with exercise (%) (n=17)			
Median	90		
Mean ± SD	89.7±4.5		
Range	78-96		
Carcinoma-related symptoms, No. (%)			
Incidental	10 (42)		
New complaints†	11 (46)		
Hemoptysis	4		
Fatigue	3		
Weight loss	3		
Chest pain	3		
Shortness of breath and cough only	3 (12)		

Table 3. **Statistical Comparison of IPF and Carcinoma vs Carcinoma-Only Groups***

Characteristics	IPF and carcinoma	Carcinoma only	*P* value
Controlled variables			
Age at diagnosis of carcinoma (y)			
No. of patients	24	532	
Mean ± SD	72.1±9.7	69.5±8.6	
Range	50.2-89.5	50.3-89.6	
Stage, No. (%)			
I	13 (56)	209 (39)	
II	1 (4)	56 (11)	
IIIa	9 (39)	267 (50)	
Unmatched variables			
Sex, No. (%)			.02
Male	21 (88)	345 (65)	
Female	3 (12)	187 (35)	
Tumor location, No. (%)			.004
Upper lobes	7 (29)	260 (49)	
Lower lobes	10 (42)	155 (29)	
Middle lobe	2 (8)	13 (2)	
More than 1 lobe	4 (17)	17 (3)	
Not specified	1 (4)	87 (16)	
Type of carcinoma, No. (%)			.004
Squamous cell	16 (67)	254 (48)	
Adenocarcinoma	7 (29)	278 (52)	
Spindle cell	1 (4)	0 (0)	
Surgical treatment, No. (%)			<.001
No	8 (33)	420 (79)	
Yes	16 (67)	112 (21)	

*IPF = idiopathic pulmonary fibrosis.

Istotype: SQC(67%)
Site : Lower lobes(42%)

In 9 pts: between metaplastic epithelium and invasive LC→ transitional area with evident cellular atypia

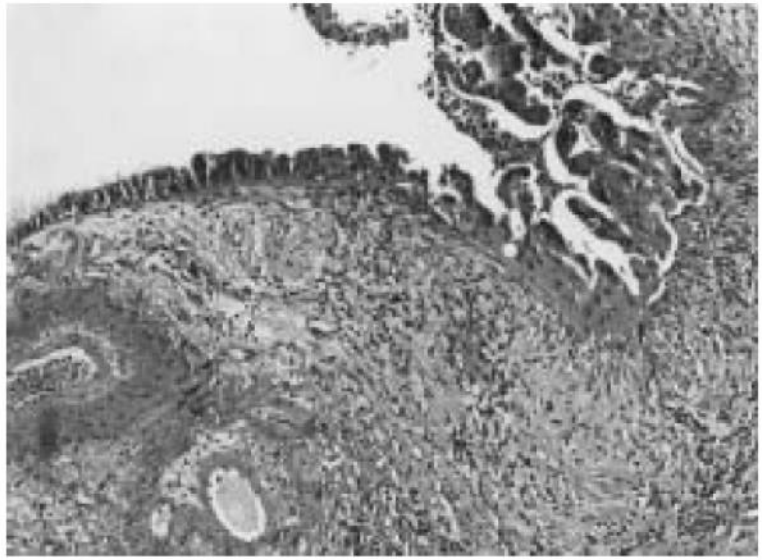


Figure 2. High-magnification photomicrograph showing bronchiolar-type epithelium with increasing cytologic and architectural atypia, near invasive adenocarcinoma (not shown) (hematoxylin-eosin, original magnification ×200).

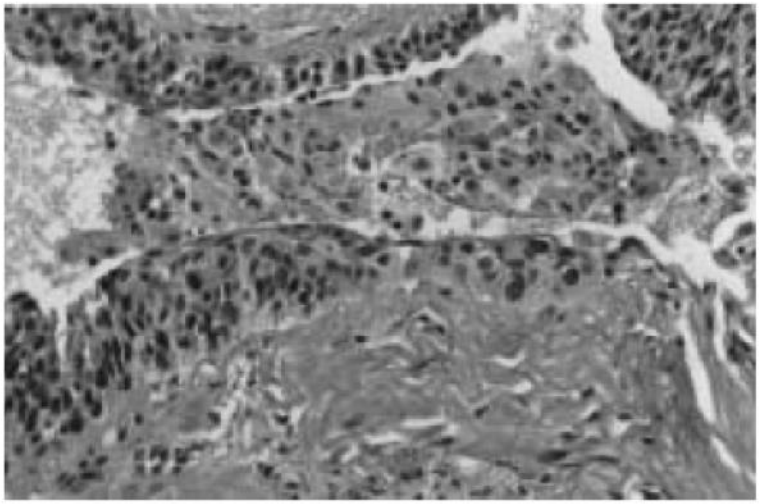


Figure 3. High-magnification photomicrograph showing squamous metaplasia with increasing cytologic atypia in proximity of invasive squamous cell carcinoma (hematoxylin-eosin, original magnification ×200).

SQC OR ADENOCARCINOMA?

Table 2
Studies reporting histologic predominance of lung cancer in patients with IPF.

Study	Number of patients with IPF-lung cancer	SCC	ADC	Year
Nagai	31	45.2%	35.2%	1992
Park	63	35%	30%	2001
Kawasaki	53	46%	46%	2001
Ozawa	21	38%	29%	2009
Lee	70	40%	30%	2014
Kreuter	42	36%	31%	2014
Tomassetti	23	39%	35%	2015

Abbreviations. IPF: Idiopathic pulmonary fibrosis, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma.

46/268 (17%) IPF and LC

45.65% Adenocarcinoma

- 28.26% SQC
- 26.09% SCLC

Incidence and radiologic-pathological features of lung cancer in idiopathic pulmonary fibrosis

Clin Respir J. 2018;12:1700–1705.

Yan Liu[1,2] | Min Zhu[2] | Jing Geng[3] | Chengjun Ban[2] | Shu Zhang[2] | Wenhui Chen[3] | Yanhong Ren[3] | Xuan He[3] | Wang Chen[3] | Huaping Dai[2,3]

54453 Pts with **NSCLC** → those with IPF (2%) showed more frequently:

-early stages

-SQC o adenok (46% vs 45%)

- mainly lower lobes

ANNALSATS Articles in Press. Published on 16-April-2019

Outcomes of Older Patients with Pulmonary Fibrosis and Non-Small Cell Lung Cancer

Stacey-Ann Whittaker Brown, MD, MPH,[1] Maria Padilla, MD,[1] Grace Mhango, MPH,[2] Emanuela Taioli, MD, PhD,[3] Charles Powell, MD,[1] Juan Wisnivesky, MD, DrPH*[2]

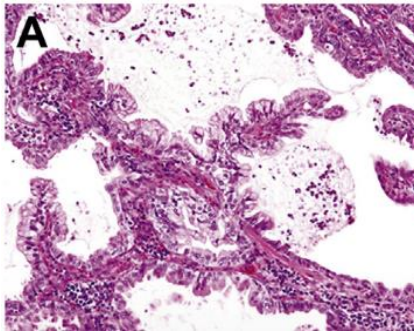
ORIGINAL ARTICLE

Clinicopathological, Immunohistochemical, and Genetic Features of Primary Lung Adenocarcinoma Occurring in the Setting of Usual Interstitial Pneumonia Pattern

Kyohei Masai, MD,[a,b,d] Koji Tsuta, MD,[c,*] Noriko Motoi, MD,[a] Kouya Shiraishi, MD,[a] Koh Furuta, MD,[a] Shigeki Suzuki, MD,[b] Keisuke Asakura, MD,[b] Kazuo Nakagawa, MD,[b] Hiroyuki Sakurai, MD,[b] Shun-ichi Watanabe, MD,[b] Nobuyoshi Hiraoka, MD,[a] Hisao Asamura, MD[d]

Journal of Thoracic Oncology; 2016;12: 2141-2149

Conclusions: UIP-ADC was associated with a poor prognosis owing to the high frequency of perioperative complications rather than the malignancy of the tumor itself. There was a high prevalence of the invasive mucinous-predominant subtype in cases of UIP-ADC. UIP-ADC also had a low prevalence of EGFR mutations and a high prevalence of KRAS mutations



Journal of Pathology
J Pathol 2018; **244:** 383–385
Published online 14 February 2018 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.5027

INVITED COMMENTARY

From bad to worse: when lung cancer complicates idiopathic pulmonary fibrosis†

Stephen B Strock, Jonathan K Alder and Daniel J Kass*

2 “Hot Topics”

- L’utilizzo della TBB/BAL come strumento diagnostico di primo livello nell’approccio iniziale: può essere utilizzato in centri con esperienza di elevate volume di broncoscopia diagnostica e con approccio routinario a MDT

- L’utilizzo della TBB/BAL in “end stage”: là dove possible sempre utile (K è una frequente complicanza nelle forme avanzate)