

BRONCHIOLITIS

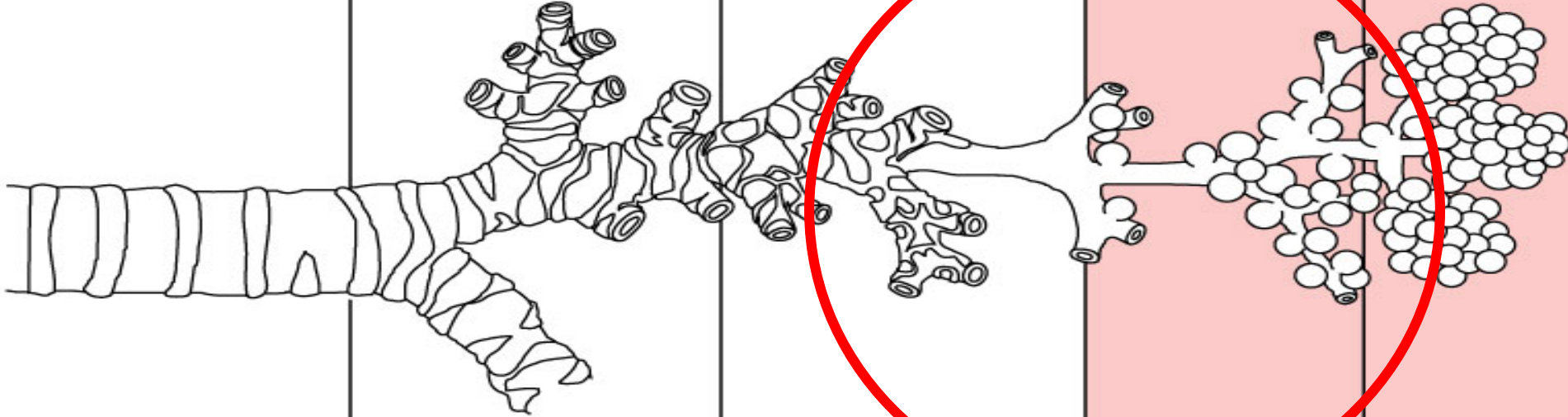
Venerino Poletti

Ospedale GB Morgagni, Forlì (I)

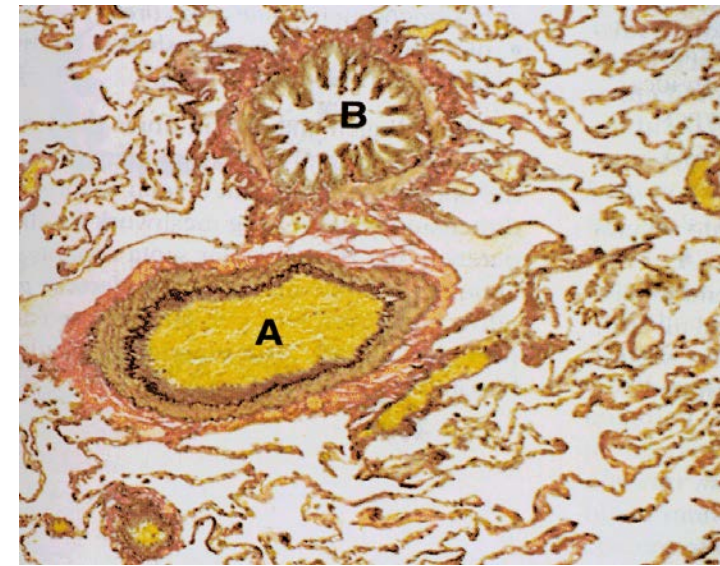
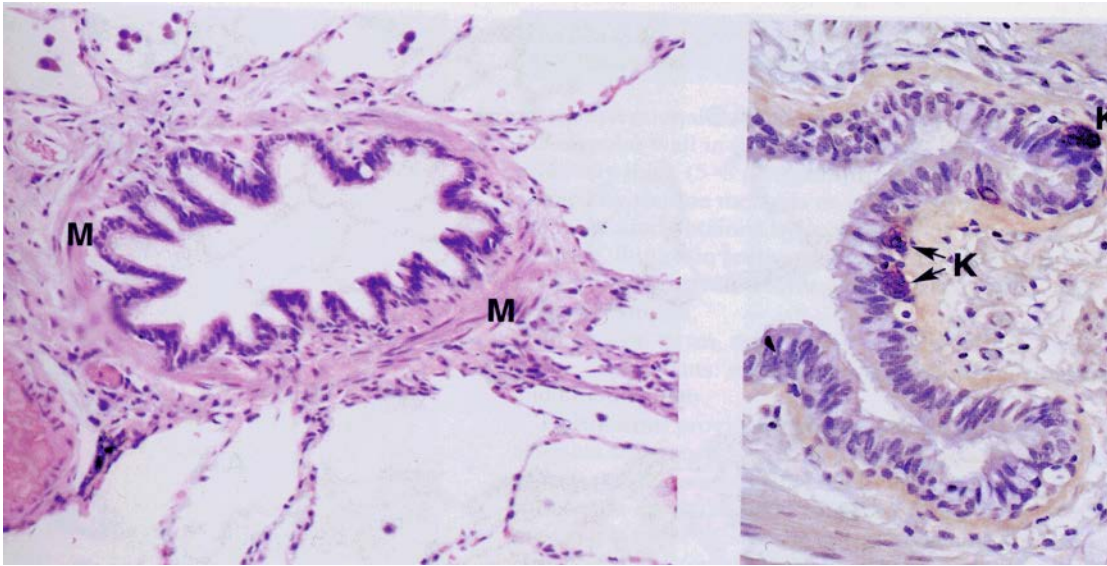
Aarhus University Hospital, Aarhus (DK)

Adult Bronchiolitis: definition

Bronchiolitis is a process centered in and around membranous and/or respiratory bronchioles with sparing of a considerable portion of the other parenchymal structures

CONDUCTING AIRWAYS			RESPIRATORY UNIT	
Trachea	Segmental bronchi	Bronchioles		Alveolar ducts
		Nonrespiratory	Respiratory	
				
Generations	8	16	24	26

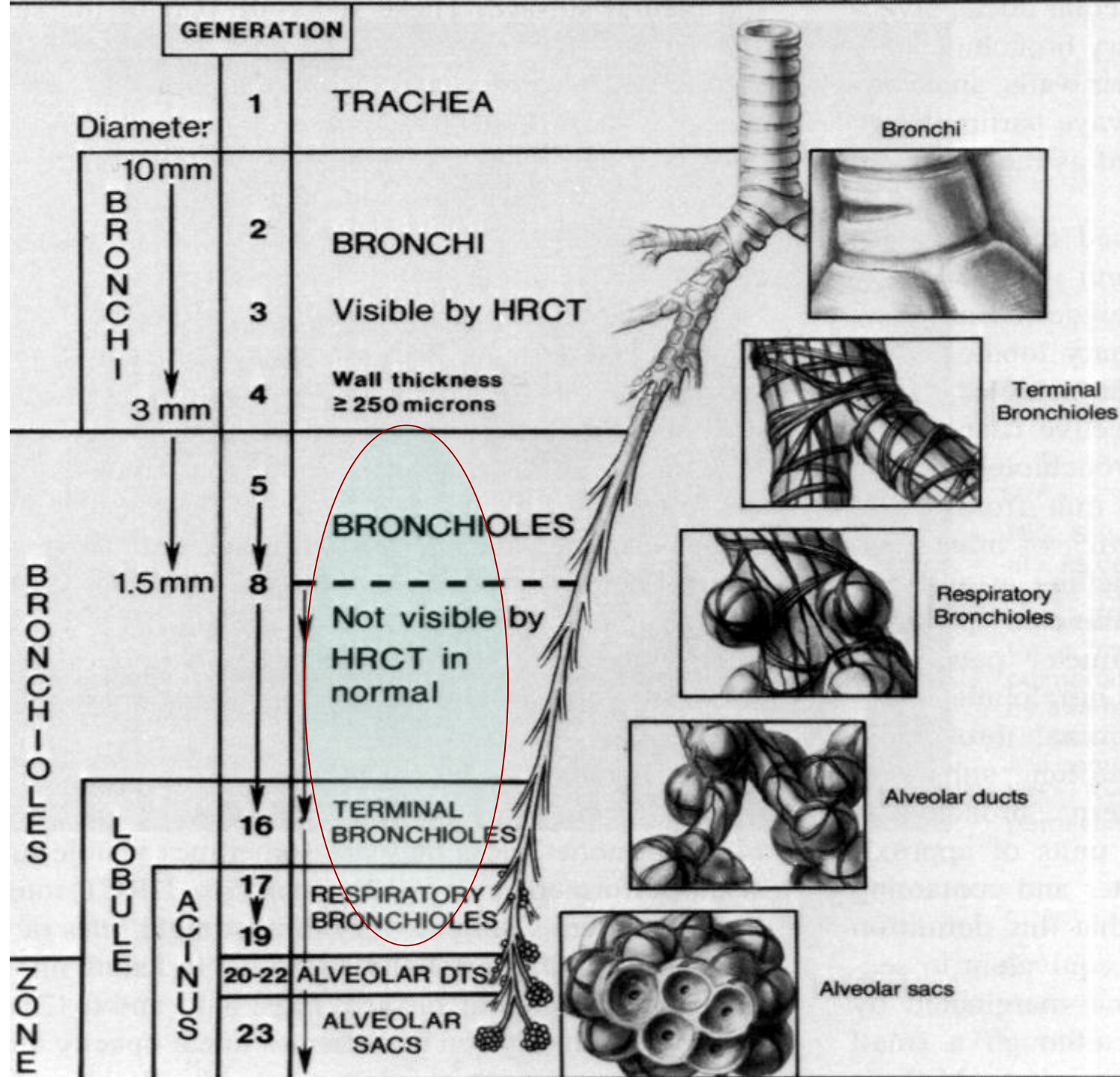
The distribution and amounts of the cellular and mesenchymal components vary from case to case and are at the basis of the variety of histopathological, radiographic and clinical aspects of bronchiolitis.



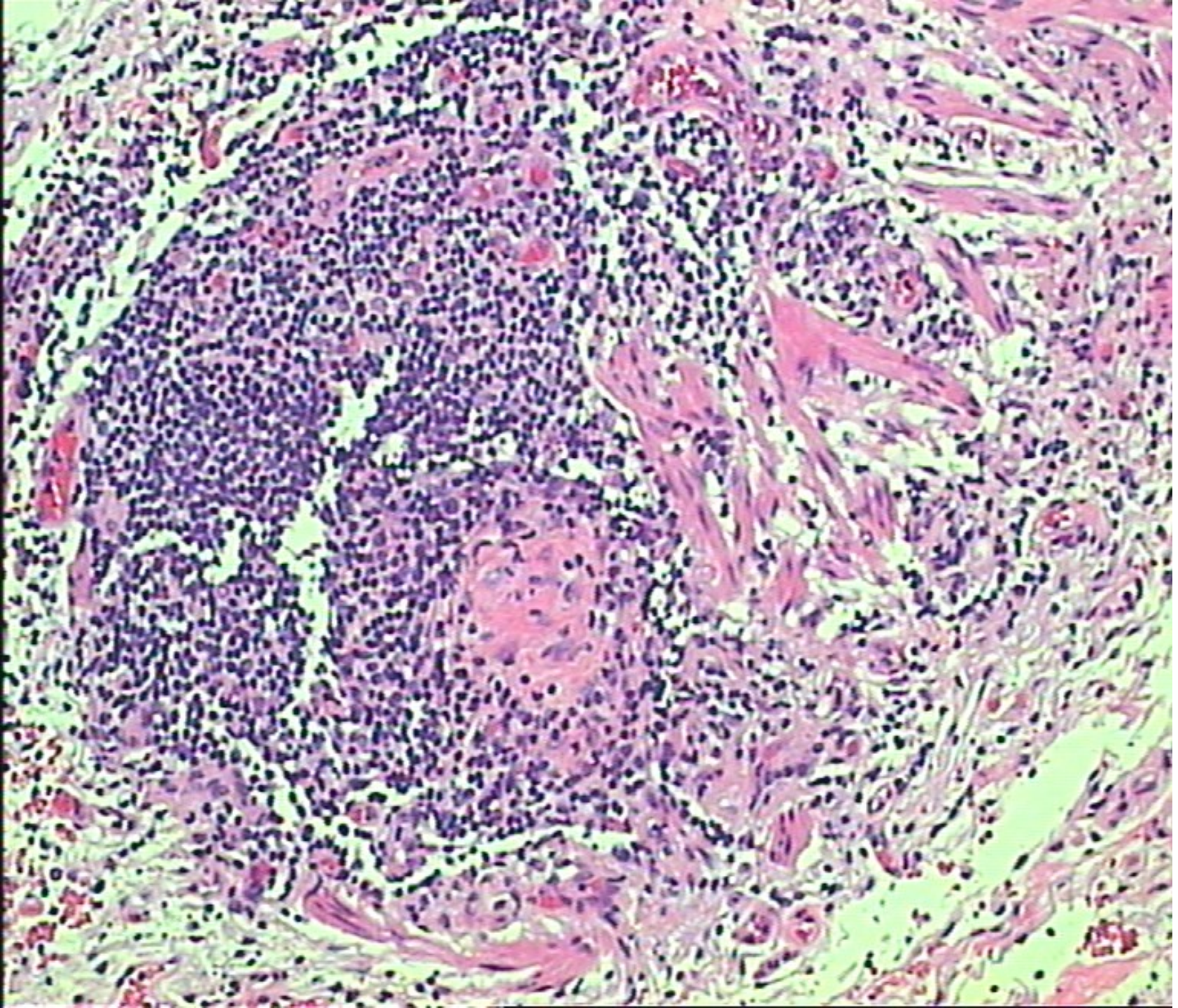
BRONCHIOLITIS

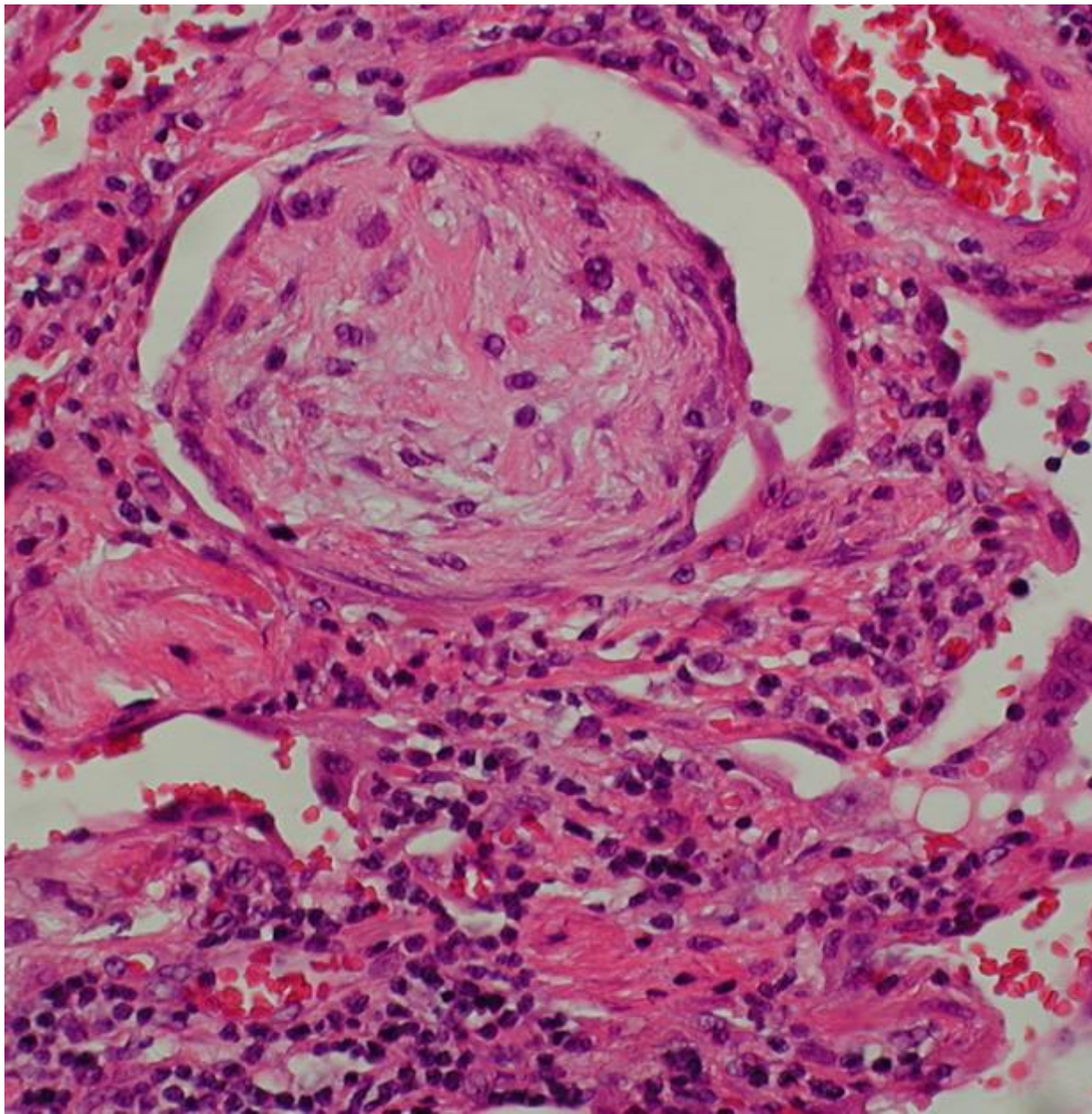
- Pathological classification
- Radiological classification
- Clinical entities

*Bronchiolar metaplasia

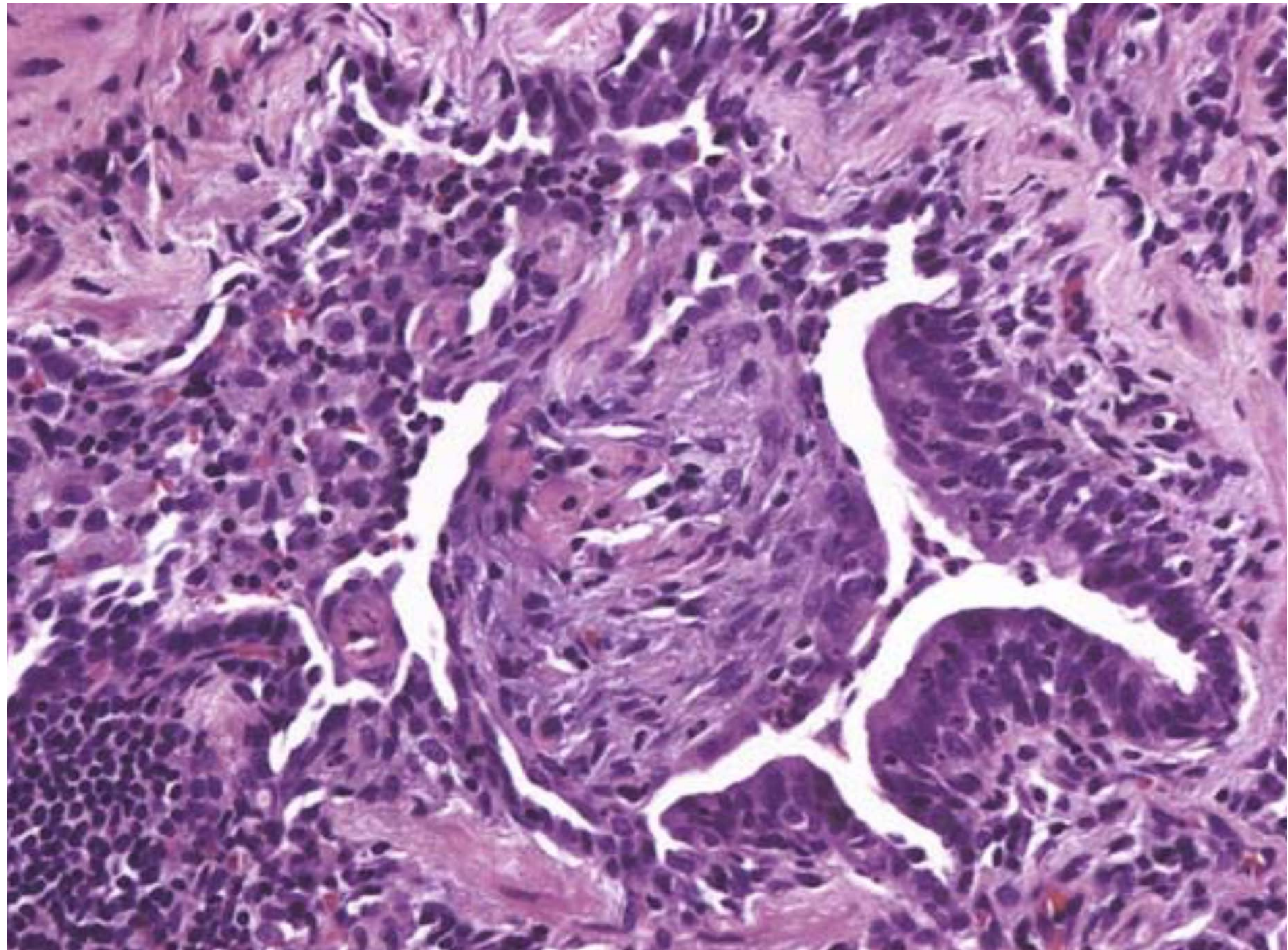


CELLULAR
BRONCHOLITIS

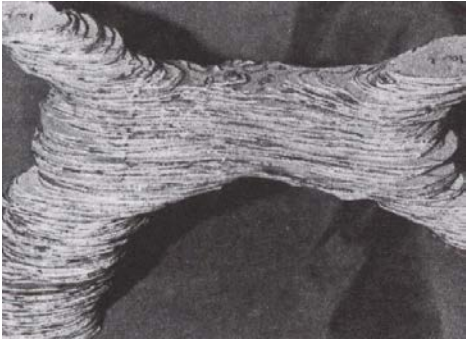




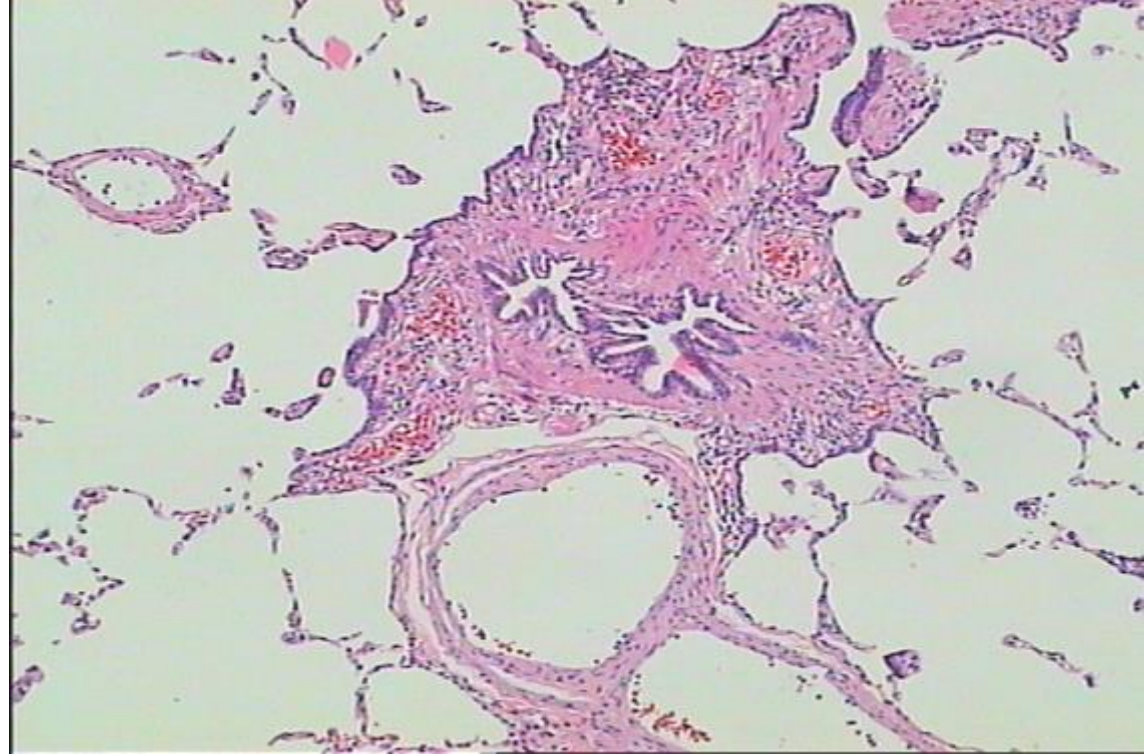
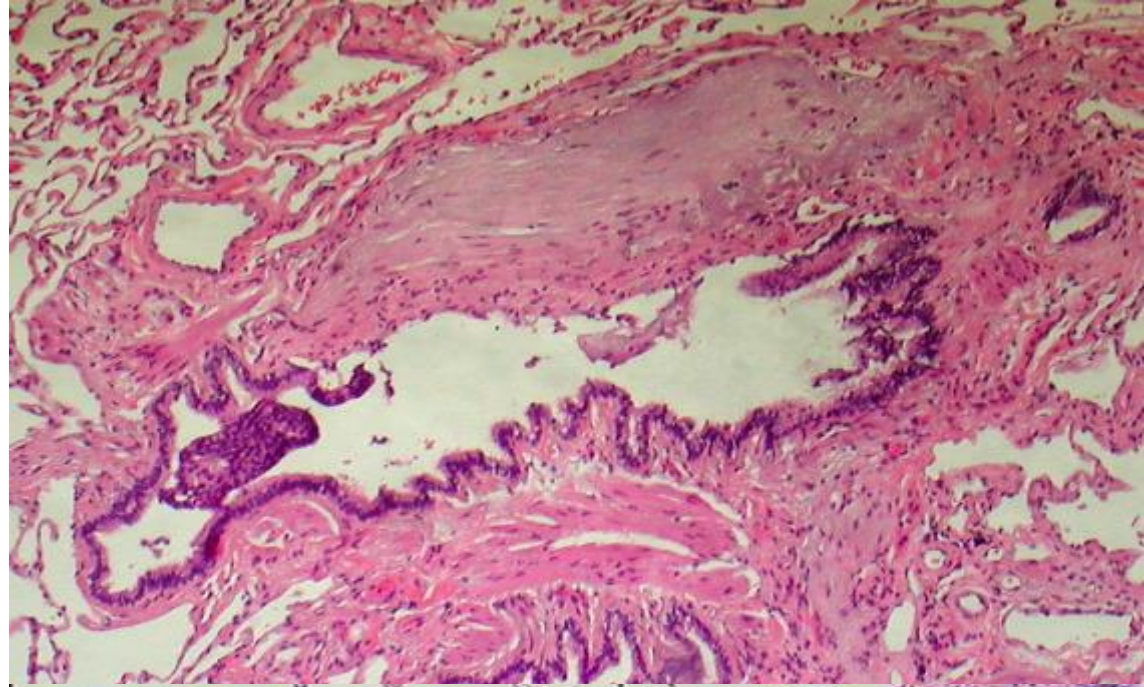
Bronchiolitis with inflammatory polyps

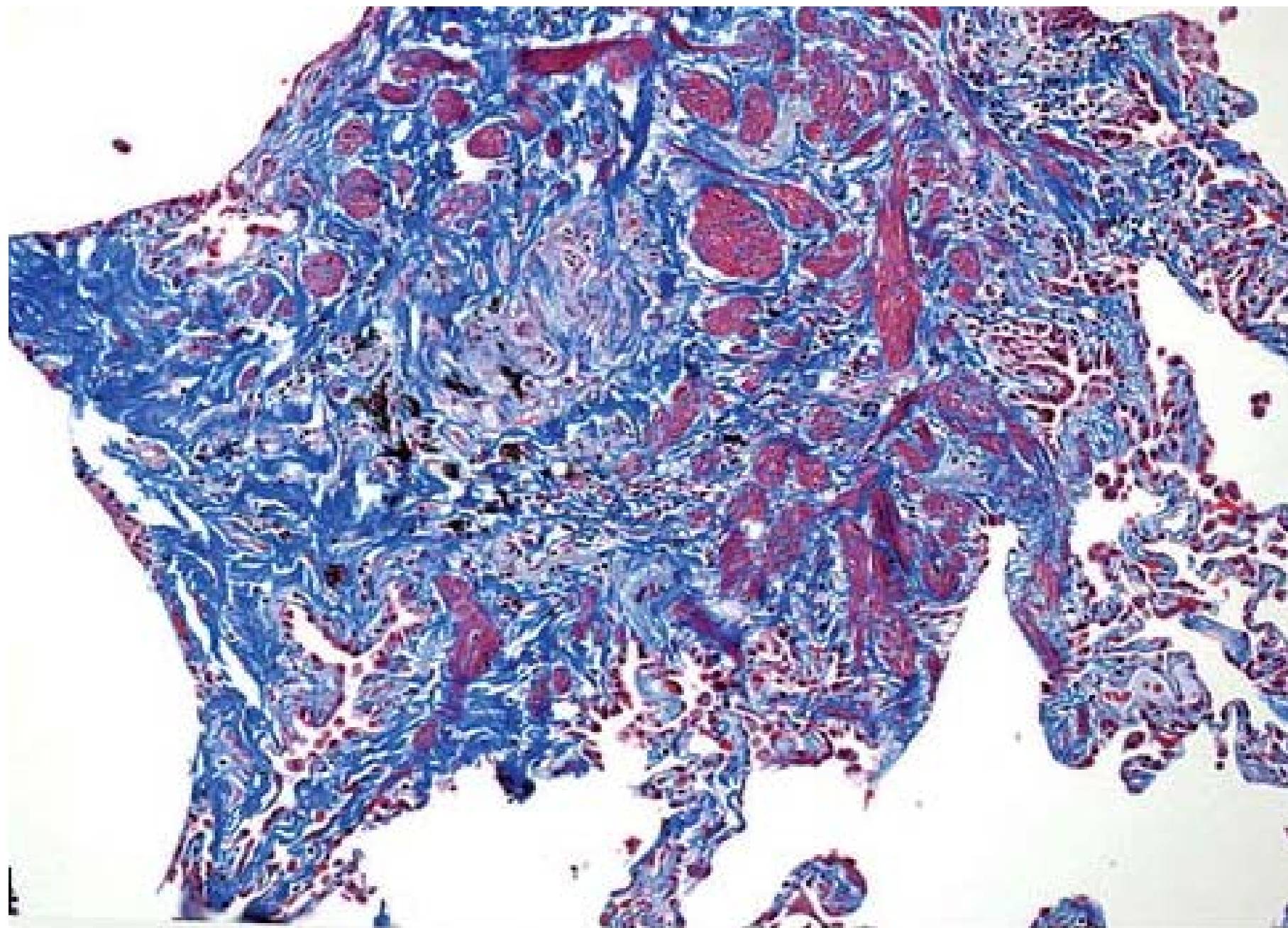


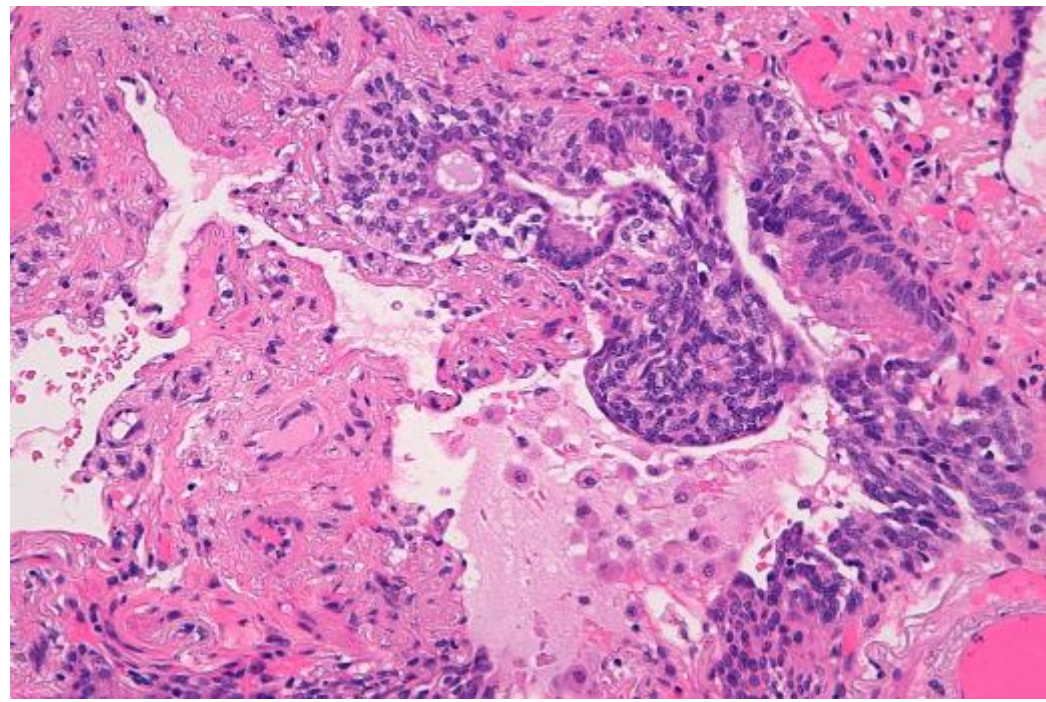
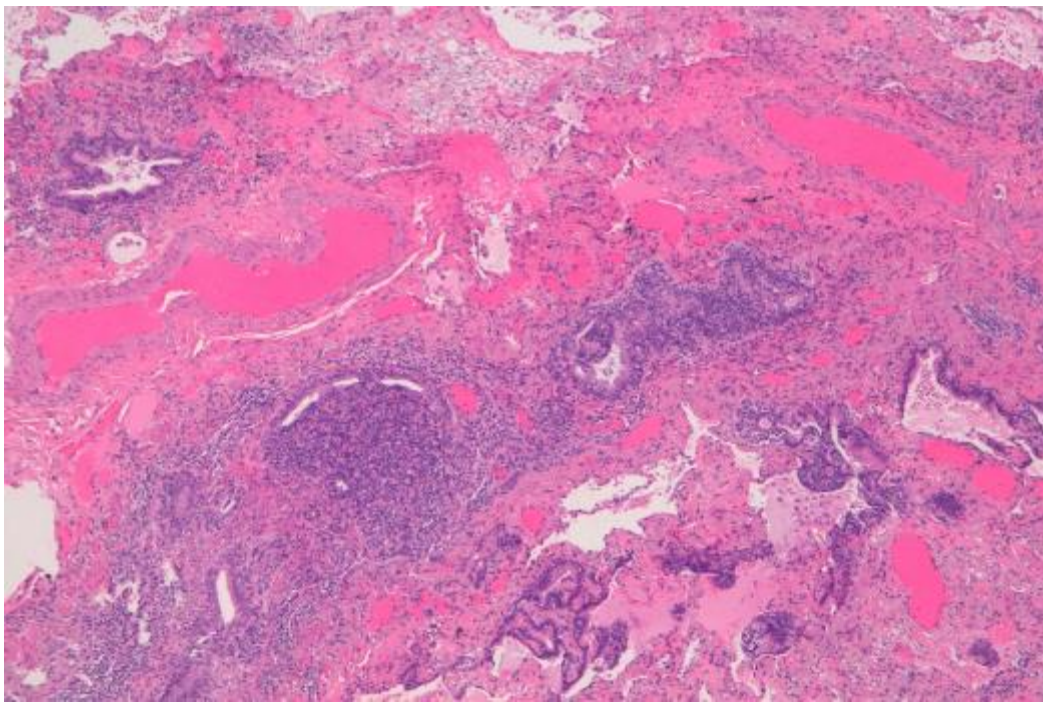
Cicatricial (constrictive) bronchiolitis



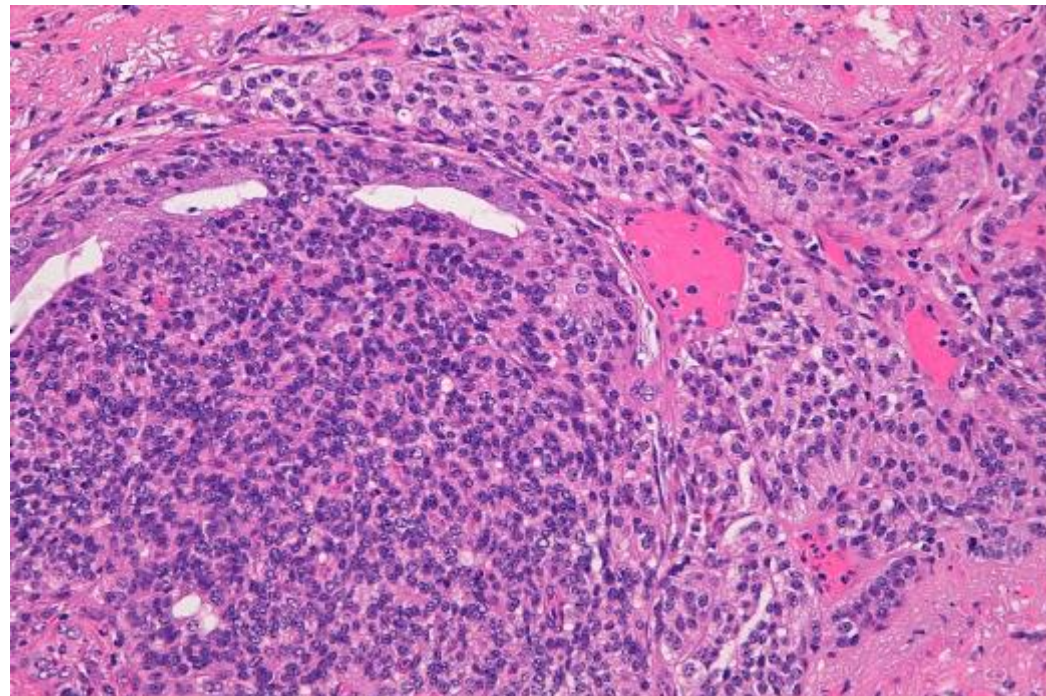
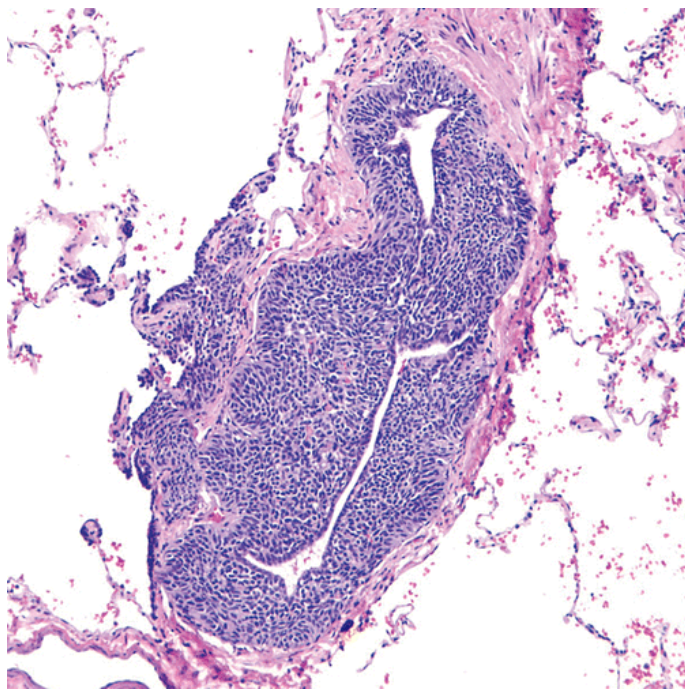
There is a mural thickening of membranous bronchioles caused by submucosal collagenization

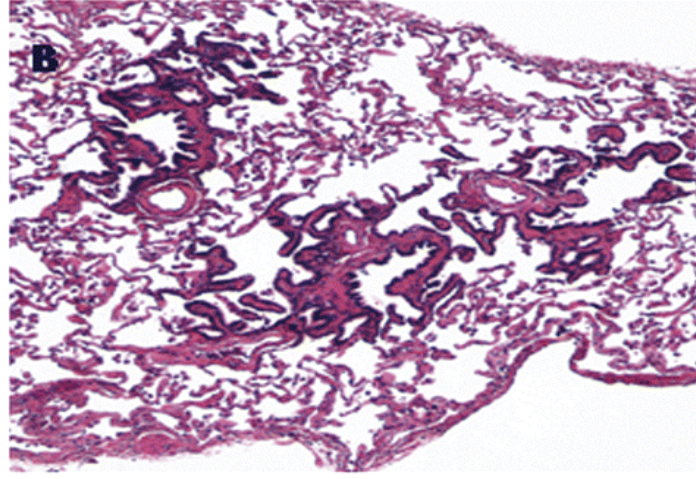
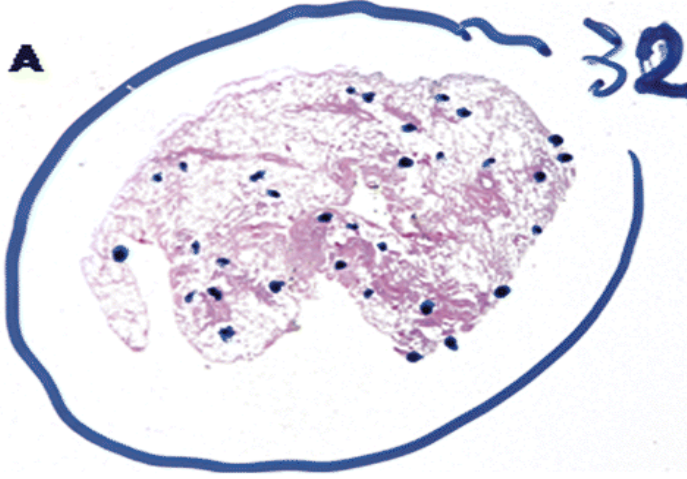






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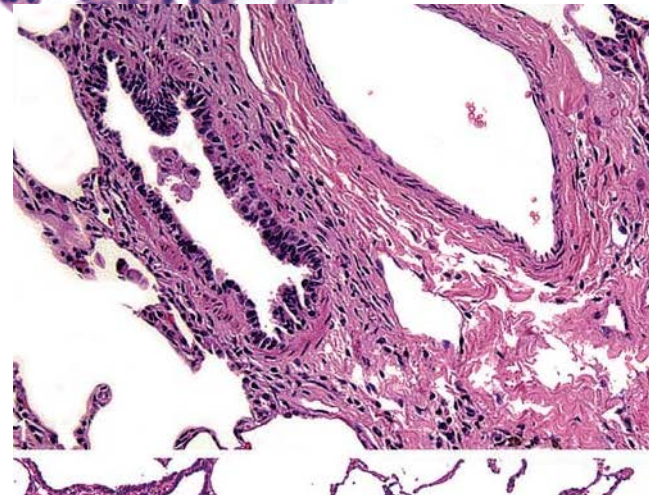
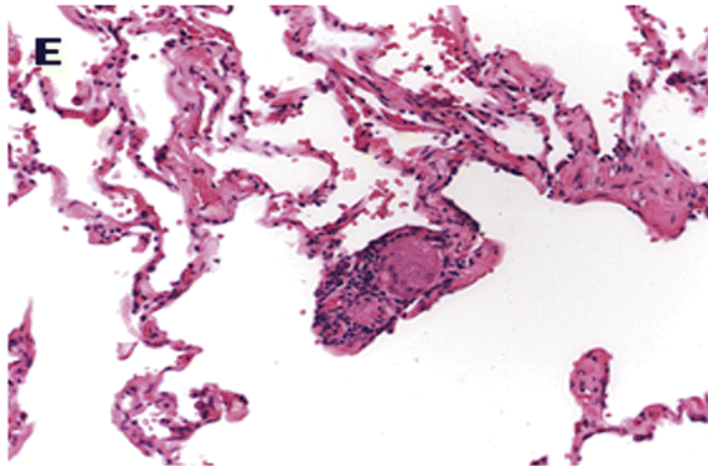
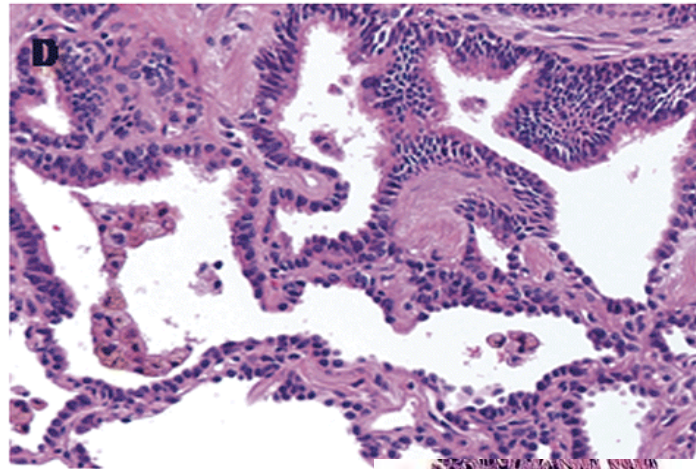
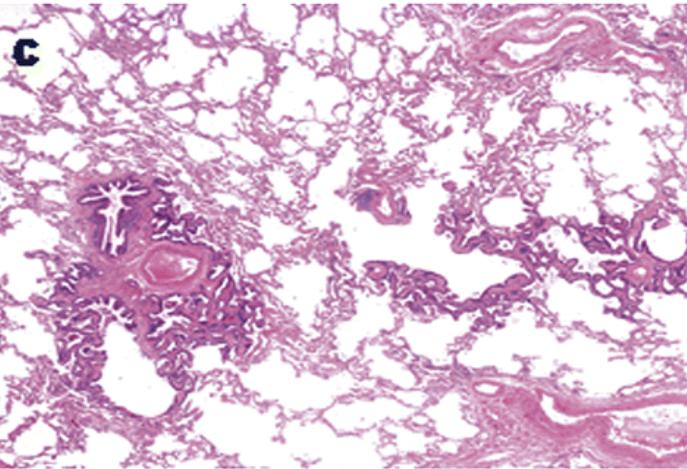


Fukuoka J, et al.

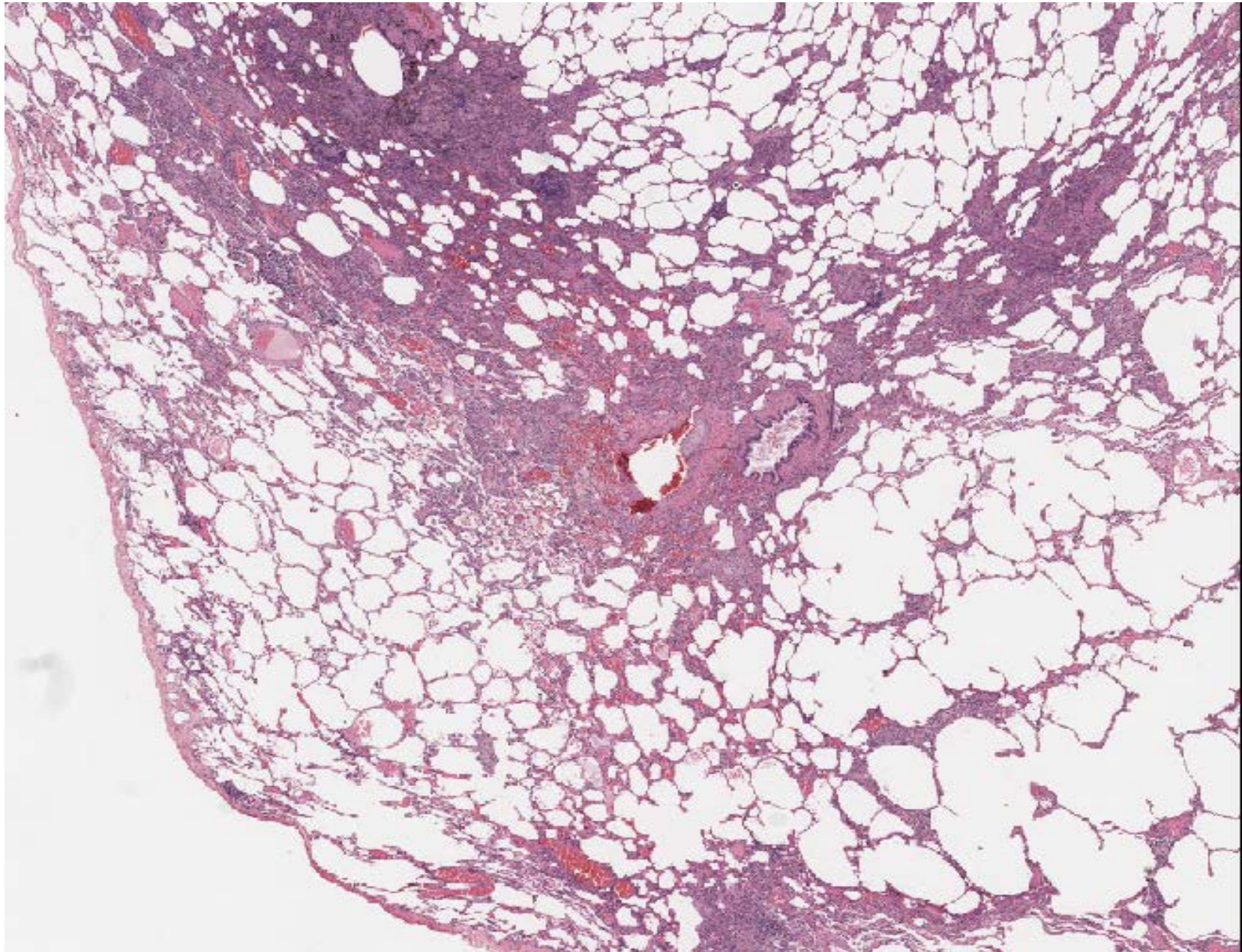
Peribronchiolar metaplasia

A common histologic lesion in diffuse lung disease and a rare cause of interstitial lung disease.

AJSP 2005, 29:948-954



Hypersensitivity Pneumonitis



Abnormalities on HRCT that reflect small airways disease can be broadly categorized into indirect and direct signs:

- ❖ widespread scarring and obliteration of the bronchioles results in the indirect sign of patchy density differences of the lung parenchyma, representing areas of under-ventilated and under-perfused lung (the so-called mosaic attenuation pattern).
- ❖ by contrast, considerable thickening of the bronchiolar walls by inflammatory infiltrate and/or luminal and surrounding exudate render the affected small airways directly visible.

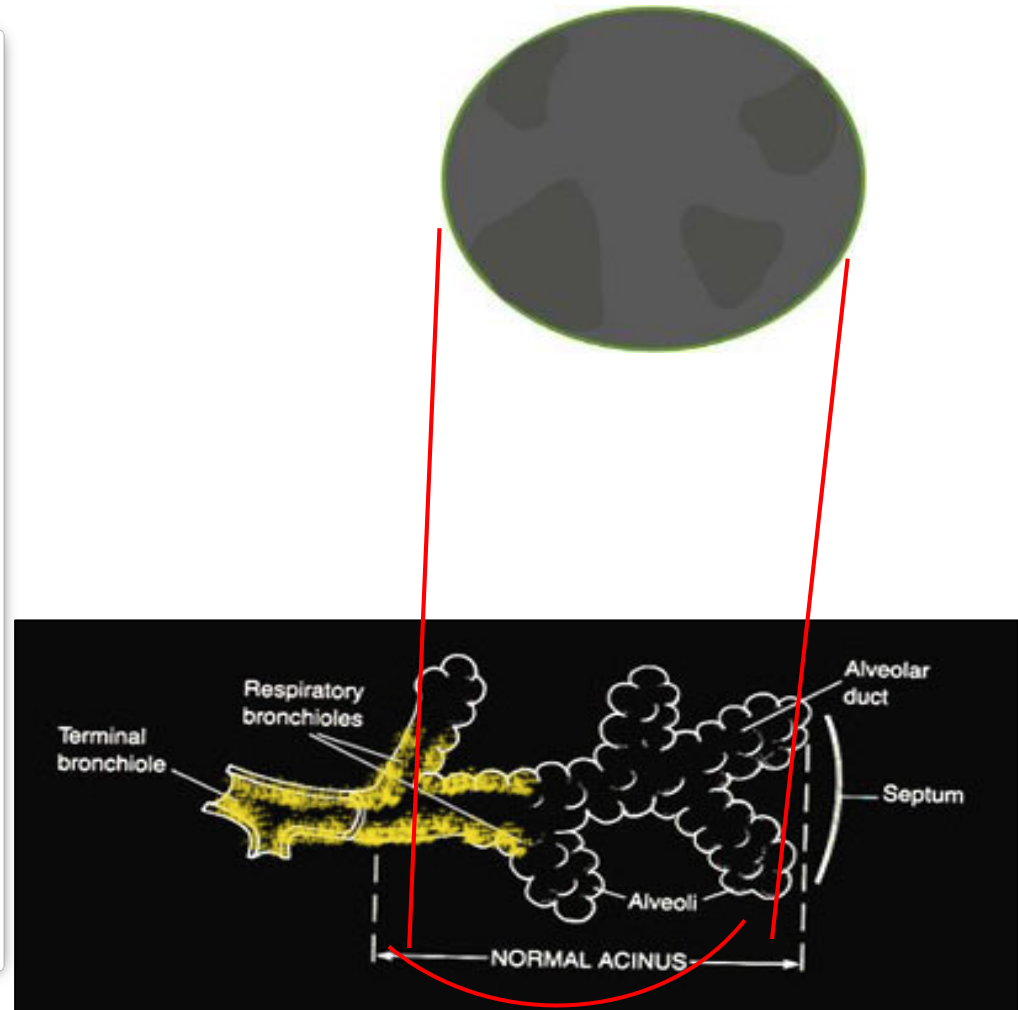
HR CT scan findings in bronchiolitis

- Indirect signs
 - Mosaic oligoemia
 - Expiratory air-trapping
- Direct signs
 - Centrilobular well defined nodules
 - “Tree in bud” pattern
 - Ground glass centrilobular nodules
- Mixed pattern
 - “Head-cheese” pattern

Indirect Signs



“mosaic oligoemia”

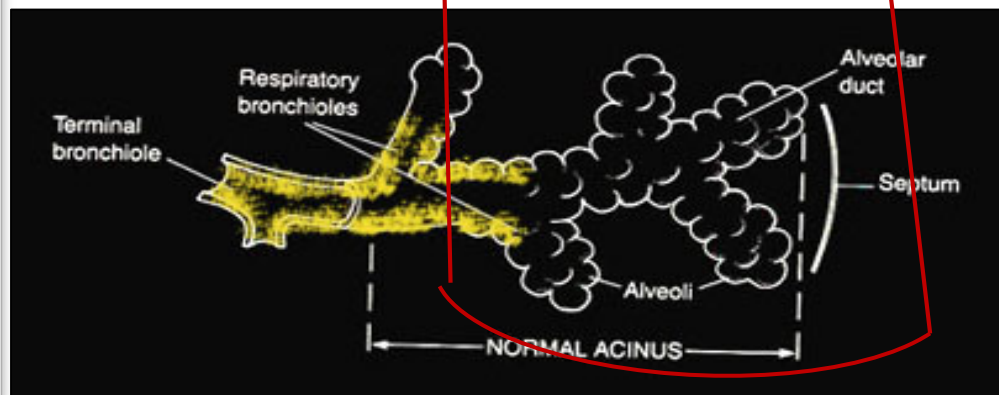
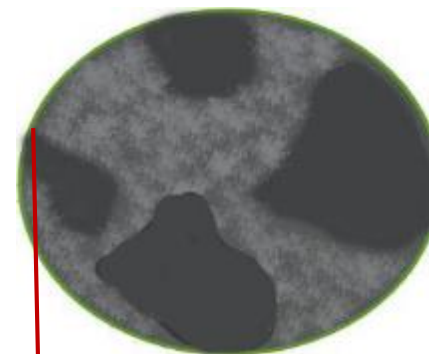


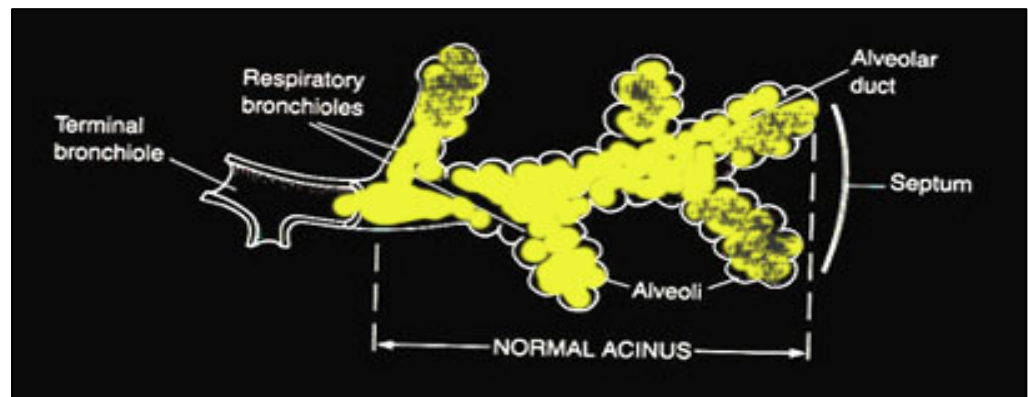
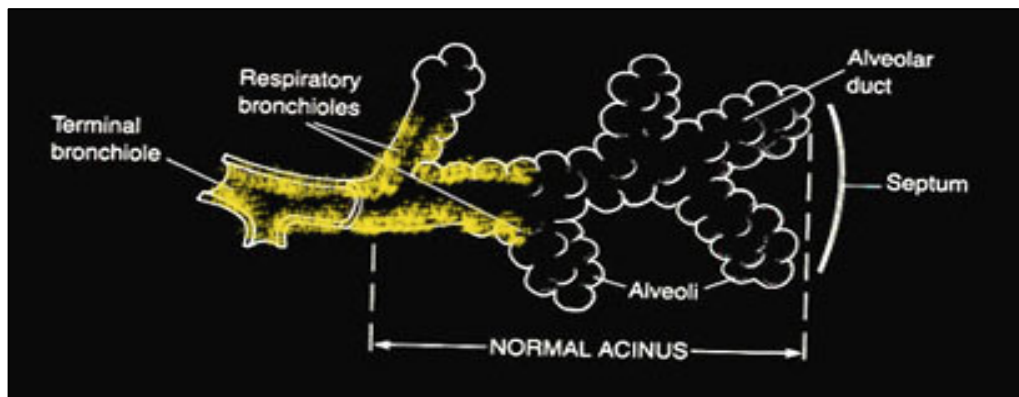
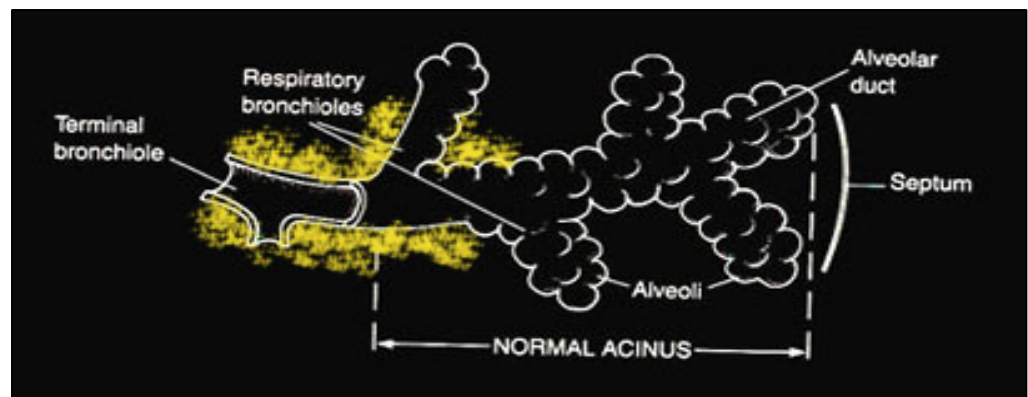
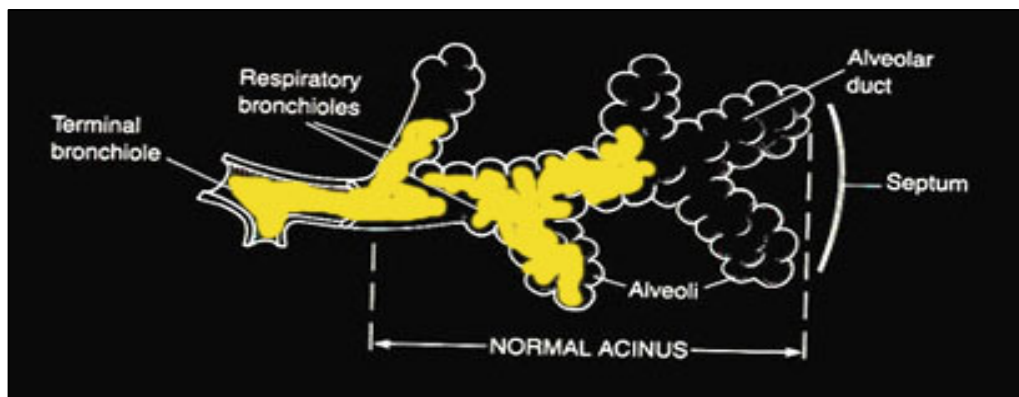
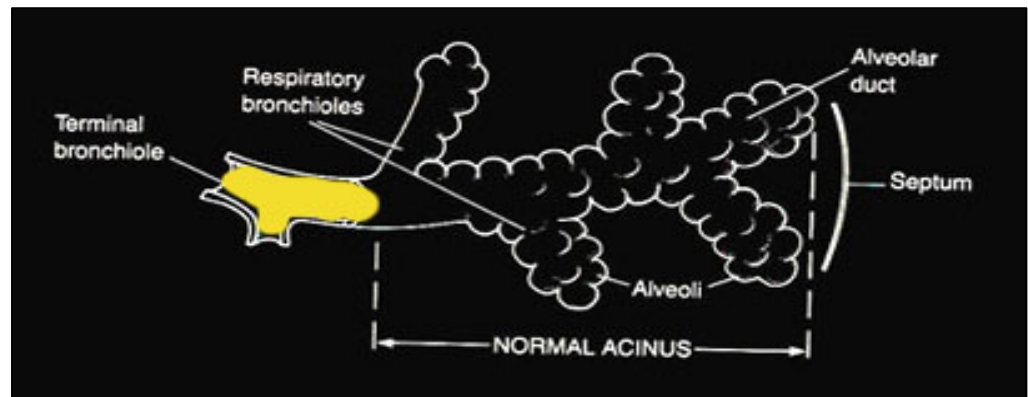
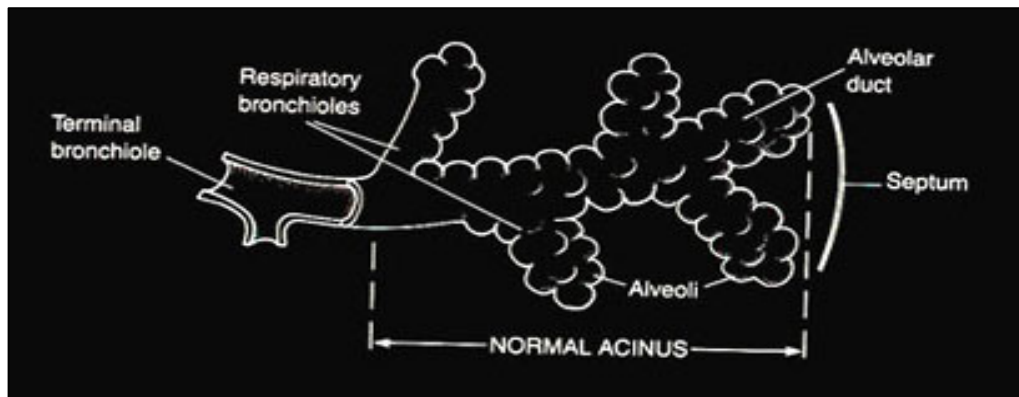
Indirect Signs



Expiratory CT

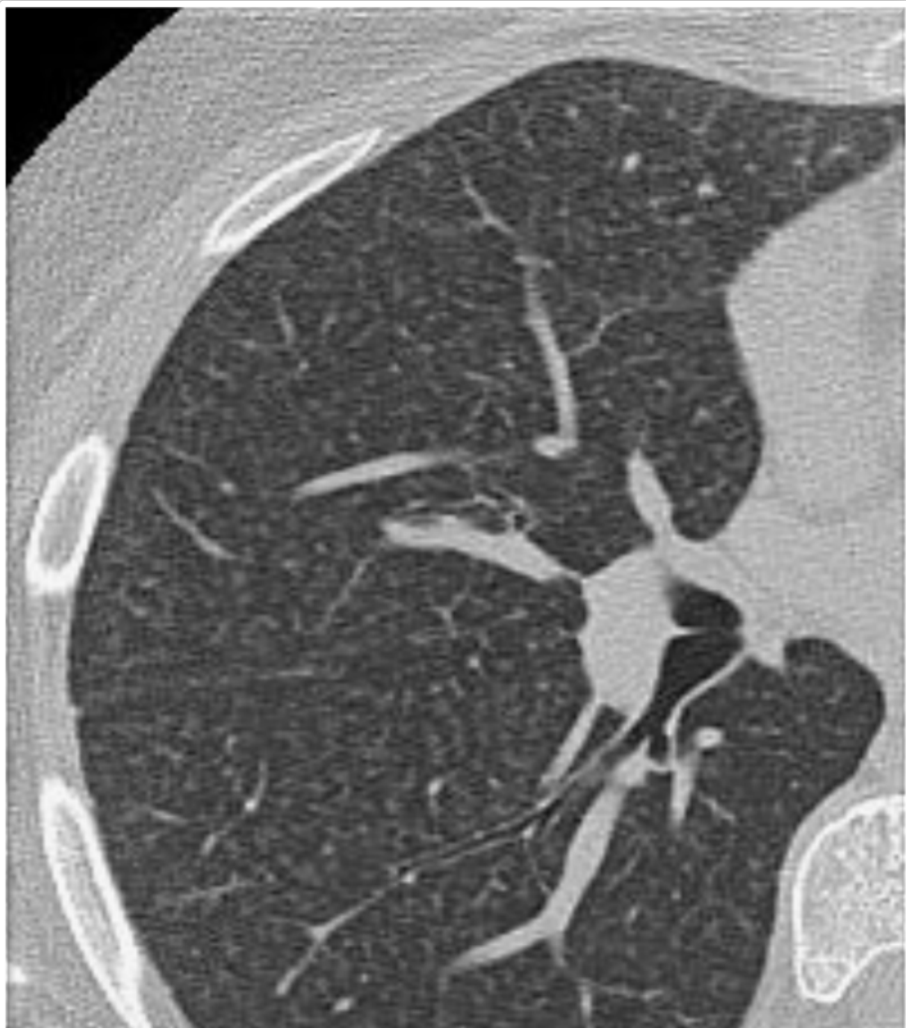
Air Trapping





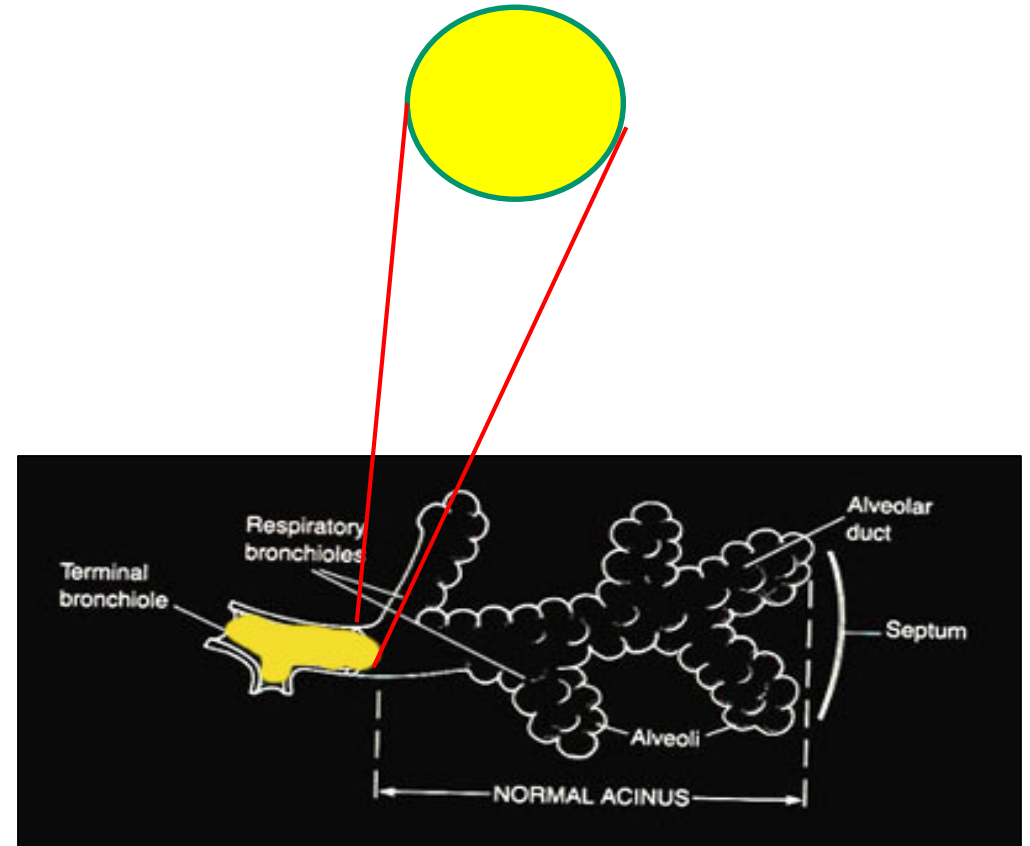
Direct signs

Direct Signs

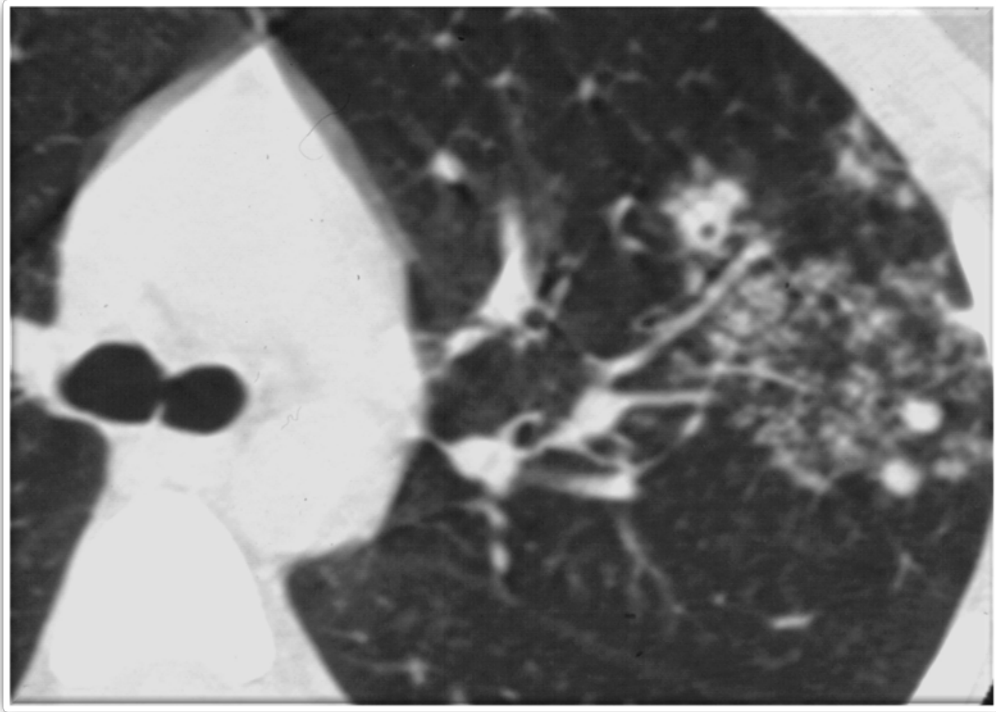


Lymphocytic (follicular)
bronchiolitis

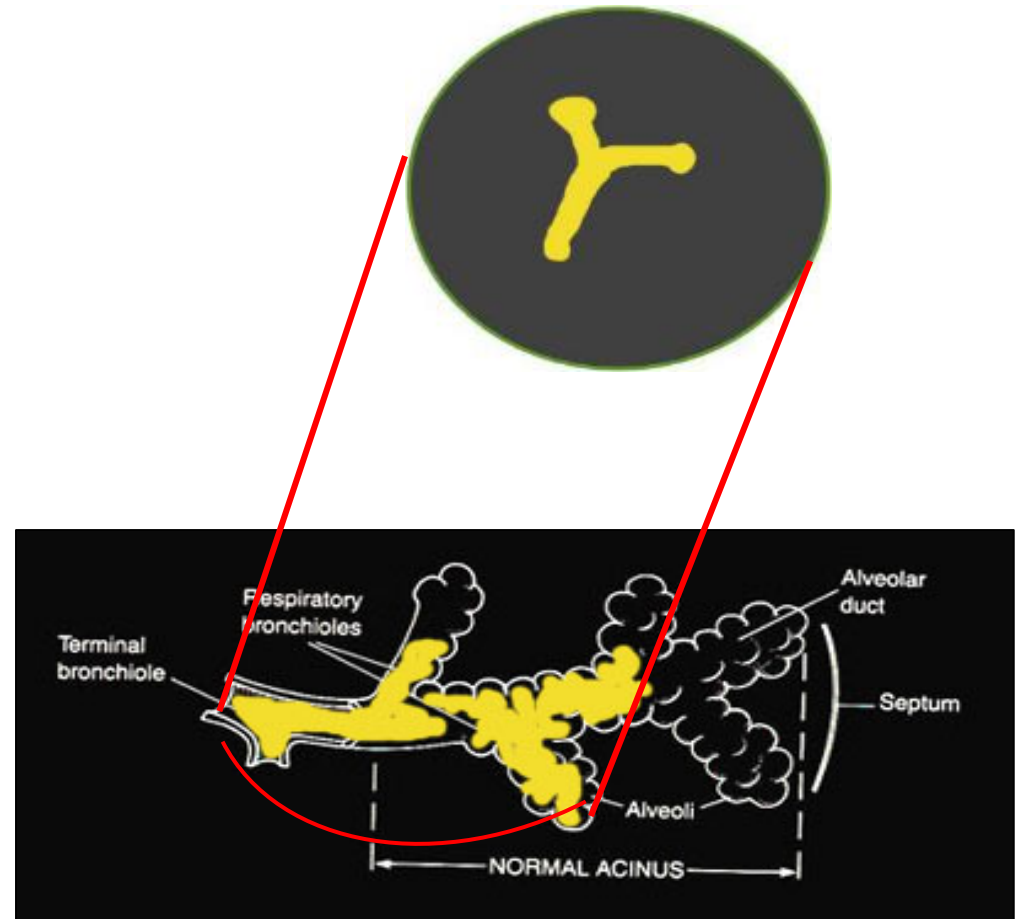
Centrilobular well defined micronodules



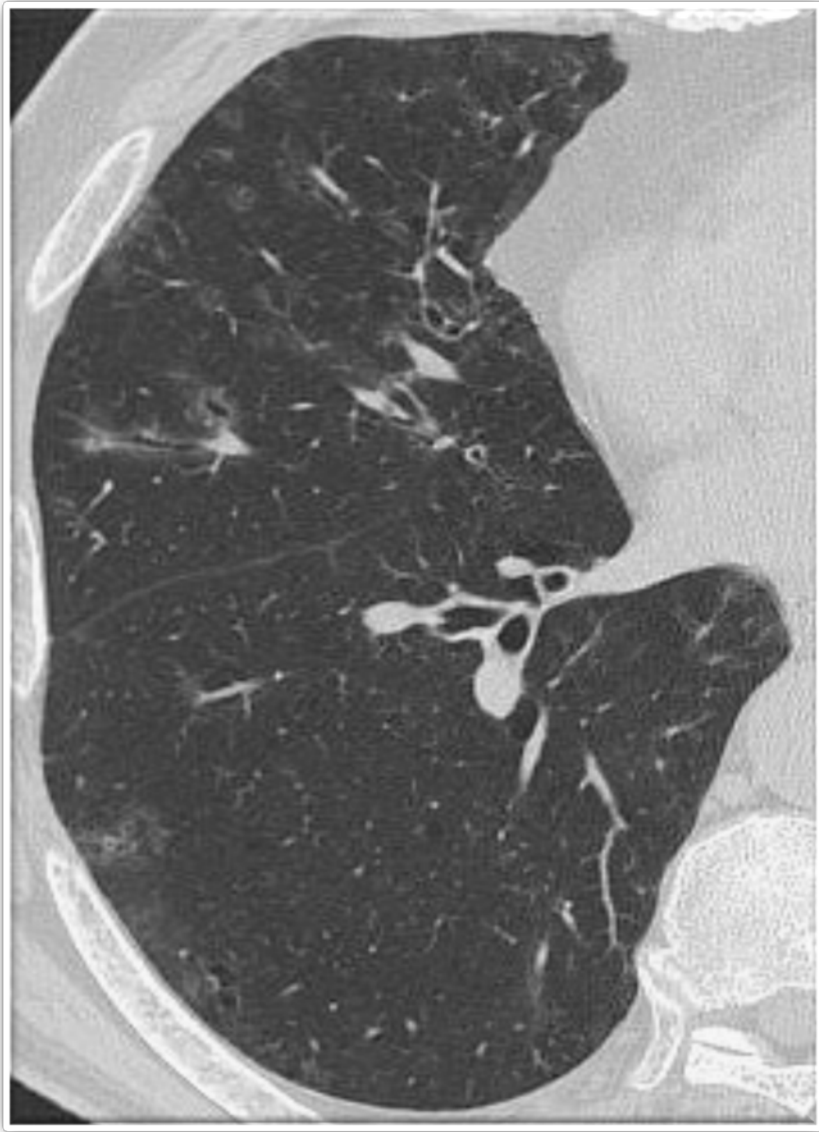
Direct Signs



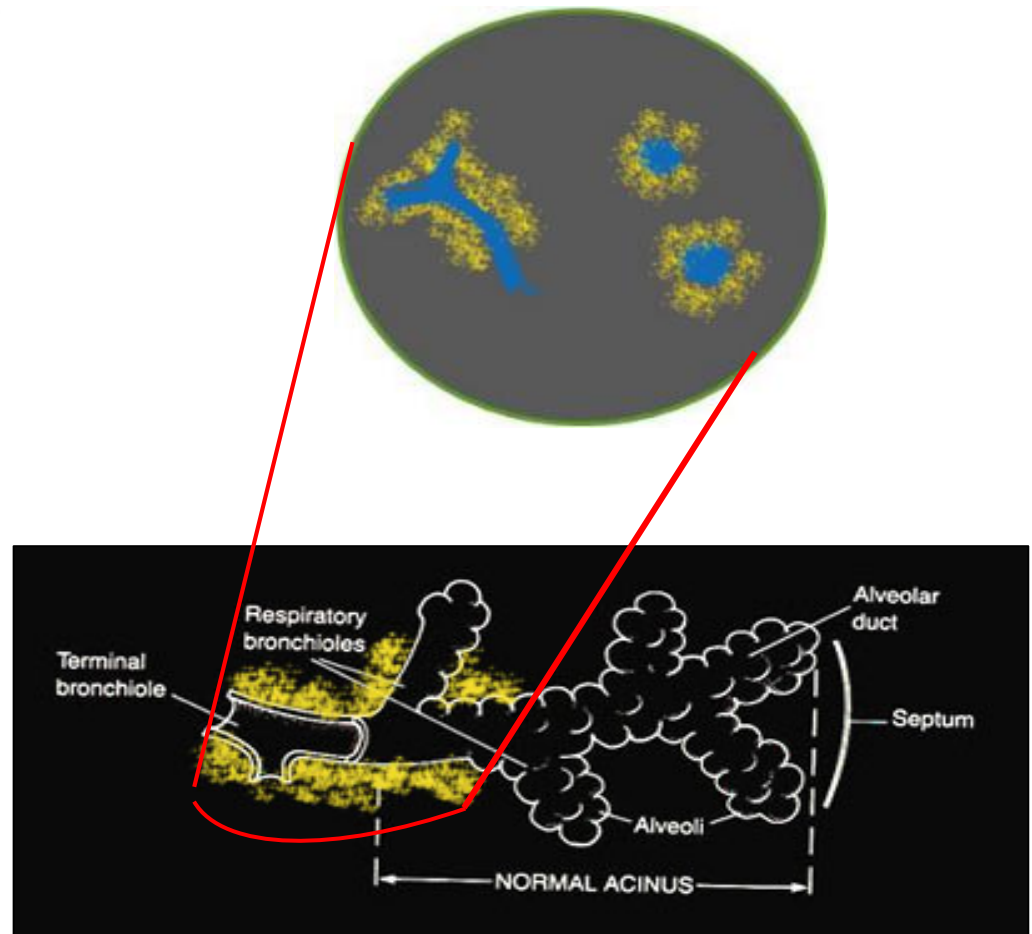
“tree in bud” pattern

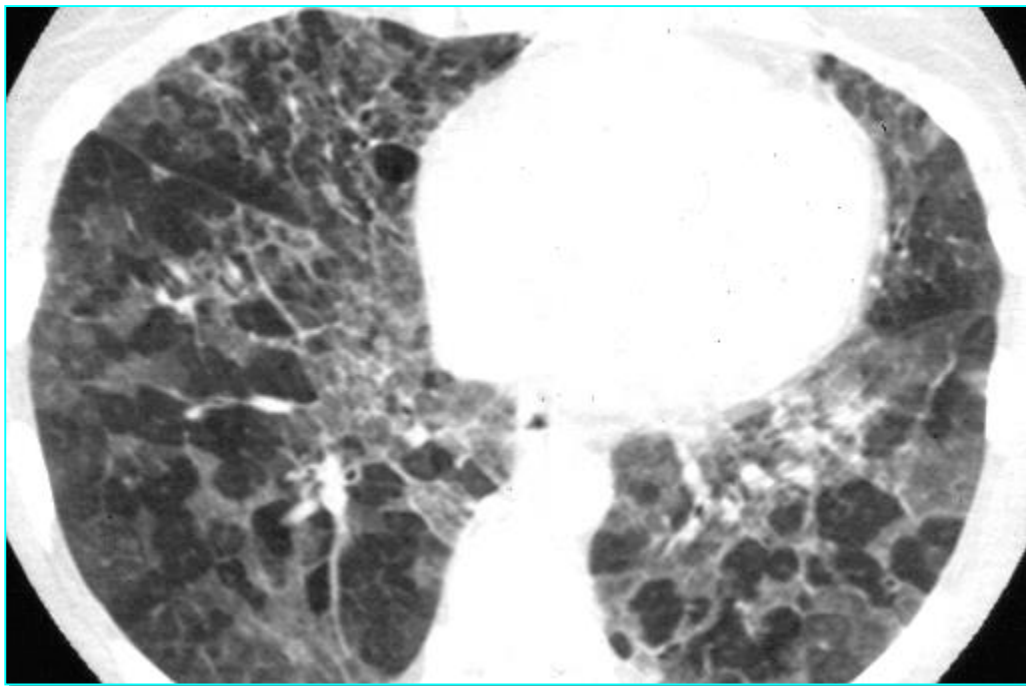
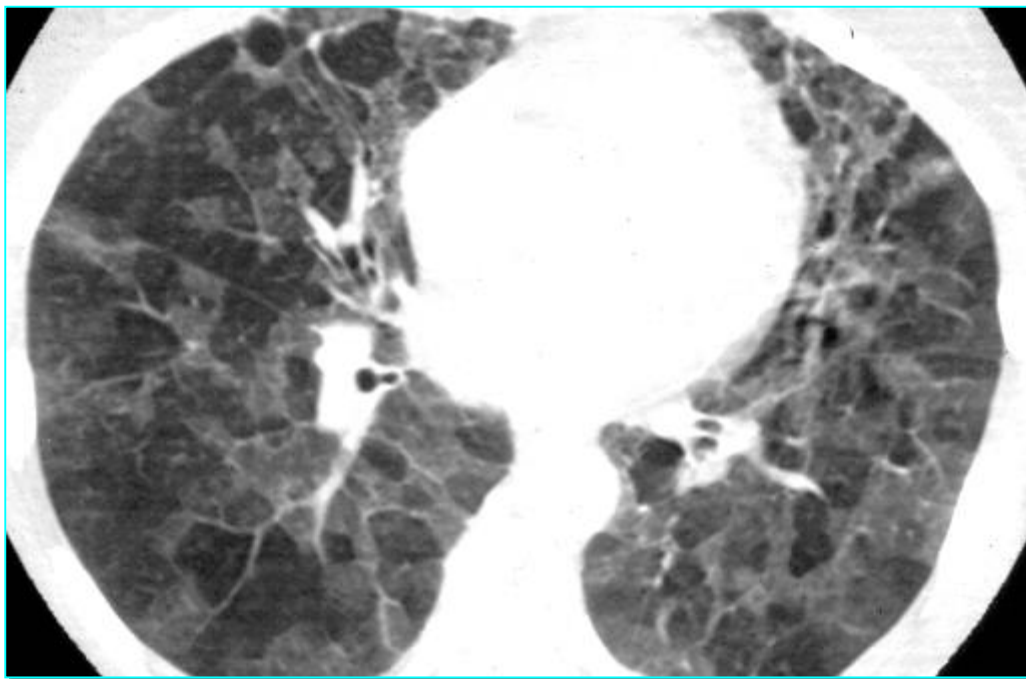


Direct Signs



Centrilobular ground glass nodules



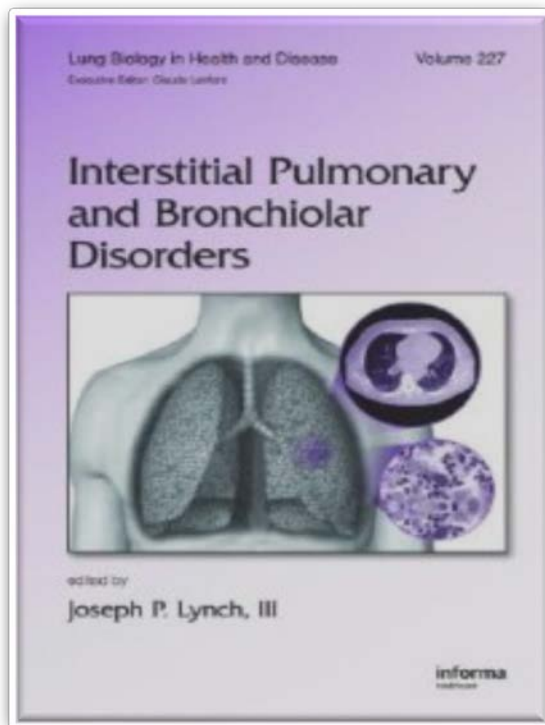


“head cheese” pattern



Table 3 Classification of HRCT Findings in Bronchiolar Diseases

CT features	Type of bronchiolitis	Structures mainly involved
Centrilobular nodules and branching lines (tree in bud)	Cellular bronchiolitis	Membranous and respiratory bronchioles
Centrilobular nodules (with ground-glass attenuation)	Cellular bronchiolitis Bronchiolitis with inflammatory polyps	Respiratory bronchioles Centrilobular airways
Low attenuation (mosaic perfusion) and expiratory air trapping	Cicatricial bronchiolitis Bronchiolitis with inflammatory polyps	Respiratory and membranous bronchioles Membranous bronchioles
Mixed pattern	Cellular bronchiolitis Bronchiolitis with inflammatory polyps, cicatricial bronchiolitis	Respiratory and membranous bronchioles

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Clinical definition of bronchiolitis is still elusive.

- **Signs and symptoms are nonspecific and polymorphous.**
- The course is usually chronic but it may be acute or subacute.
- Pulmonary function tests show more frequently an obstructive impairment but in the early phases can be normal.
- Signs: inspiratory squeaks. Cough in the latest phase of forced expiration
- Specific laboratory markers for bronchiolitis are not yet identified.

Bronchioles: silent zone

Clinical classification of bronchiolitis

- Inhalation bronchiolitis

 - Toxic fume inhalation*

 - Irritant gases and mineral dusts*

 - Organic dusts*

- Infectious and postinfectious bronchiolitis

- Chronic aspiration

- Drug induced bronchiolitis

- Collagen-vascular disease-associated bronchiolitis

- Paraneoplastic pemphigus associated bronchiolitis

- Inflammatory bowel disease associated bronchiolitis

- Post-transplant bronchiolitis

- Neuroendocrine cell hyperplasia with bronchiolar fibrosis

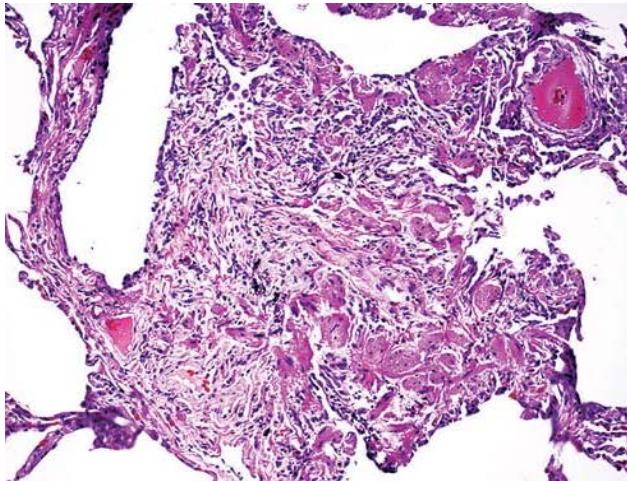
- Diffuse panbronchiolitis

- Cryptogenic bronchiolitis

- Miscellanea
 - Lysinuric protein intolerance*
 - Ataxia-Telangiectasia*
 - Familial form of immunodeficiency*
 - IgA nephropathy*
 - Associated to lichen planus*
 - Stevens–Johnson syndrome*

“fume-related” bronchiolitis

- Toxic and irritant gases and fumes [nitrogen dioxide, sulfur dioxide, ammonia, chlorine, phosgene, butter flavorings (diacetyl)]
- Grain dusts
- Mineral dusts (talc, stearate of zinc powder, asbestos, iron oxide, aluminium oxide...)
- Organic dusts (EAA,)
- Free-base cocaine
- Incinerator fly ash
- Cigarette smoke
- Thionyl chloride



Clinical Pathology Workshop Summary

Nylon Flock–Associated Interstitial Lung Disease

WILLIAM L. ESCHENBACHER, KATHLEEN KREISS, M. DIANE LOUGHEED, GLENN S. PRANSKY, BRIAN DAY, and ROBERT M. CASTELLAN

OPEN ACCESS Freely available online

PLOS ONE

Increased Respiratory Disease Mortality at a Microwave Popcorn Production Facility with Worker Risk of Bronchiolitis Obliterans

Cara N. Halldin^{1,2*}, Eva Suarthana^{1,2}, Kathleen B. Fedan², Yi-Chun Lo^{1,3}, George Turabelidze³, Kathleen Kreiss²

The New England Journal of Medicine

CLINICAL BRONCHIOLITIS OBLITERANS IN WORKERS AT A MICROWAVE-POPCORN PLANT

KATHLEEN KREISS, M.D., AHMED GOMAA, M.D., Sc.D., GREG KULLMAN, Ph.D., KATHLEEN FEDAN, B.S., EDUARDO J. SIMOES, M.D., M.Sc., M.P.H., AND PAUL L. ENRIGHT, M.D.

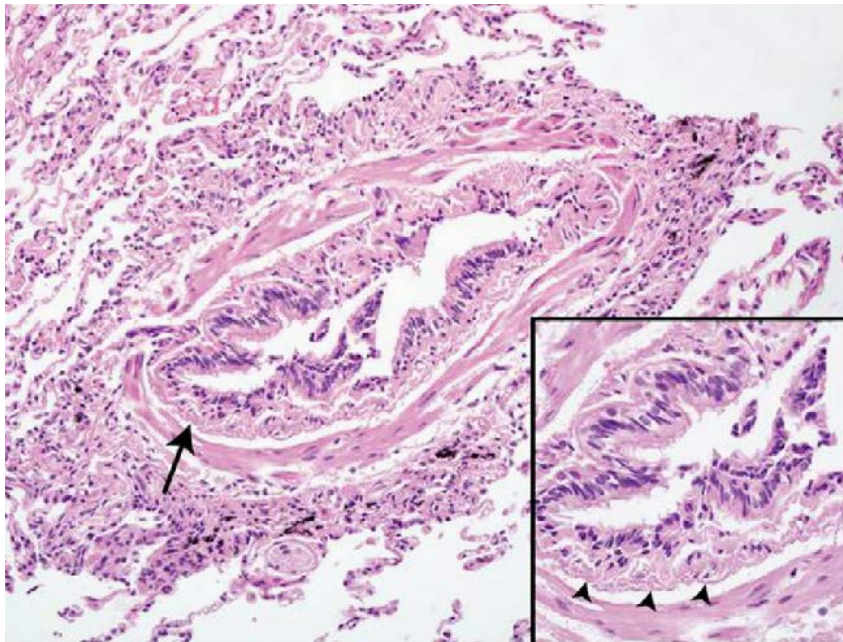


ELSEVIER

respiratoryMEDICINE

An International collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients

Mostafa Ghanei^{a,*}, Henry D. Tazelaar^b, Marco Chilosi^c, Ali Amini Harandi^a,
Mohammadreza Peyman^a, Hassan Mohammad Hosseini Akbari^a,
Hassan Shamsaei^a, Moslem Bahadori^d, Jafar Aslani^a, Azam Mohammadi^e

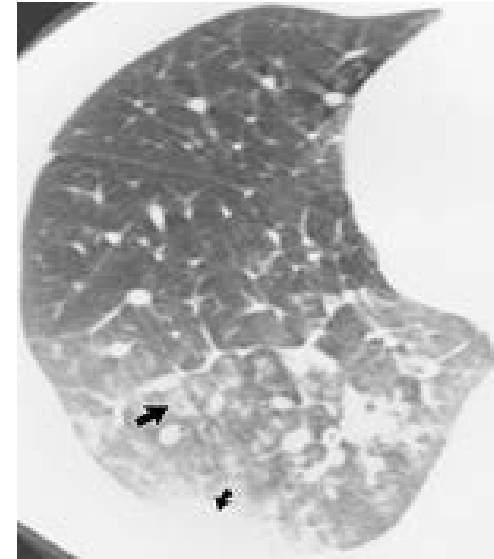
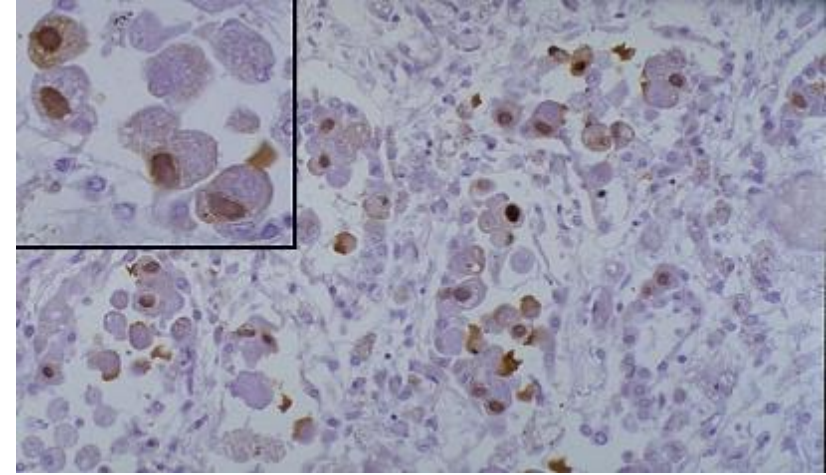


Infectious and post-infectious bronchiolitis in adults

Cases due to *Adenovirus* (serotypes 3, 7 and 21), *HHV*, *RSV*, *CMV*, *Mycoplasma pneumoniae*, *Mycobacteria*, *Bordetella pertussis*, influenza have been described.

Uncommon causes of infectious bronchiolitis are: *Legionella pneumophila*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Aspergillus* or *Mucor*, *Nocardia*, Rubeola, Measles, *Enteroviruses*, HIV, Malaria, *Cryptosporidium* species, Microsporidia (*Encephalitozoon hellem*)

Diagnosis: HRCT, Serology, BAL,
Microbiological investigations,
.....Biopsy



Swyer–James or McLeod syndrome

- Swyer–James syndrome results from viral injury to the lung (before the age of 8 years)
- Unilateral transradiancy on plain chest radiography in Swyer–James syndrome reflects a combination of hypoplasia of the pulmonary vasculature and obliterative bronchiolitis
- The affected lung is small or normal in volume

Diffuse bronchiolar disease due to chronic occult aspiration.

Mayo Clin Proc. 2006 , 81:172-6.

Mayo Clin Proc 2018, 93:752-762

*Mean age 50 years (age range, 41-59 years)

*M/ 1:1

*Persistent dyspnea, cough, and lung infiltrates.

*History of gastroesophageal reflux

*HRCT: bronchial wall thickening/centrilobular nodules/tree in bud opacities

*Lung biopsy: bronchiolocentric organizing pneumonia with giant cells that contained material consistent with food

Drug induced bronchiolitis

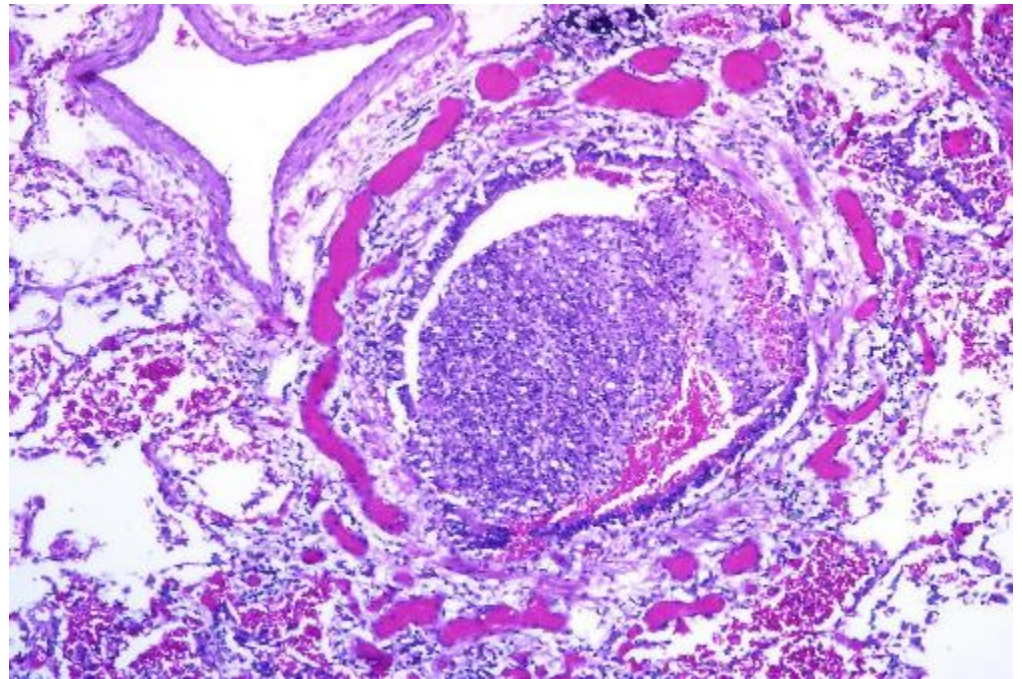
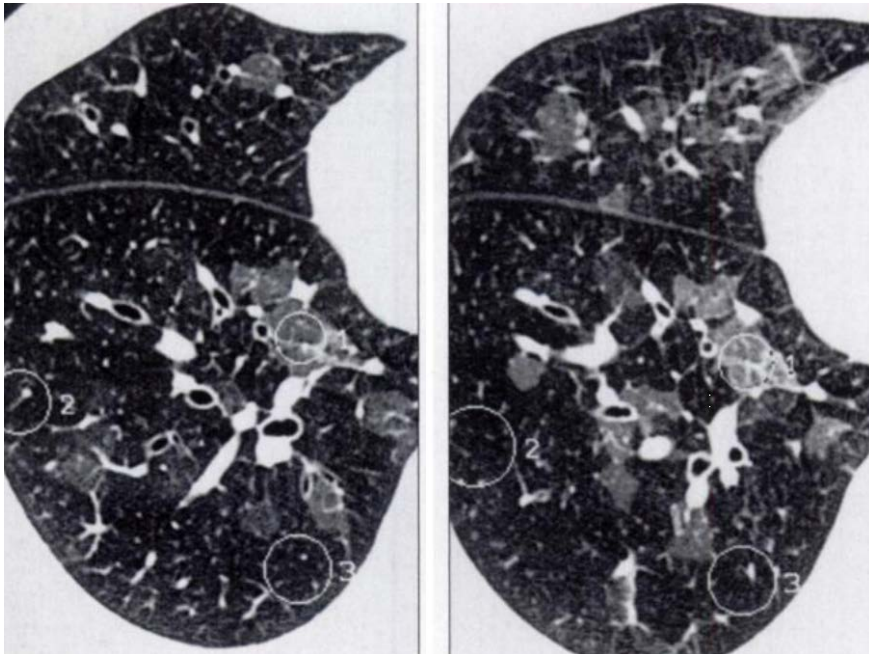
Drugs related bronchiolar damage more frequently presents with a clinical-radiological pattern and pathologic findings of BOOP.

Obstruction than did type 1. Scores for quantitative attenuation generated by computer were helpful in assessing air-trapping and correlating it with pulmonary function findings may apply to patients with bronchiolitis obliterans from other causes.

Bronchiolitis obliterans (also known as constrictive bronchiolitis) is a rare disease of respiratory bronchioles characterized by submucosal and peribronchiolar fibrosis [1, 2]. Because patients with

lution CT scans (i.e., diffuse bronchial air-trapping [mosaic attenuation]) are regardless of the cause of disease [4]. Although the relationship between high resolution CT abnormalities and pulmonary

AJR 1997



Drug induced bronchiolitis (case reports –short series)

- D-Penicillamine
- Gold
- Tiopronin
- Busulfan
- Carmustin
- Lomustin
- Topotecan
- Imatinib
- Immune check point inhibitors



Iatrogenic pulmonary lesions

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^b Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital du Bocage Centre Hospitalier Universitaire (CHU) de Bourgogne, Dijon, France

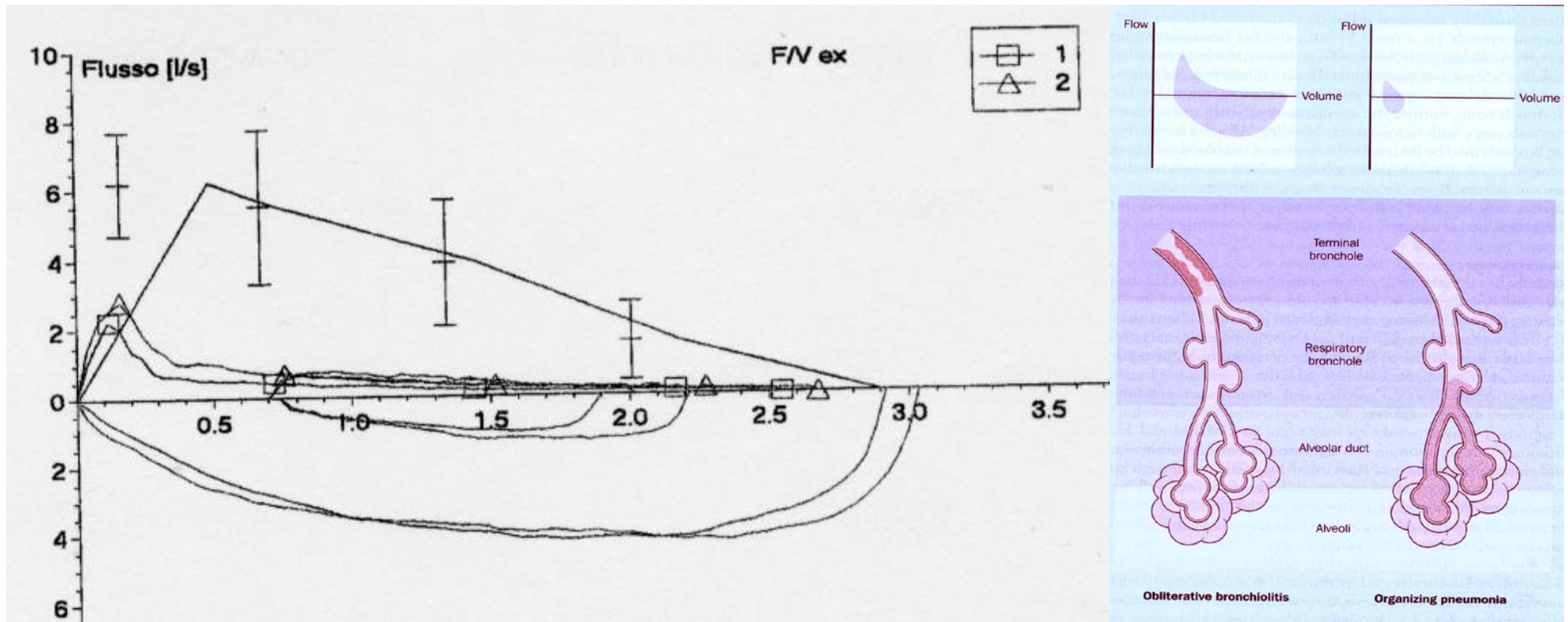
^c UFR des Sciences de Santé, Université de Bourgogne, Dijon, France

^d INSERM U866, Faculté de Médecine, Dijon, France



Collagen-vascular disease and bronchiolitis

Rarely dyspnea and cough often associated with inspiratory rales and mid-inspiratory squeaks are observed in middle-aged women with seropositive rheumatoid arthritis (or less frequently in patients with juvenile rheumatoid arthritis, SLE, Scleroderma, Bechet's disease) and/or evidence of advanced autoimmune exocrinopathy (Sjogren's syndrome)

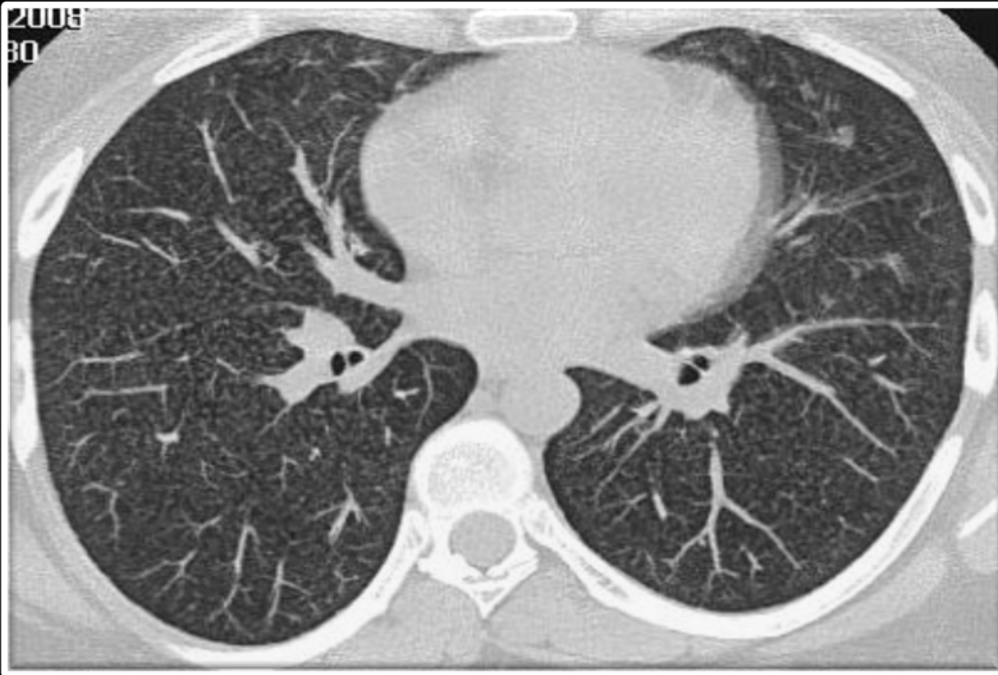
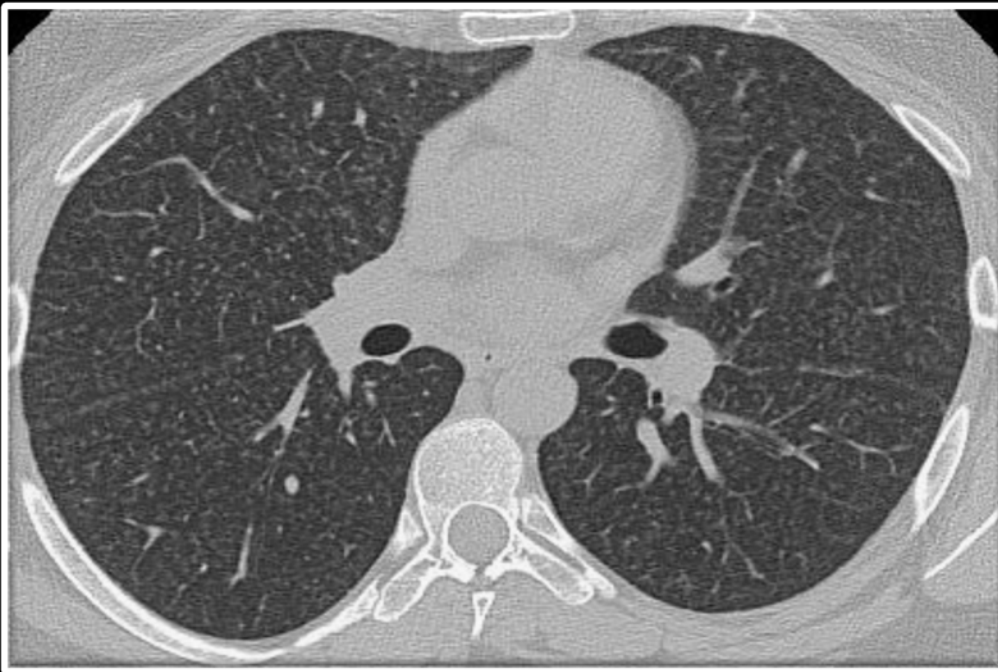




**BRONCHIOLITIS OBLITERANS
AND RHEUMATOID ARTHRITIS**

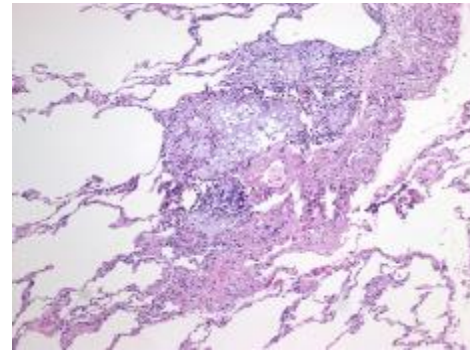
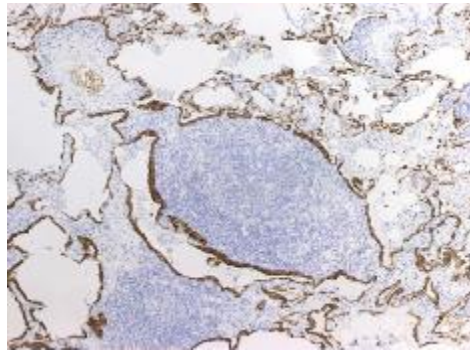


Sjogren syndrome

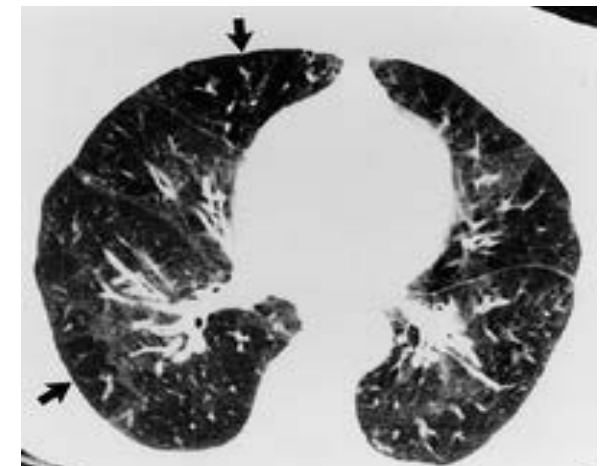
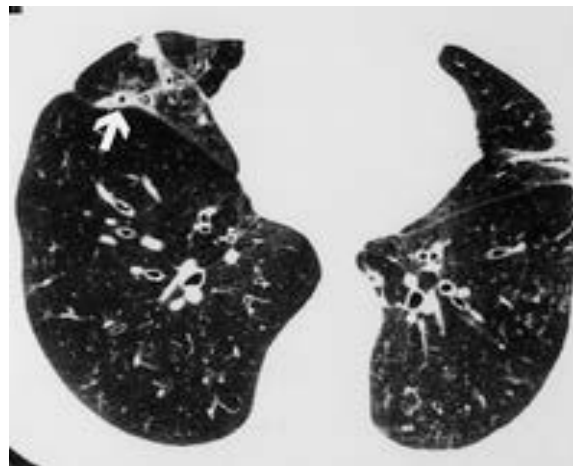


Collagen-vascular disease and bronchiolitis

Histology: cellular/follicular bronchiolitis; cicatritial bronchiolitis/DPB pattern



HRCT shows bilateral patchy areas of low attenuation or centrilobular nodules and branching lines. Bronchiectasis can also be documented



Constrictive bronchiolitis associated with paraneoplastic autoimmune multi-organ syndrome

FABIEN MALDONADO,¹ MARK R. PITTELKOW² AND JAY H. RYU¹

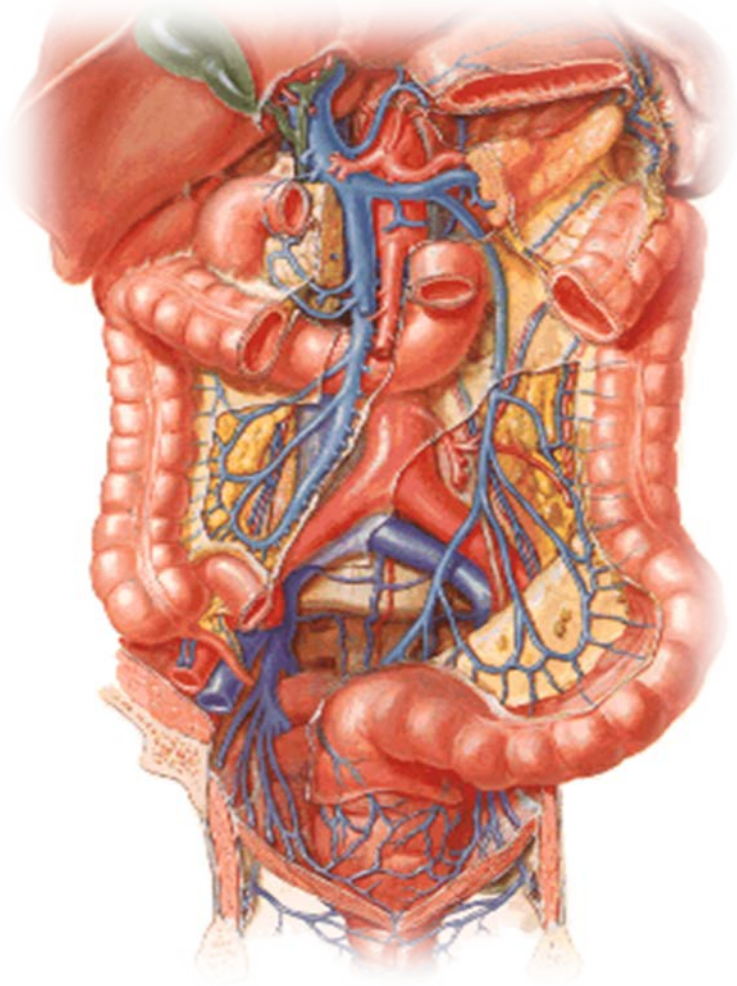
Respirology 2008

Table 2 Three patients with PAMS-associated constrictive bronchiolitis

Case no.	Age (years), gender	Smoking history	Underlying neoplasm	Respiratory symptoms	Chest CT	Pulmonary function	Outcome [†]
1	33, female	No	Castleman’s disease	Dyspnoea	Diffuse air-trapping, minimal hazy infiltrates	Very severe obstruction	Died from respiratory failure at 18 months
2	56, male	No	T-cell lymphoma	Dyspnoea, productive cough	Bilateral bronchiectasis, diffuse air trapping	Very severe obstruction	Died from pneumonia and sepsis at 13 months
3	56, male	Past	Chronic lymphocytic leukaemia	Dyspnoea	Diffuse air trapping, bronchiectasis in the right lower lobe and mediastinal and hilar lymphadenopathy	Severe obstruction	Alive at 16 months

[†] Time interval for outcome is from the date of diagnosis for paraneoplastic autoimmune multi-organ syndrome.
NA, not available.

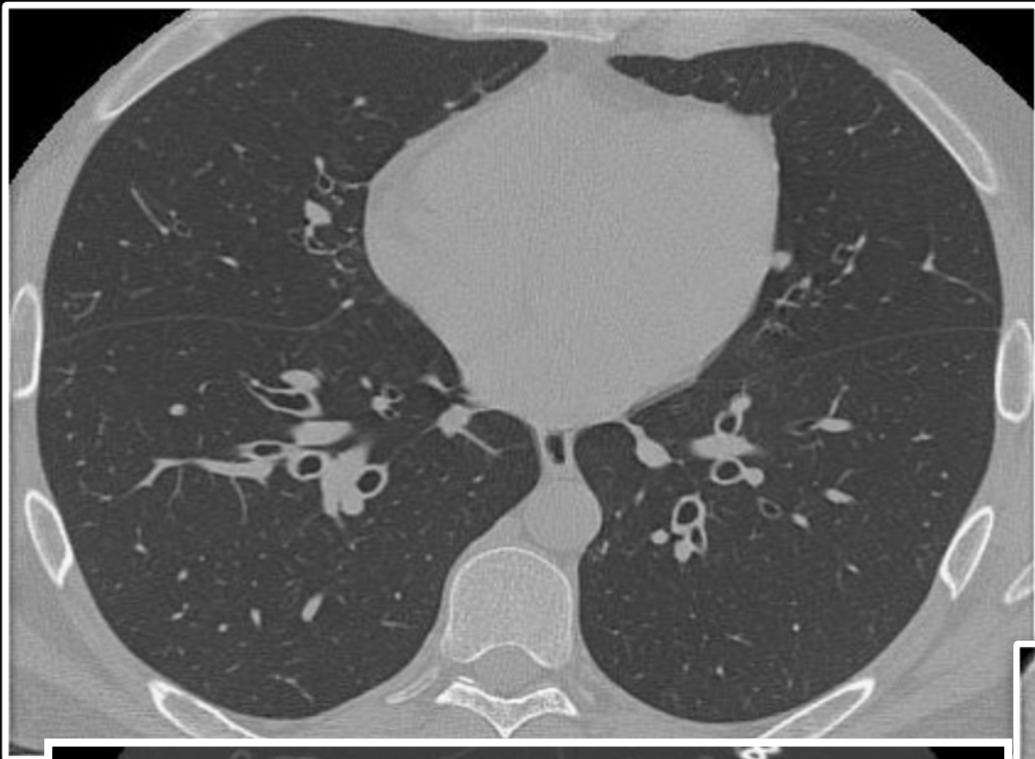




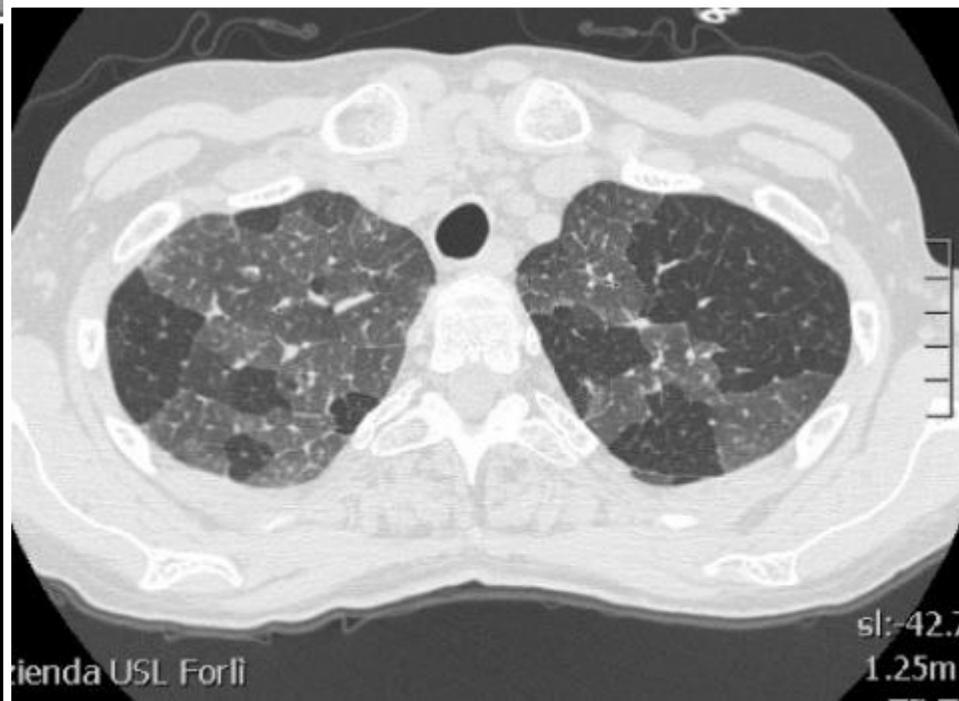
Pulmonary complications occur in an estimated 0.21% of patients with **IBD**, ulcerative colitis being most often associated with lung problems.

The most common presentation is large airway disease, such as tracheobronchitis, chronic bronchitis, or bronchiectasis. Bronchiolitis is extremely rare.

Cellular bronchiolitis with intraluminal accumulation of neutrophils and chronic inflammation in the wall, cicatricial bronchiolitis, and epithelial ulceration, aspects similar to that described in diffuse panbronchiolitis, have been reported in patients with ulcerative colitis.



Male, 34 y/o,
Ulcerative Colitis
Dyspnea



Post-transplant bronchiolitis obliterans syndrome (BOS)

- Allogeneic bone marrow transplant (<10%)
- Lung transplant (50-80% at 5 years)

TABLE 3 Grading (staging) of bronchiolitis obliterans syndrome (BOS)[#]

BOS Grade	Spirometry % of baseline [†]	
	1993 Classification	2002 Classification
0	FEV ₁ ≥ 80%	FEV ₁ >90% and FEF _{25-75%} >75%
0-p ⁺	Not included	FEV ₁ 81–90% and/or FEF _{25-75%} ≤ 75%
1	FEV ₁ 66–80%	FEV ₁ 66–80%
2	FEV ₁ 51–65%	FEV ₁ 51–65%
3	FEV ₁ ≤ 50%	FEV ₁ ≤ 50%

The peak incidence is between 7 and 12 months

Allogeneic BM-stem cells
transplant: BO 10% of Pts

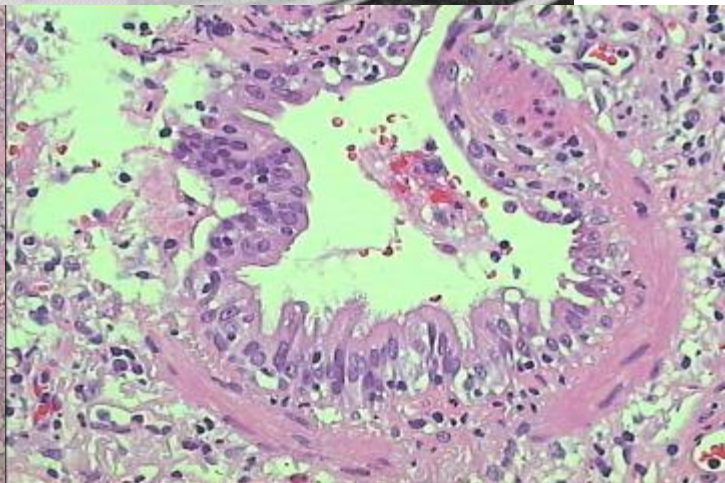
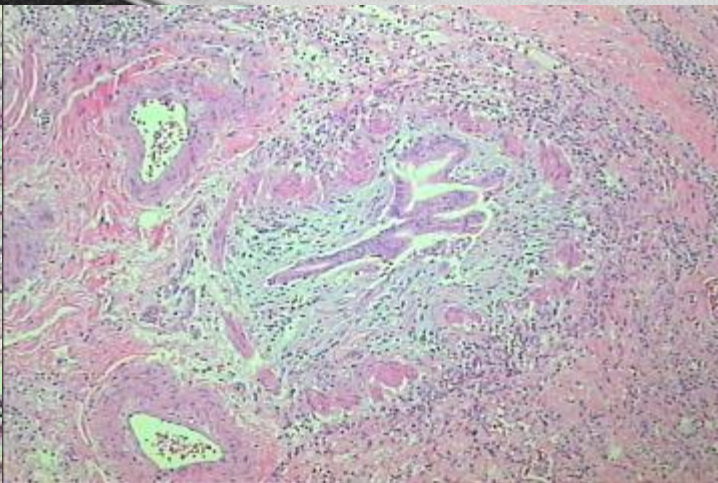
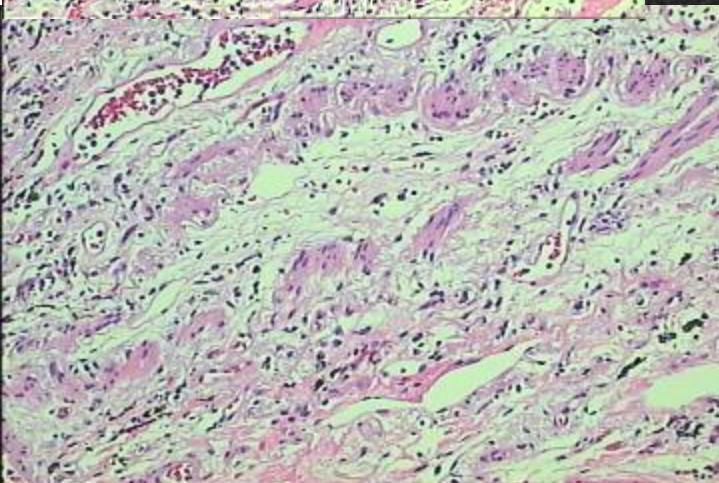
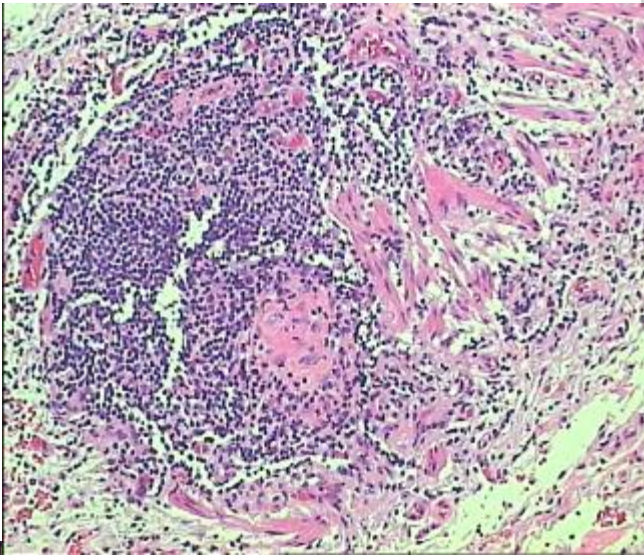
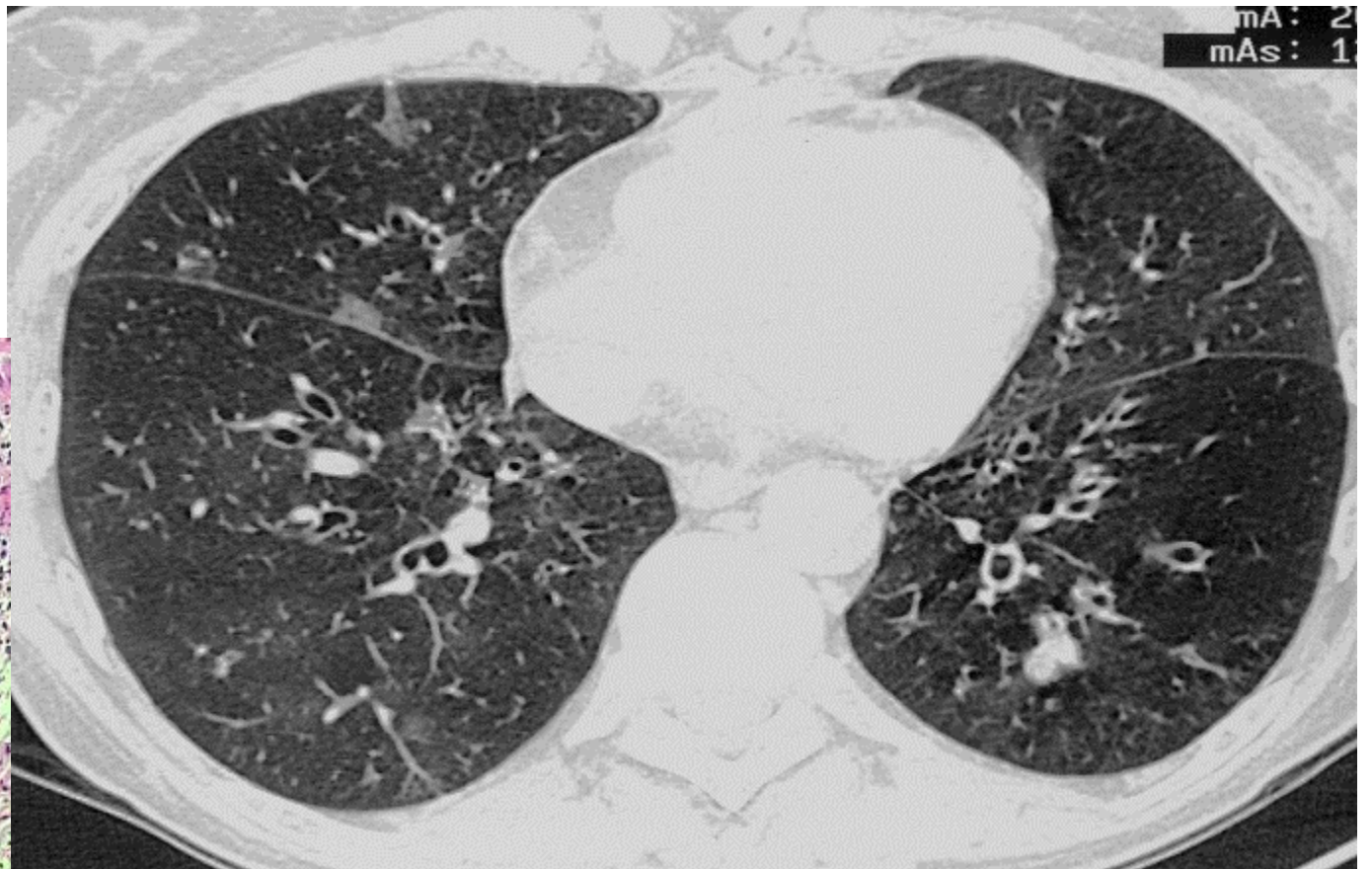


TABLE 7 Risk factors associated with bronchiolitis obliterans syndrome

Primary graft dysfunction (PGD)

Acute cellular rejection

Lymphocytic bronchiolitis

Humoral rejection (*e.g. de novo* anti-human leukocyte antigen antibodies)

Gastro-oesophageal reflux and microaspiration

Infection

Viral

Bacterial

Fungal

Persistent neutrophil influx and sequestration (bronchoalveolar lavage neutrophilia)

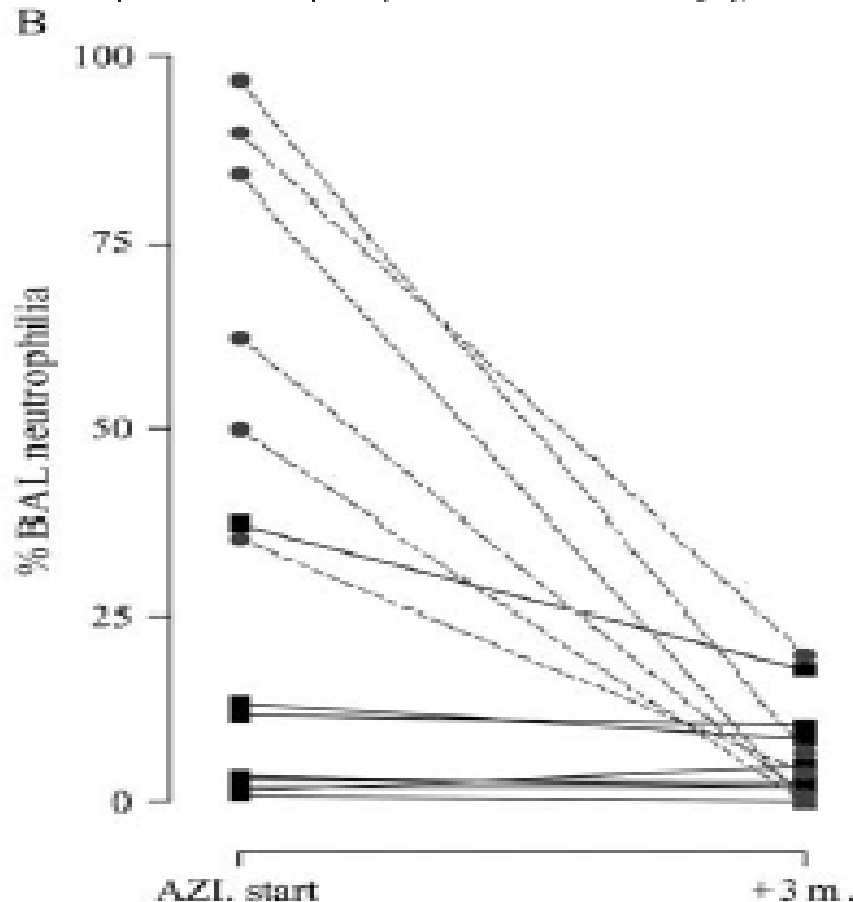
Autoimmunity (collagen V sensitisation)

MACROLIDES AND BRONCHIOLITIS OBLITERANS SYNDROME

Azithromycin Reduces Airway Neutrophilia and Interleukin-8 in Patients with Bronchiolitis Obliterans Syndrome

Geert M. Verleden*, Bart M. Vanaudenaerde*, Lieven J. Dupont, and Dirk E. Van Raemdonck

Departments of Respiratory Disease and Thoracic Surgery, and Lung Transplantation Unit, University Hospital Gasthuisberg, Leuven, Belgium



**Azithromycin 250 mg/d for 5 d. then
250 mg 3 t/wk**

Effect of Azithromycin in Airflow decline-free survival
After Allogeneic Hematopoietic Stem Cell Transplant: the
ALLOZITHRO Randomized Clinical Trial
Bergeron A, et al. JAMA 2017, 318: 557-566

Among pts undergoing allogeneic HSCT for hematological malignancy, early administration of azithromycin resulted in worse airflow decline-free survival than did placebo.

Table 3. Emerging phenotypes of CLAD: key features*

Entity	Classic BOS	NRAD	RAS
Time of Onset	<ul style="list-style-type: none">• Late (usually 2-3 years post-transplant, but may occur earlier)• ≈80% prevalence at 10 years post-transplant	<ul style="list-style-type: none">• Usually occurs early (e.g. 3-6 months post-transplant)	<ul style="list-style-type: none">• Tends to occur later but may occur at any time• Accounts for approximately 1/3 of CLAD cases
Physiology	<ul style="list-style-type: none">• Obstructive (FEV1 ≤80% of stable baseline value)	<ul style="list-style-type: none">• Obstructive (FEV1 ≤80% of stable baseline value)	<ul style="list-style-type: none">• Restrictive (e.g. FEV1 ≤80% and TLC ≤90% of stable baseline values)
HRCT Imaging	<ul style="list-style-type: none">• Air trapping often present• No/minimal infiltrates• ± bronchiectasis	<ul style="list-style-type: none">• Changes of bronchiolitis (“tree-in-bud”, thickened airway walls, peri-bronchiolar infiltrates often present)• ± air trapping	<ul style="list-style-type: none">• Parenchymal infiltrates usually present (DAD often present)• ± bronchiectasis• ± air trapping
Histopathology	<ul style="list-style-type: none">• OB (difficult to diagnose via transbronchial biopsy)	<ul style="list-style-type: none">• Cellular bronchiolitis	<ul style="list-style-type: none">• Fibrosis (thickened septae and pleurae)• DAD often present• ± OB
Clinical course	<ul style="list-style-type: none">• Typically progressive but may stabilize• Recipients may have coexistent chronic bacterial infection	<ul style="list-style-type: none">• High likelihood of significant response to azithromycin (may no longer meet criteria for persistent BOS if recipient is an azithromycin responder)	<ul style="list-style-type: none">• Tends to be relentlessly progressive• Significantly worse prognosis than BOS
Other	<ul style="list-style-type: none">• Usually responds poorly to pharmacologic therapies• Can have outcome similar to primary transplant following lung retransplantation	<ul style="list-style-type: none">• BAL neutrophilia (e.g. ≥15% on differential cell count) correlates with response to azithromycin therapy	<ul style="list-style-type: none">• Increased risk of RAS if new onset DAD detected >90 days post-transplant

*Infection, other pathologies (e.g. acute cellular rejection, lymphocytic bronchiolitis, antibody-mediated rejection), and/or other causes of allograft dysfunction (e.g. significant gastroesophageal reflux, pleural disorders, anastomotic dysfunction, obesity, thromboembolic disease, recurrent primary lung disease, etc.), must be ruled out.

Abbreviations: BAL = bronchoalveolar lavage; BOS = bronchiolitis obliterans syndrome; CLAD = chronic lung allograft dysfunction; DAD = diffuse alveolar damage; NRAD = neutrophilic reversible allograft dysfunction; OB = obliterative bronchiolitis; RAS = restrictive allograft syndrome

DIFFUSE IDIOPATHIC PULMONARY NEUROENDOCRINE HYPERPLASIA w/t BRONCHIOLITIS

In 1992 Aguayo et al reported 6 patients, all nonsmokers, with moderate chronic airflow obstruction, progressive dyspnea.

•Women • airflow obstruction • bronchiolar neuroendocrine

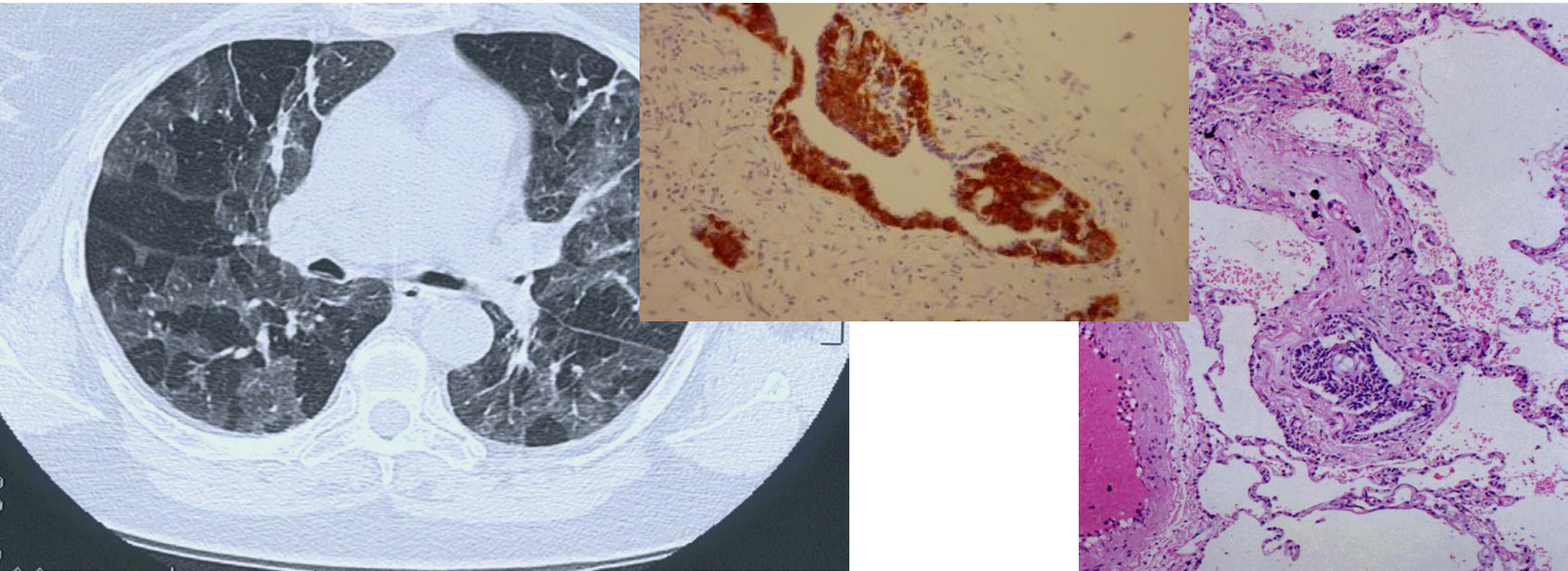


TABLE 1] Subject Characteristics

Characteristic	Value
No. subjects	30
Sex	
Male	0 (0)
Female	30 (100)
Tobacco use	
Former	11 (37)
Never	19 (63)
Median (range) age at diagnosis, y	62 (45-75)
Symptoms prior to diagnosis	
Cough	8 (27)
< 5 y	1 (3)
5-10 y	0 (0)
> 10 y	7 (23)
Dyspnea	6 (20)
< 5 y	3 (10)
5-10 y	1 (3)
> 10 y	2 (7)
Combination	13 (43)
< 5 y	3 (10)
5-10 y	3 (10)
> 10 y	7 (23)
Diagnosis prior to DIPNECH	
Asthma	12 (40)
COPD	3 (10)
Bronchiolitis	4 (13)
No diagnosis given	8 (27)
Records unavailable	3 (10)
Pulmonary function at diagnosis	
FEV ₁ , % predicted	49.8 ± 23.9
FVC, % predicted	59.1 ± 19.4
FEV ₁ /FVC	63.4 ± 14.0
RV, % predicted	223.6 ± 97.9
Dlco, % predicted	74.7 ± 17.2
Treatment	
Oral steroids	14 (46)
Inhaled steroids	20 (67)
Octreotide LAR	11 (37)
Resection of a carcinoid	9 (30)

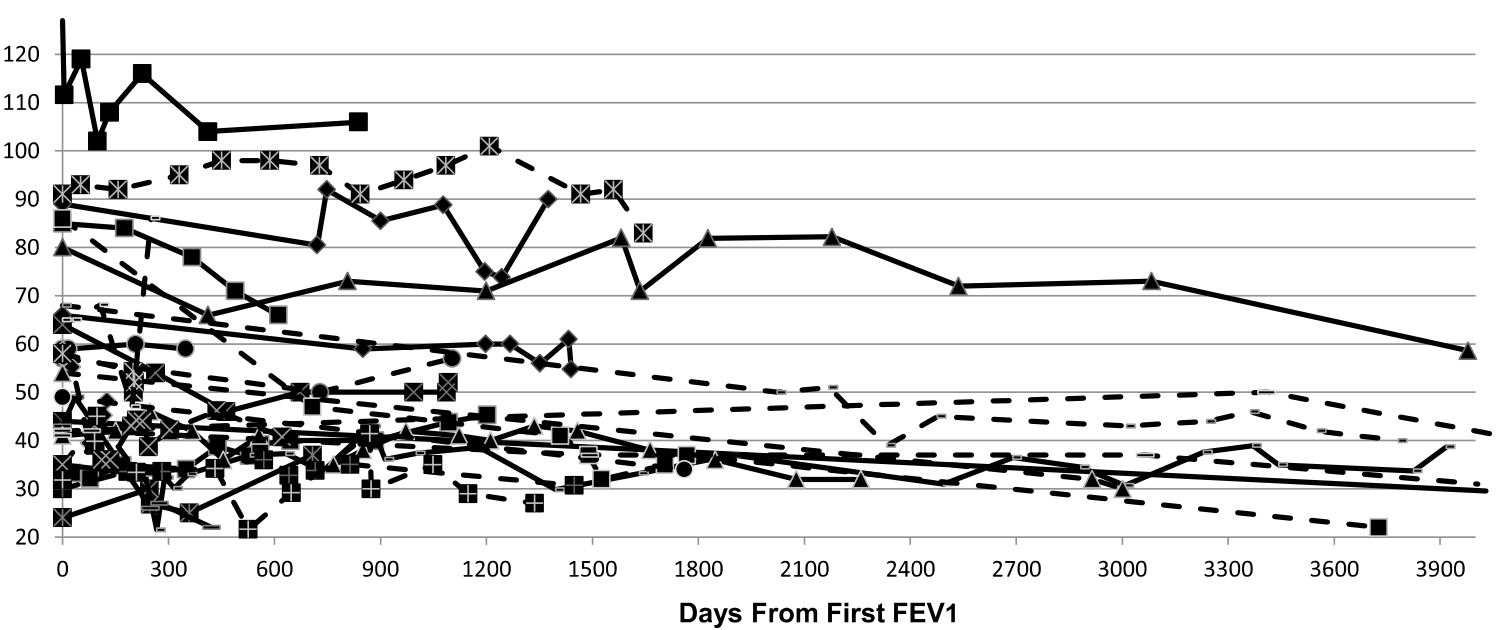


TABLE 4] Proposed Diagnostic Criteria for DIPNECH

Major Criteria	Surgical Lung Biopsy	Per World Health Organization Criteria ^a
Minor criteria	1. Clinical presentation	Woman, aged 45-67 y, cough ± dyspnea for 5-10 y
	2. Pulmonary function	Increased RV, TLC, fixed obstruction, low DLco that corrects with VA
	3. High-resolution CT scan	Diffuse pulmonary nodules 4-10 mm, > 20 nodules, mosaic attenuation or air trapping > 50% of lung
	4. Transbronchial biopsy	Proliferation of pulmonary neuroendocrine cells
	5. Serum markers	Elevated serum chromogranin A levels

TLC = total lung capacity; VA = alveolar volume. See Table 1 legend for expansion of other abbreviations.
^aGeneralized proliferation of pulmonary neuroendocrine cells ± fibrosis, excluding other pathology that may induce reactive proliferation.

DIFFUSE PANBRONCHIOLITIS

Homma H. Diffuse panbronchiolitis. Nihon Kyobu Shikkan Gakkai Zasshi 1975, 13: 383-395

Homma H et al. Diffuse panbronchiolitis: a disease of the transitional zone of the lung. Chest 1983, 83: 63-69

Poletti V et al. Diffuse panbronchiolitis observed in an Italian. Chest 1990, 98: 515-516

Randhawa P et al. Diffuse panbronchiolitis in North America: report of three cases and review of the literature. AJSP 1991, 15: 43-47

SERIES “RARE INTERSTITIAL LUNG DISEASES”
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Number 4 in this Series

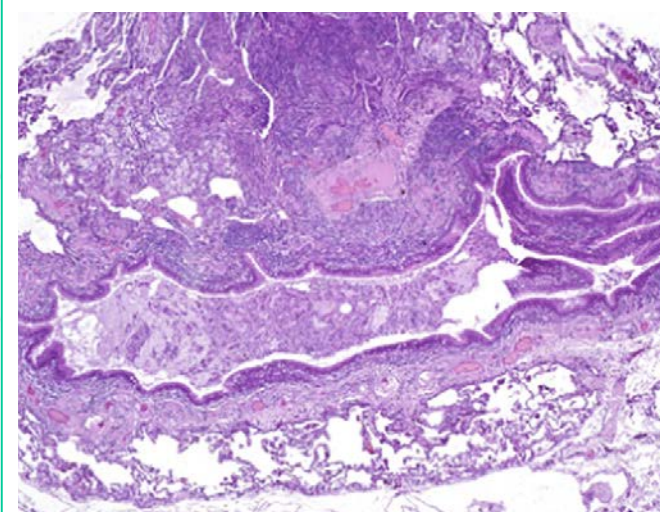
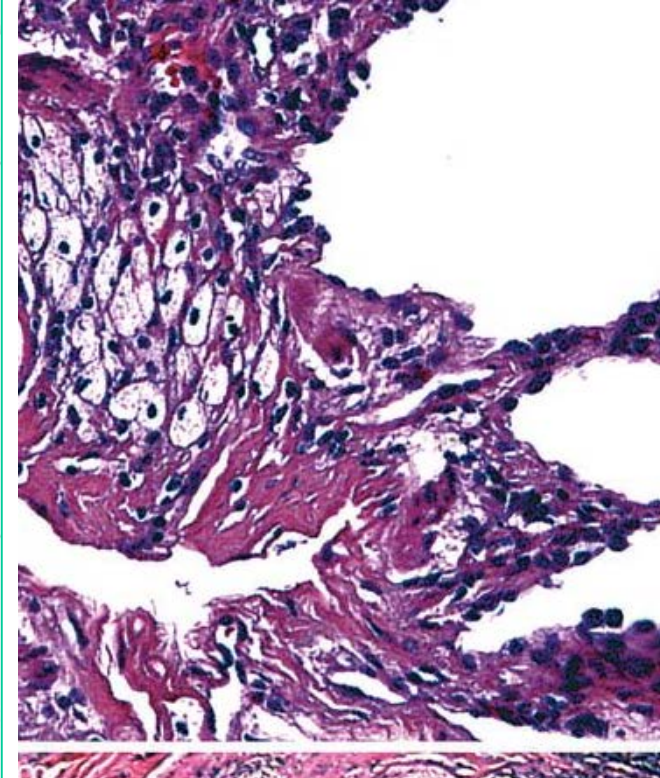
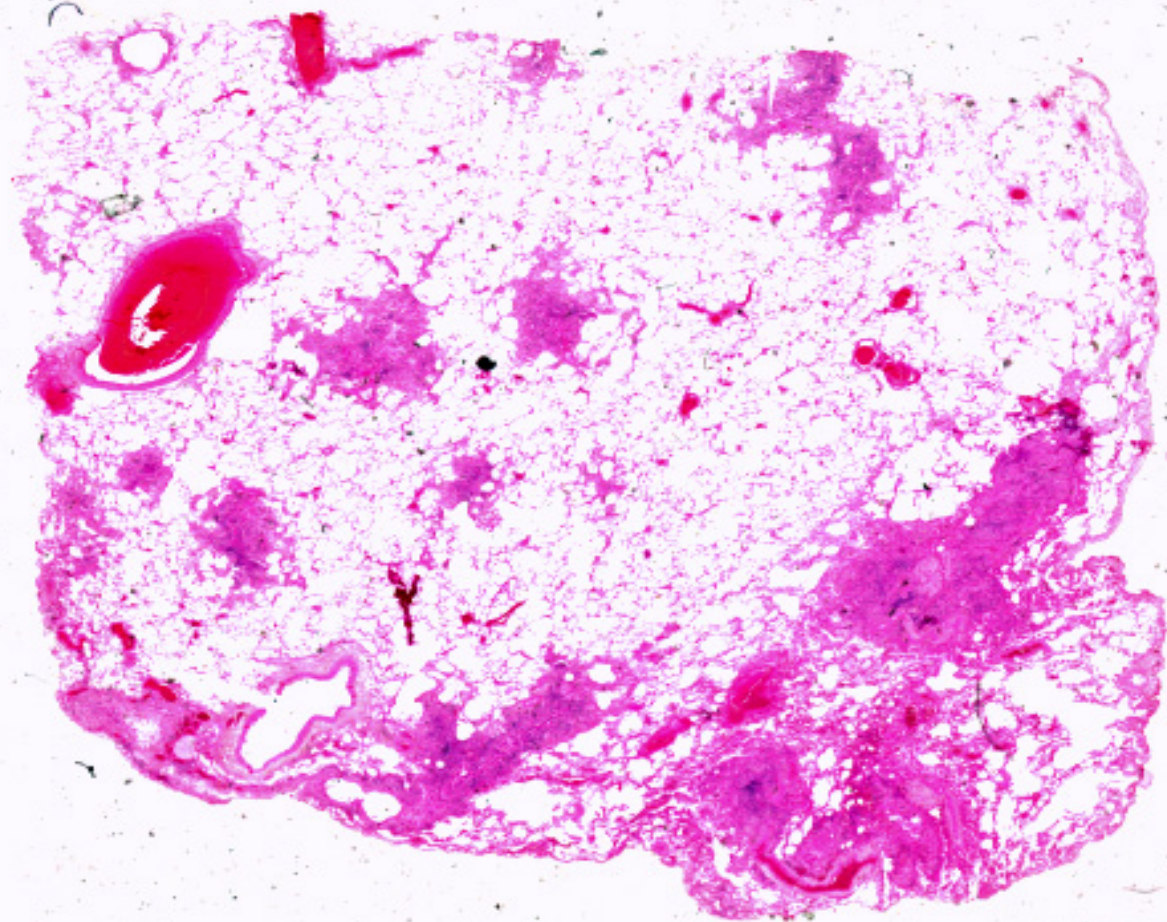
Diffuse panbronchiolitis

V. Poletti^{*,#}, G. Casoni^{*}, M. Chilosi[†] and M. Zompatori⁺

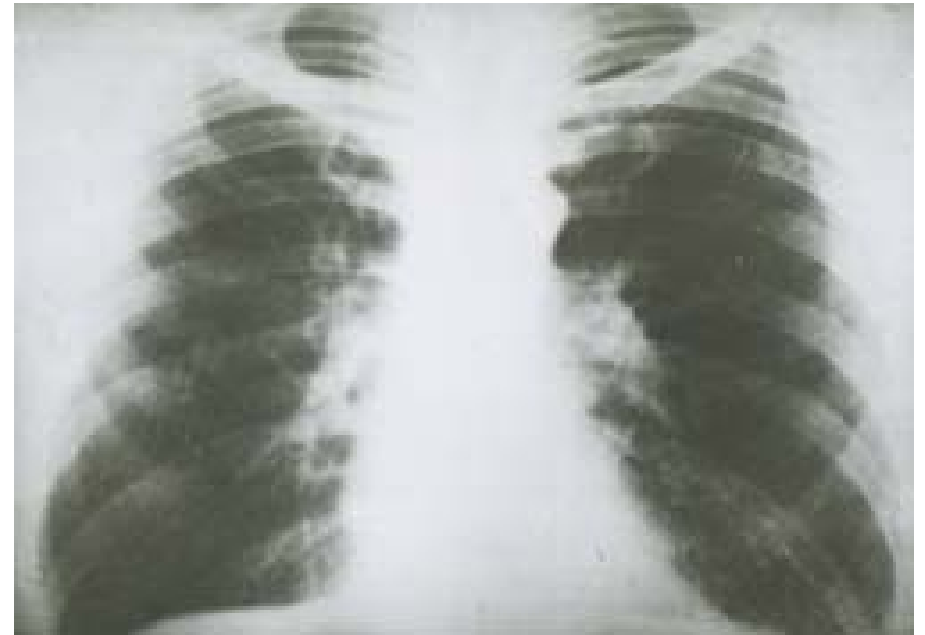
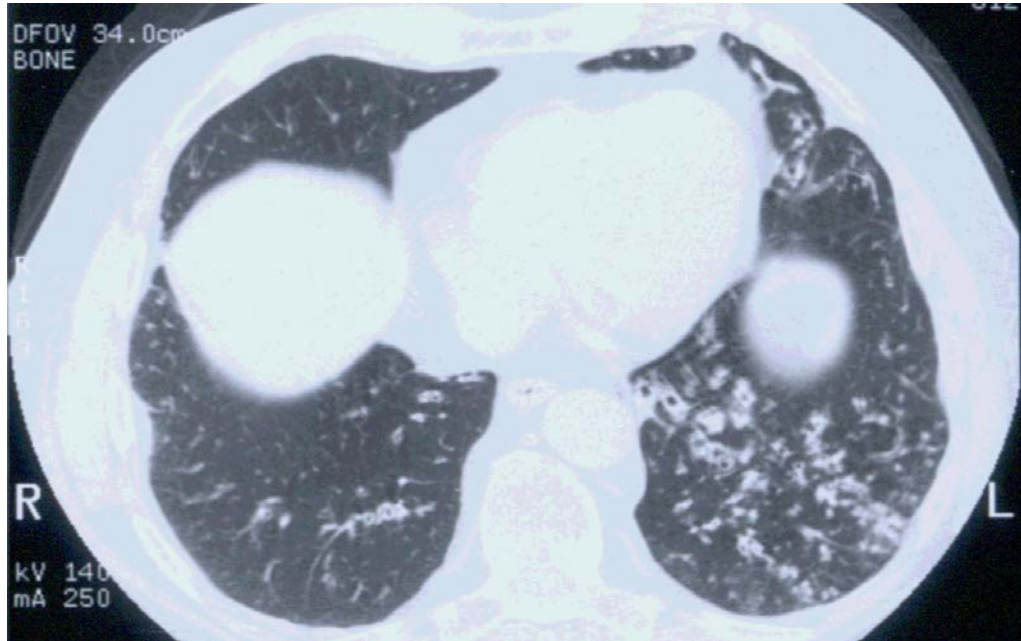
TABLE 2 Diagnostic criteria for diffuse panbronchiolitis

1. Persistent cough, sputum and exertional dyspnoea
2. History of chronic paranasal sinusitis
3. Bilateral diffuse small nodular shadows on a plain chest radiography film or centrilobular micronodules on chest computed tomography images
4. Coarse crackles
5. FEV₁/FVC <70% and P_{a,O_2} <80 mmHg
6. Titre of cold haemagglutinin ≥ 64

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; P_{a,O_2} : arterial oxygen tension. Cases definitely established should fulfil criteria 1, 2 and 3, along with at least two of criteria 4, 5 and 6. These parameters are useful for carrying out an epidemiological analysis. In countries in which the disease is very rare, surgical lung biopsy is required to make a diagnosis. Criteria are taken from a working group of the Ministry of Health and Welfare of Japan [67]. 1 mmHg=0.133 kPa.



DPB:Imaging



HRCT Scan

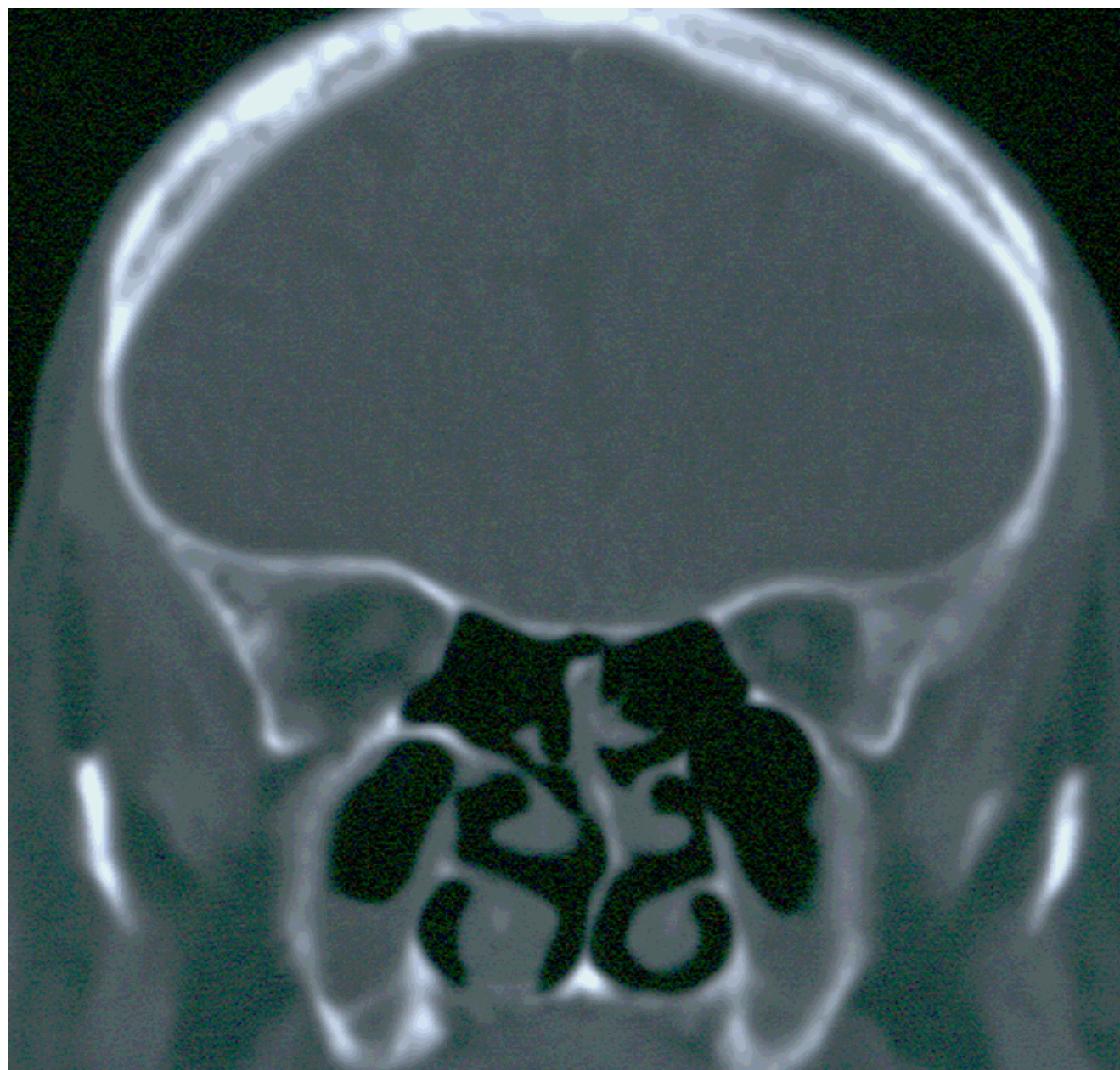
tree in bud pattern

cystic lesions

bronchiectasis

Ancillary finding

pansinusitis



Diffuse Panbronchiolitis-DPB

Epidemiology

Male female ratio 1.4/1

2/3 nonsmokers

Prevalence 11/100,000

Pathogenesis

*Neutrophyl accumulation

*Lymphocytitc accumulation

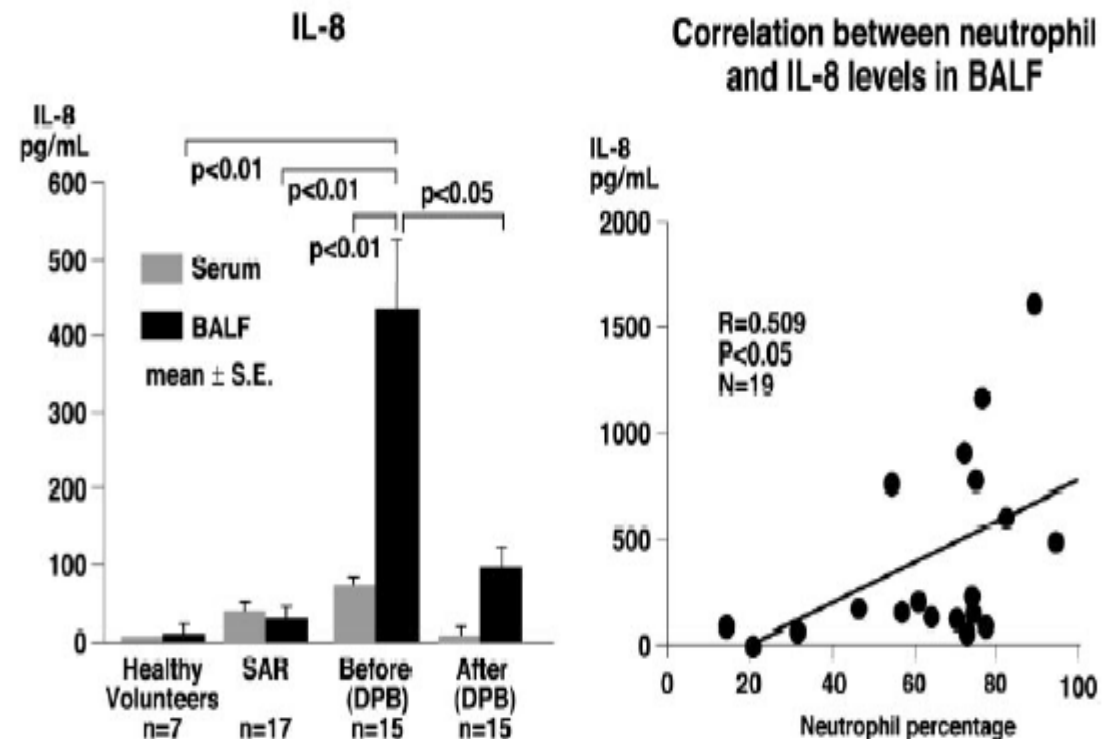
*CD1a+ cells

*genetic predisposition (HLA-Bw54)

Lin X, et al. Macrolide for DPB Cochrane Collaboration, 2015

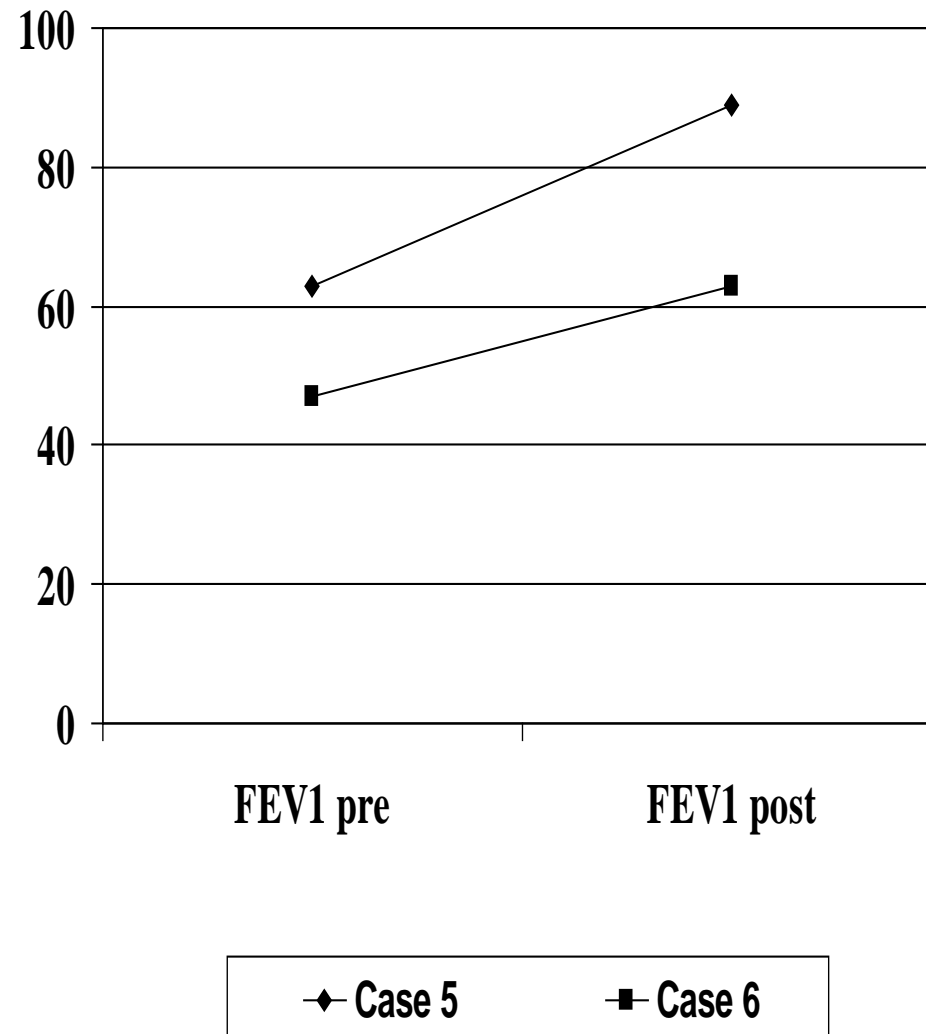
Only one RCT (19 participants) with significant methodological limitations was included in this review. It found that the computerised tomography images of all participants treated with a long-term, low-dose macrolide (erythromycin) improved from baseline, while the images of 71.4% of participants in the control group (with no treatment) worsened and 28.6% remained unchanged. Adverse effects were not reported.

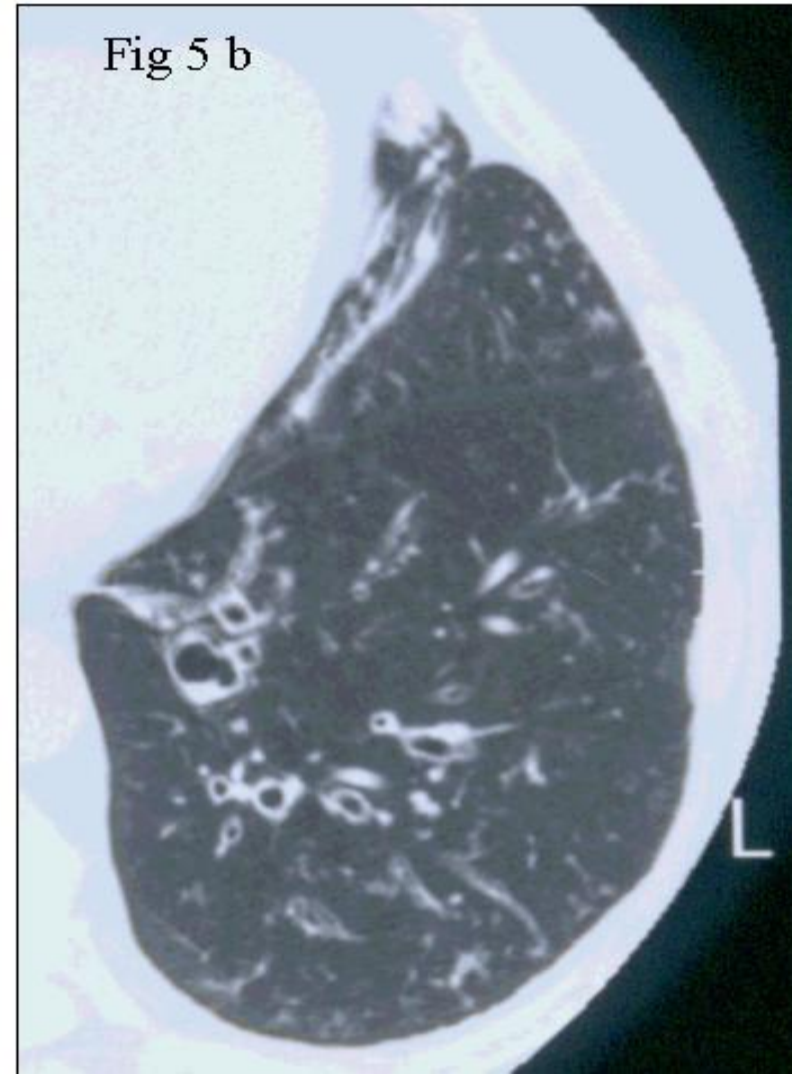
IL-8 levels in BALF before and after macrolide



Sakito O, et al. Respiration 1996, 63: 42-48

Effects of low dose macrolides in two DPB cases





Macrolide effects in DPB

