

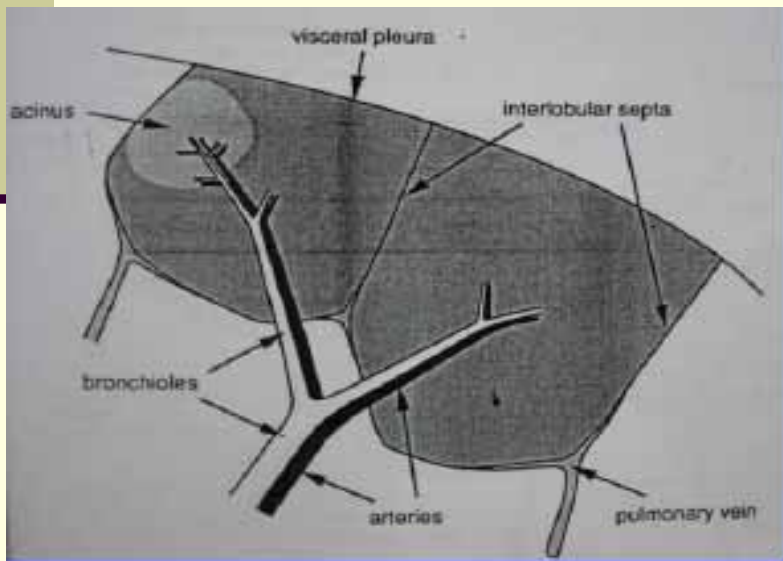
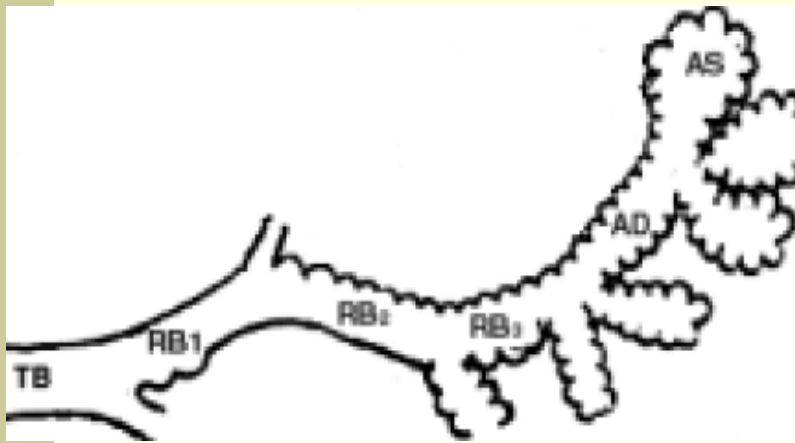
BRONCHOLAR DISEASES



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**DEPT OF PULMONARY & CRITICAL CARE MEDICINE
PGIMER, CHANDIGARH**

Anatomy Of Bronchioles



- Diameter is about 1 to 2 mm
- Cartilage are absent
- Directly embedded in the lung parenchyma
- Caliber influenced by lung volume
- Nutrition by bronchial circulation
- Normal bronchioles (0.6mm) not visible on CT

Historical Background

- Bronchiolitis recognized since 1800
- BO first described by Reynaud 1835
- Wilhelm Lange coined term bronchiolitis in 1901
- Franenkel in 1902 described histopathology of BO due to NO₂
- Term BOOP was used since 1985
- Last two decades HRCT has greatly contributed.

Classification

There are four classification schemes commonly used

- Clinical classification
- Histological classification
- HRCT findings
- Clinico-pathological

Clinical Classification

1. Inhalation injury
 2. Post infectious
 - * Acute bronchiolitis
 - * Bronchiolitis obliterans
 3. Drug-induced reaction
 4. Idiopathic
 - * Not associated disease
 - * Associated with organ transplantation
 - * Associated with CTD
 - * Other rare associations
- (Penn.CC et al Clin Chest Med 1993;14:645-654)

Histological Classification

1. Cellular bronchiolitis

Follicular b., Respiratory b., Diffuse panbronchiolitis

2. Bronchiolitis with inflammatory polyps or intraluminal polyps

BOOP

3. Constrictive (cicatricial) bronchiolitis

hyperplasia and bronchiolar fibrosis
particle-induced small airways disease

4. Pan-bronchiolar fibrosis and bronchiolar metaplasia (Lambertosis)

(Venerino. *p Res. Crit Care Med.* 2003;24:1-13)

HRCT Classification

1. Centrilobular nodular and branching lines (tree-in-bud)
2. Ground glass attenuation and/or alveolar consolidation
3. Low attenuation (Mosaic perfusion) and expiratory air trapping
4. Mixed or different pictures

(Muller NL, et al Radiology 1995;196:3-12)

Clinico-pathological

Primary bronchiolar disease

Respiratory B., Acute B.

Constrictive B., Follicular B.

Diffuse Pan B., Mineral dust airway disease

Other primary bronchiolar disease

Bronchiolar involvement in ILD

Respiratory bronchiolitis associated with ILD/DIP

Organizing pneumonia(BOOP,proliferative B.)

Hypersensitivity pneumonitis

Other ILD(PLCH,Sarcoidosis,IPF)

Broncholitis involving large airway disease

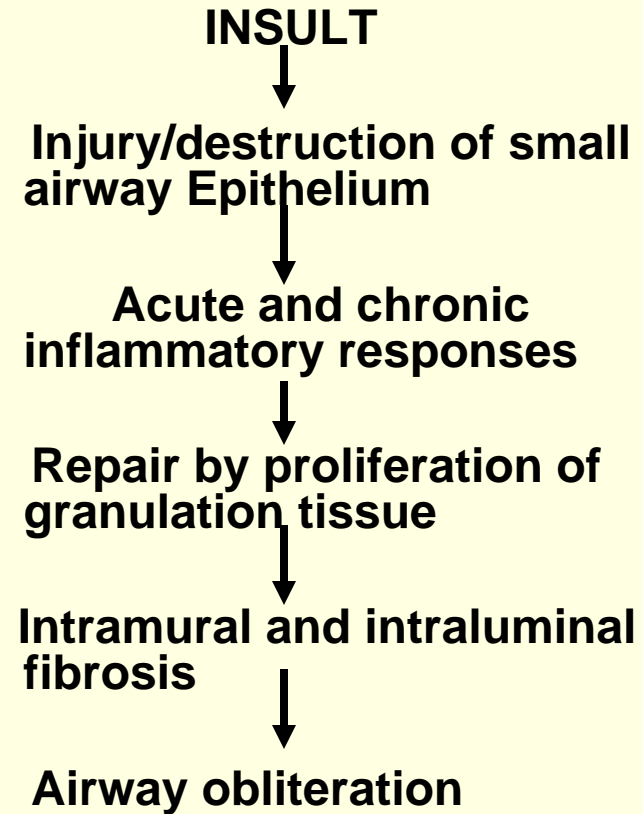
Ch.Bronchitis,Bronchiectasis, Asthma

(Ryu JH et al-Am J. Resp Crit. Care Med 2003;168:1277-1292)

Pathogenesis

Histopathology patterns of bronchiolitis related to

- **Type of insult**
- **Extent and severity of the initial insult**
- **Predominate site of injury (Bronchioles, AD or both)**



Diagnosis Of Bronchiolar Disease

- History
- Chest examination= Wheezing, or crepitation.
- Pulmonary function test
- Chest X-ray
- HRCT-thorax
- Bronchoalveolar lavage
- Histopathology
- Blood biochemical/ serological

Diagnosis (PFT)

- Spirometric indices: MMEF25-75%, FEF 75-85%, Vmax 25%, FVC/FET
- Helium-oxygen flow-volume curves
- Single breath nitrogen washout curve
- Frequency dependence of compliance
- Residual volume measurement
- Closing volume measurement

Diagnosis (PFT)

- BO ↓ attenuation on HRCT correlates best with MEF-25 above RV
- Bronchiolar wall thickening correlated with global air trapping (reflected by the RV:TLC ratio)
(Hansell DM et al. Radiology 1997;203)
- HRCT correlation were between SaO₂ and the extent of GGA, (A-a)o₂ and the extent of area of hypo attenuation
(Park JS et al. J Comput. Asst. Tom 2002;26)
- Possible BO defined by >12% decline in FEV₁ in HLTRs, Bilateral LTRs or >13% decline in FEV₁ among single LTRs or a 30% decline in FEF_{25-75%}
(Patterson GM et al. J Heart Lung Tr. 1996)
- Ventilation distribution (Single breath nitrogen or helium washout curve) were more sensitive than conventional PFT in prediction of onset of BO
(Estenne M et al. Am J Resp Crit Car Med 2000; 162)

Bronchoalveolar lavage

- COP presence of foamy macrophage and occasionally mast cells and plasma cells, ↓ratio of CD4 to CD8 cells, ↑ activated T cells
- More striking increases in BAL neutrophils are present in patient with BO
- BO: ↑ BAL TNF α and ↓ IL-18. TNF α levels were associated with a poor prognosis

(Huaber H et al. Bone Marrow Trans. 2002;30)

HRCT

DIRECT SIGNS

- Increased soft tissue in or around the bronchioles
- Thickening of the bronchiolar wall by inflammatory cells (tree-in-bud pattern)
- Poorly defined centrilobular nodules
- Bronchiolectasis in chronic bronchiolitis.

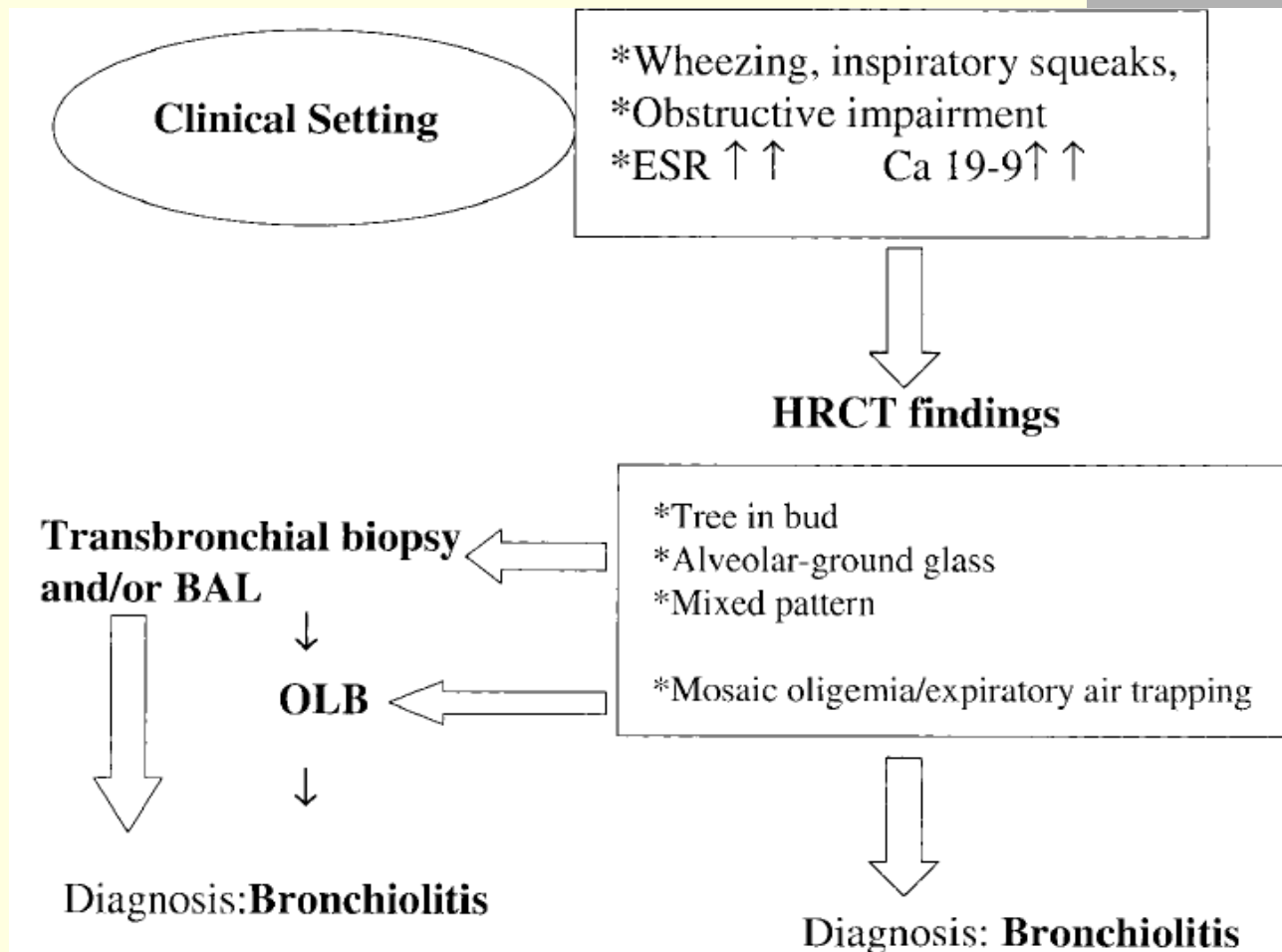
INDIRECT SIGN

- Air trapping at expiratory CT
- Area of ↓ density of lung parenchyma
- Reduction of caliber of pulmonary vessels

Blood Examination

- Rh factor, ANA, Anti-centromere Ig G to exclude CTD
- ANCA to exclude vasculitis
- MPO-ANCA for Diffuse panbronchiolitis
- Ca 19-9: for DPB, Idiopathic B., OB related to GVHD

Algorithm for practical approach

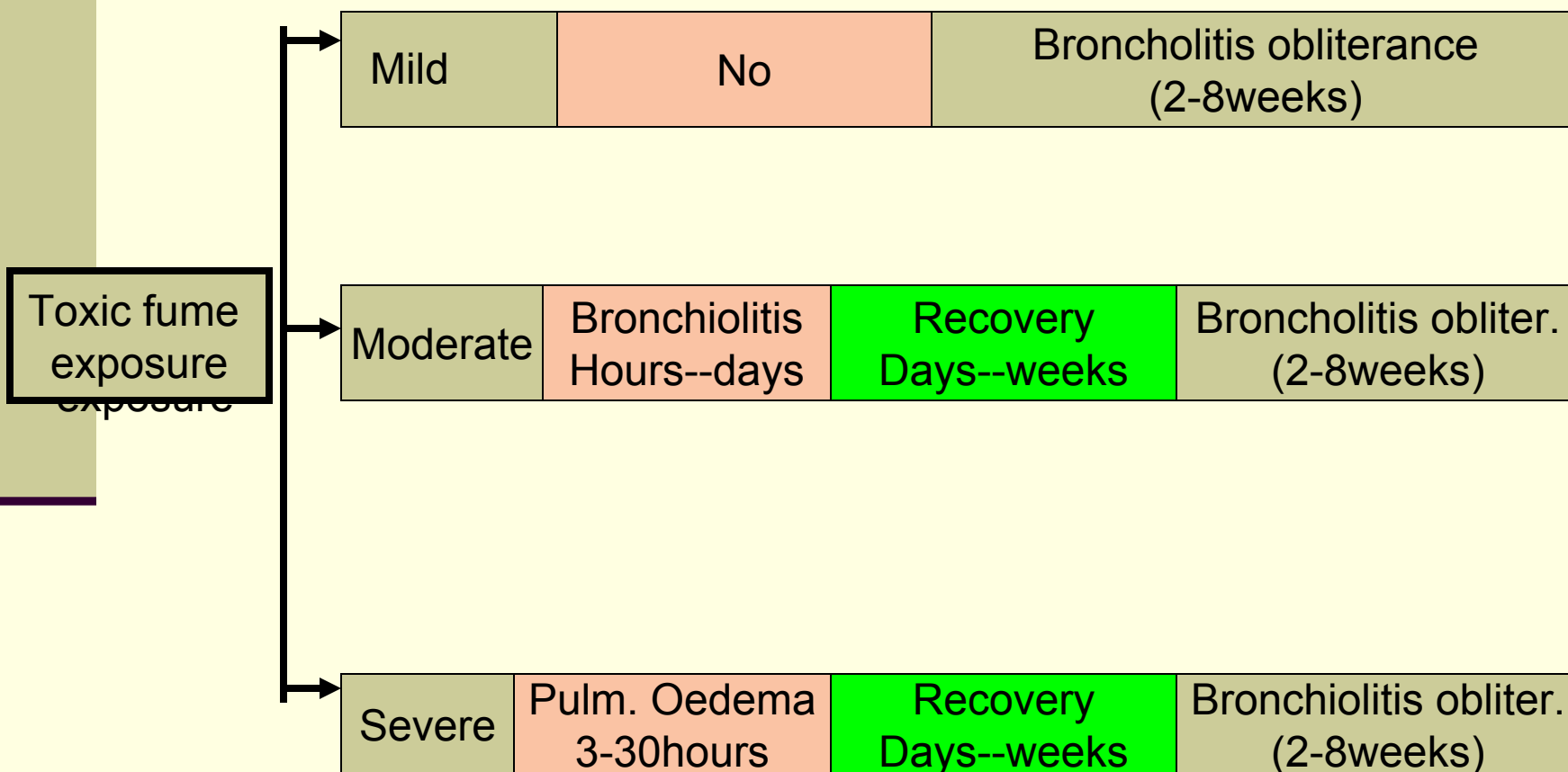


(Venerio et al. Crit care Med. 2003;24)

Toxic Fume Exposure

- Severity of lung injury depend upon
 - Type of solubility of the agent
 - Concentration of the gas
 - Duration of the exposure
- After exposure there may be
 - Reactive airway dysfunction syndrome
 - Constrictive bronchiolitis

Clinical spectrum



Treatment

- Hospital observation for 48 hours
 - ↓
 - Weekly or biweekly for 6 to 8 weeks
- Respiratory dysfunction – Corticosteroids continued for minimum 8 weeks
- Occasionally- Bronchodilators

Acute Infectious Bronchiolitis

- More frequent in children
- Injury to epithelial cells
- Common histological pattern-Constrictive bronchiolitis
- Only sporadic cases of BO secondary to infection (measles, VZV, pertussis) reported in adult

Acute infectious bronchiolitis

- Acute bronchiolitis--RSV, Para influ., adenovirus, M.pneum. VZV
- Bronchiolitis Obliterans--HSV, CMV, rubeola, M.pneum., Klebsiella, P. carinii
- Acute stage - viral like illness
- Later stage - cough, dyspnea, tachypnea, cyanosis
- Exam.- chest wall retraction, rales, crepitation

Acute infectious bronchiolitis

■ CXR

Normal or hyperinflation

Reticulonodular opacity

Patchy consolidation, atelectasis

■ HRCT

Centrilobular nodules, branching lines

Focal area of consolidation

Histopathology

- Epithelial necrosis → epithelial proliferation
- Dense plugs of alveolar debris → partial or complete obstruction
- Lymphocyte infiltration
- Involves adjacent peribronchilar space and alveolar walls

Idiopathic Forms Of Bronchiolitis

There are 3 forms

1. Cryptogenic adult bronchiolitis (CAB)
2. RB-ILD
3. Cryptogenic organizing pneumonia (COP)
or Idiopathic BOOP

Cryptogenic adult bronchiolitis

- Approximately 4% of all of OLD
- Rare clinico - pathological syndrome
- Middle aged women with non-productive cough, SOB
- Diagnosis largely on exclusion
- CXR-
 - *Normal, bronchial wall thickening with hyperinflation
- HRCT
 - *Normal, Expiratory air trapping and bronchial wall thickening
 - *Diffuse ground glass opacity and mosaic attenuation

Histopathology (CAB)

- Cellular constrictive bronchiolitis, with both acute and chronic inflammatory changes.
- Airway obliteration and mucous stasis.
- Normal or hyperinflation parenchyma
- Mild focal interstitial fibrosis.

Respiratory bronchiolitis - LID

- Found in current or previous smokers
- M:F=1.6:1
- Common age groups, 40 to 50 years
- Presented with, dyspnea (70%), cough (58%), coarse rales (33%).
- Essentially a benign disease
- Better outcome than other ILD's

RB-ILD (Histopathology)

- Inflammatory process in membranous and RB
- Tan-brown pigmented macrophages
- Bronchiole may be ectatic with mucous stasis, and mildly thickened walls
- Evidence of extension of bronchiolar metaplastic epithelium in to surrounding alveoli.

RB-ILD (Radiology)

CXR

1. Diffuse fine reticulonodular with normal lung volume (80%)
2. Bronchial wall thickening, prominence of peribronchovascular interstitium, small regular or irregular opacities

HRCT

- Diffuse or patchy ground glass opacities or fine nodules
- Mild emphysema, atelectasis or linear or reticular opacities

RB-ILR (Radiology)

- In current smokers, parenchymal micronodules (27%), areas of ground-glass attenuation (21%), dependent areas of attenuation (34%), and emphysema (21%) were all significantly more prevalent than in nonsmokers

- Areas of ground-glass attenuation, seen on HRCT, were found to correspond to accumulation of pigmented macrophages and mucus in the alveolar spaces, variably associated with mild interstitial inflammation and/or fibrosis.

(RemjJM, Radiology 1993;186)

- HRCT features were central bronchial wall thickening proximal to segmental bronchi (90%), peripheral bronchial wall thickening distal to segmental bronchi (86%), centrilobular bronchioles (71%), and areas of ground-glass attenuation (57%).

(Heyneman LE, AJR-1999;173)

- segmental and lobar air trapping in current smokers (26%), exsmokers (27%) and nonsmokers (8%).

(Mastora I. Radiology 2001;218)

Key clinical issues

- **Diagnosis of RBILD is constructed from clinical, functional, HRCT and, histological findings, HRCT findings are usually the most discriminatory diagnostic feature.**
- **HRCT features occasionally overlap with DIP, DIP is a very rare, the ground-glass attenuation of DIP is generally more intense and regional than RBILD.**

(Elkin SL et al. Resp Crit Care Med 2001;22:387–397)
- **HRCT distinction between RBILD and HP can pose difficulties, However, the smoking history is a key discriminate**
- **RBILD were characterized by significant increases in macrophage numbers and significant lower percentages of other cellular components.**

(Veeraraghavan S et al. Eur Respir J 2003;22:239–244)
- **BAL profile of RBILD is wholly distinct from that of HP, in which a prominent BAL lymphocytosis is the rule**

SHOULD RB-ILD AND DIP BE VIEWED AS TWO ENDS OF THE SAME DISEASE SPECTRUM?

Classified as separate entities, despite their common relationship to smoking, histological and HRCT similarities.

- The clinical course and presenting features. RBILD appears to be a more benign disease process than DIP
- RBILD is characterized by micronodular on HRCT that are not seen in DIP, and the BAL profiles of the two diseases differ
- Therapeutic strategy in RBILD, in which the value of treatment may be marginal in many cases, contrasts with the more vigorous approach that is usually appropriate in DIP.

Cryptogenic organizing pneumonia (idiopathic BOOP)

- Common age groups 50 to 60 years
- Equal in both sexes
- Relation with smoking-50% non-smokers, 25% ex-smokers, 25% current smokers
- Nonproductive cough(72%), exertion dyspnea(66%), develop sub-acutely
- Occasionally bronchorrhea, hemoptysis, and chest pain
- Inspiratory crackles(74%), wheezing is rare, clubbing <5%
- ESR and C-RP levels are increased, blood leukocyte counts (increased proportion of neutrophils).

Histopathology

- Lesions are usually patchy and peribronchiolar, and within the airspace
- Intraluminal buds of granulation tissue
 - “butterfly” pattern
- Foamy macrophages in alveolar spaces
- Severe fibrotic changes
- Lung architecture is not severely disrupted

Radiology (Typical COP)



- Bilateral, diffuse alveolar opacities Irregular linear, nodular infiltration
- The opacities may migrate
- Late-honeycombing



- Patchy airspace consolidation, ground glass opacities
- Bronchial wall thickening and dilation
- Periphery opacities often in the lower lung zone.

Other patterns of Cryptogenic Organizing Pneumonia (different from typical COP)

FOCAL SOLITARY COP

- Nodular or mass lesion on chest x-ray, in upper lobes.
- Margins on HRCT, smooth, spiculated or cavitated
- Spontaneous hydropneumothorax

INFILTRATIVE COP

- Combines interstitial and small alveolar opacities
- Alveolar opacities are multiple and small

Miliary pattern

- Considered as a bronchiolar disorder with satellite and accessory organizing pneumonia

Other imaging patterns

- Multiple and/or cavitory nodules or masses, pneumatocele, linear subpleural bands, or opacities with a perilobular pattern

Multiple alveolar opacities other than COP (BOOP)

- Infectious pneumonia
- Pulmonary TE with infarction
- Chronic aspiration pneumonia
- Chronic eosinophilic pneumonia
- Bronchoalveolar carcinoma
- Low grade primary pulmonary lymphoma
- Wegener's granulomatosis
- Hypersensitivity pneumonitis

Organizing pneumonia: disease associated

- **Organizing pneumonia of infectious origin- Bacteria, Viruses, Parasites, Fungi**
- **drug-induced organizing pneumonia** improvement of organizing pneumonia after withdrawal, without corticosteroid treatment.
- **Organizing Pneumonia “Primed” By Radiation Therapy**

Identified in women receiving radiotherapy to the breast for cancer, incidence is 2.5%. The mean interval varies from 14 weeks to 8.8 months,
- **Connective Tissue Disease**

Difference between COP/BOOB

OB

- Onset-acute, sudden
- Rales >70%, wheeze rare
- CXR-Focal alveolar infiltration
- PFT-Restrictive
- BAL-Lympho (>20%)
- Biopsy-intralobular polyp extends to AD alveoli
- Resp to CS-Excellent

- Onset-chronic
- Wheezing, rhonchi
- CXR-Normal, or hyperinflation
- PFT-pure obstructive
- BAL-Poly (>40%)
- Biopsy-narrowing bronchiolar lumen, spare AD and alveoli
- Res.to CS.-poor

Treatment and Prognosis

- The treatment depends first on its cause or the underlying disorder.
- Prednisone of 0.75 mg /kg/day for 4 weeks, then 0.5mg/kg/ day for 4 weeks, then 20 mg/day for 6 weeks, then 5 mg/ day for 6 weeks.
(Lazor R et al. Am J Respir Crit CareMed 2000;162:571–577)
- Prognosis of typical COP is excellent, rapid improvement and no long-term sequelae
- Based on transbronchial biopsies, cases with an organizing process involving fibrin responded poorly to corticosteroids
(Yoshinouchi et al Respir Med 1995;89:271–278)
- Progressive COP cyclophosphamide and azathioprine have been used, but not evaluated.
(Purcell IF et al Respir Med 1997;91:175–177)
- Poor prognostic factors:non-idiopathic BOOP, predominantly interstitial pattern on CT,Lack of BAL lymphocytosis,Type 2 Masson bodies on biopsy

Bronchiolar Disease In CTD

- Airflow obstruction arise from inflammatory or fibrotic disorders
- Small airways complicated by CTD are, COP,OB, FB, and bronchiectasis
- Medication use to treat CTD also responsible
- Disease associated with broncholitis are, RA, SLE, PSS, Sjogren'n syn. polymyositis, dermatomyositis

Rheumatoid Arthritis

- Middle aged women with long standing seropositive RA
- Involvement may give rise to, OB, COP, FB, BALT, and bronchiectasis
- Traction bronchiectasis, bronchiolectasis are common HRCT features.
- Bronchiectasis predominantly affects the lower lung zones(LL,ML,lingual)

Scleroderma (PSS)

- Common pulmonary lesions are,
 - Fibrosing alveolitis
 - Pulmonary HTN
 - Recurrent aspiration pneumonia
- Defect is mainly restrictive, 15-30% obstructive lesion
- NSIP is most common in PSS
- Diffuse alveolar damage is rarely observed

Systemic lupus erythematosus

- Bronchiolar disease is rare in SLE
- SLE patient may develop
 - Rapidly progressive airway obstruction
 - Early obliterative bronchiolitis
 - BOOP (reported 2 patients)
- COP may be found in acute lupus pneumonitis

Sjogren's Syndrome

- Obstructive airway disease reported with SS
- Desiccation of tracheo-bronchial tree
- BOOP has been reported in SS
- Mononuclear cell infiltration around narrowed small airways (constrictive bronchiolitis)

Organ Transplantation-BMT

- Pulmonary complication in 40-60% patients with BMT
- Severe obstructive pulmonary disease is 10-17%, in chronic GVHD.
- BO is most frequent complication
- BO is most common in allogeneic BMT

BMT

- Risk factors are recurrent sinusitis, old age GVHD, methotrexate for GVHD, Acquired hypogammaglobulinemia
- Nonproductive cough, Dyspnea with exertion, Nasal congestion, wheeze
- CXR, 80% normal, Diffuse interstitial infiltrates
Late stage- pneumothorax
- HRCT, Lobar, segmental area of lung attenuation
Narrowing of pulmonary vessels

BMT (treatment)

- Control underlying causes
- Reverse established OB or prevent progression
- Treat any reversible air flow limitation
- Prevent and treat super infection
- Managing respiratory failure

LT and HLT

- Major obstacle to prolong survival following LT is BOS
- In BOS, fibrosis and obliteration of airway lumen (“Vanishing lung disease”).
- According to ISHLT, BO within the first year the single most important risk factor for 5 year mortality among LTR.

Histopathology Of Lung (Allograft rejection)

1. Allograft rejection

Perivascular lymph. infiltration (CD8)

Extend to alveolar space & interstitium

Necrosis of epithelial cells

2. Bronchiolitis obliterans

Circumferential narrowing lumens

Fibrosis, granulation tissue

Necrosis bronchial epithelial cell

Smooth muscle cells, myofibroblast

Obliterate airway

Histopathology Of Lung (Allograft rejection) Cont.

3. Lymphocytic bronchitis/bronchiolitis

Lymp. Infiltration in TB and RB

Involve bronchial epithelium, mucosa

Acute cellular rejection

4. Bronchiolitis obliterans-organizing pneumonia

Fibromyxomatous GT filling TB & RB

Extends in to AD & AS

“organizing pneumonia” distal to AD

Alveolar architecture is preserved

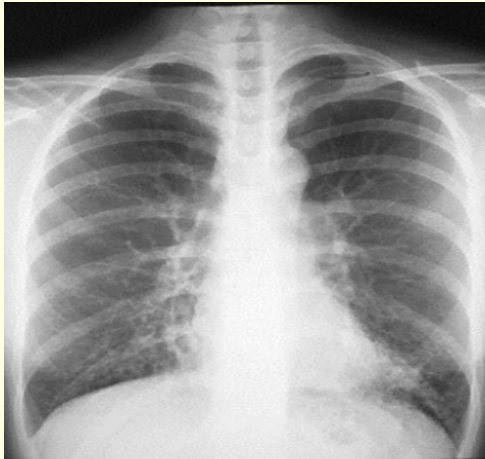
Diffuse Panbronchiolitis

- First described by Yamanaka
- M:F=1.4:1
- 2/3 of patients were non-smokers
- Common in Japan, China, Korea
- HLA Bw54 association in 63%

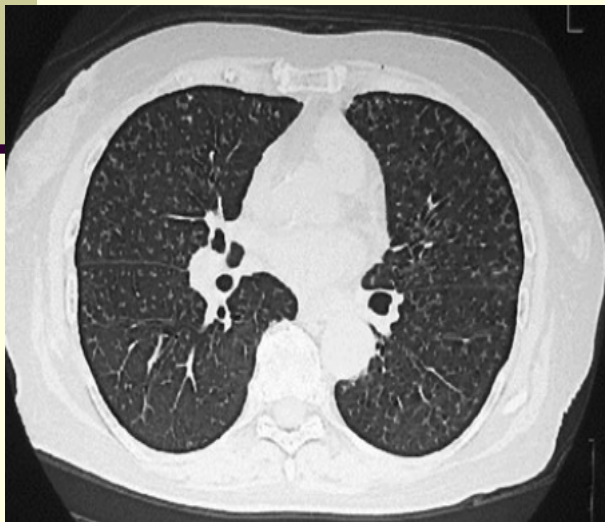
Histopathology

- Thickening of the walls RB
- Infil. With lymphocytes, plasma cells, histiocytes
- Alveolar wall are not affected
- Secondary ectasia of proximal bronchioles

Radiological Finding



- Bilateral, diffuse, small, nodular shadows with pulmonary hyperinflation
- Advanced cases- Ring-shadows, tram line
- Centrilobular distribution
- Early- nodular opacities
- Later- nodule, linear with bronchial wall thickening
- Advanced- large cystic opacities with dilated proximal bronchioles



Differential diagnoses for DPB

- Chronic bronchitis
- Bronchiectasis
- Infectious bronchiolitis
- Primary ciliary dyskinesia
- Cystic fibrosis
- Hypogammaglobulinaemia
- Rheumatoid arthritis-related bronchiolitis
- Inflammatory bowel disease-related bronchiolitis
- Idiopathic chronic bronchiolitis

Diagnostic criteria

(A working group of the Ministry of H & FW of Japan 1998)

1. Persistent cough, sputum and exertional dyspnea
2. History of current chronic sinusitis
3. Bilateral diffuse small nodular shadows on plain chest x-ray or centrilobular micronodules on chest CT image
4. Coarse crackles
5. FEV1/FVC <70%, and Pa2 <80 mm Hg
6. Titer of cold hemagglutinin >64

Clinical guidelines for DPB

Macrolides should be applied soon after the diagnosis is made, as there is a better clinical response in the earlier stage

- First choice: erythromycin 400 or 600 mg orally
- Second choice: clarithromycin 200 or 400 mg orally or roxithromycin 150 or 300 mg orally"

Assessment of response and duration of treatment

- Although clinical response within 2–3 months, continued for 6 months, response should be assessed
- completed after a period of 2 yrs when clinical manifestations, radiological findings and pulmonary function measurements have improved
- in advanced cases with extensive bronchiectasis or respiratory failure, treatment should be continued for 2 yrs

(Nakata K, Annual Report (MH&FW) Japan,2000:111)

Bronchiolitis Obliterans

OB should be suspected in case of

1. Rapid progression of symptoms i.e. dry cough and dyspnea.
2. Severe airflow obstruction not attributable to other causes or to COPD.
3. Lack of physiologic improvement following treatment with bronchodilators.
4. Greater than 25% neutrophils in bronchoalveolar lavage (BAL) fluid analysis.

(Kindt C G et al. Am Rev Respir Dis 1989;1140:483-492)

Classification of Bronchiolitis Obliterans

Clinical Classification

- Inhalation injury
- Associated with organ transplantation
- Post-infectious
- Associated with connective tissue disease
- Drug- or chemical-induced reactions
- Idiopathic
- Others: RB-ILD, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, chronic eosinophilic pneumonia, proliferative phase of ARDS, Wegener's granulomatosis, radiation pneumonitis, ulcerative colitis

Pathological Classification

- BOOP or proliferative bronchiolitis
- Constrictive bronchiolitis

Features Of BO

- SOB, exercise limitation
- Airflow obstruction (\downarrow FEV1 and EFR)
- Recurrent LRTI
- Isolation of *P. aeruginosa* from respiratory culture
- Increase neutrophils in BAL

Staging Of Bo (ISHLT,2002 Revised)

- BOS 0= FEV1 >90% & FEF25-75 >75% BL
- BOS OP= FEV1 81-90% & FEF25-75% BL
- BOS-1= FEV1 66-80% of BL
- BOS-2= FEV1 51-65% of BL
- BOS-3= FEV1 <50% of BL

(Estenne M et al. J. Heart Lung Tran. 2002;21:297-310)

HRCT finding

- Bronchial wall dilatation
- Bronchial wall thickening
- Patchy regions of low attenuation (Hyperlucency)
- Mosaic pattern (low and high area of attenuation)
- Air trapping on expiratory CT scan

Management of BO

Treat specific complications

- Treat/prevent episode of acute allograft rejection
- Supplemental oxygen (when hypoxemia documented)
- Bronchodilators (for symptomatic relief)

Treatment of BOS of unproven value, but consider:

- Intensification of immunosuppressive therapy
- Intravenous pulse methylprednisolone (1 g daily 3 days, oral taper)
- Substitution of mycophenolate mofetil for azathioprine
- Substitution of tacrolimus (or sirolimus) for cyclosporine
- Addition of methotrexate or cyclophosphamide
- Cytolytic therapy (antithymocyte globulin, antilymphocyte globulin, OKT3)
- Interleukin-2 receptor antagonists (e.g., daclizumab, basiliximab)
- Aerosolized cyclosporine, Aerosolized corticosteroids
- Total lymph node irradiation, Extracorporeal phototherapy
- Azithromycin

Follicular Bronchiolitis

- Presence of abundant lymphoid tissue, with prominent germinal centers, situated in the walls of bronchioles
- Causes – Idiopathic, CTD, AIDS, Viral, M. pneumonia
- Usually present with – progressive dyspnea, cough, fever and recurrent pneumonia
- PFT- Obstructive, restrictive and mixed pattern

Follicular Bronchiolitis

- CXR- Diffuse reticulonodular pattern
- HRCT- Nodular opacities in peri-bronchovascular or subpleural distribution
 - patchy area of ground-glass opacity
 - Mild bronchial dilatation with wall thickening
- Treatment – underlying disease
 - bronchodilators, corticosteroids
 - Erythromycin reported to be benefit

(Hayakawa H, Am J Resp Crit Care Med. 1996;154:1531)

Bronchiolitis → Asthma

- Bronchiolitis severity to be an independent risk factor for subsequent wheezing within the first decade of life

(Sigurs N et al *Am J Respir Crit Care Med* 2000;161:1501–1507)

- Viral pathogens other than RSV that cause bronchiolitis may contribute to the future development of asthma.

- Severe RSV bronchiolitis is associated with a 30 to 40% likelihood of subsequent asthma.

(Sigurs N. *Am J Respir Crit Care Med* 2005;171:137–141)

Conclusions

- Bronchiolar abnormalities are commonly encountered on lung biopsy specimens and HRCT
- Various histopathologic patterns with confusing nomenclature and redundancies/ overlap
- When faced with a bronchiolar abnormality the clinician needs to ask three questions:
 - (1) is the bronchiolar abnormality the predominant lesion causing disease?
 - (2) what is the histopathologic pattern of the bronchiolar lesion?
 - (3) what is the clinico–physiologic–radiologic context?
- Prognosis is determined by the underlying histopathologic pattern

THANK YOU