Cystic lung diseases
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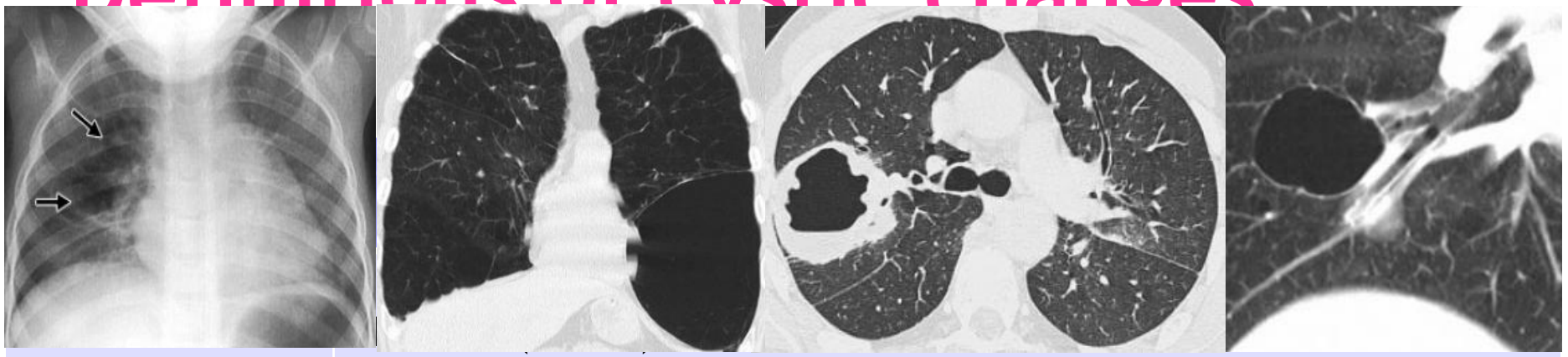
Introduction

- A diverse group of lung disorders
- Characterized by the presence of multiple regular / irregular spherical parenchymal lucencies bordered by a thin wall and having a well defined interface with normal lung
- Classified based on underlying pathophysiologic mechanisms - neoplastic, congenital, genetic, lymphoproliferative, infectious, inflammatory, smoking related…

Am J Respir Crit Care Med 2015; 191: 1354-1366

Definitions of cystic changes



Cavity	A gas-filled space within consolidation, mass or nodule Typically thick walled (>2mm), more irregularly shaped than cyst
Bulla	An airspace (size>1cm) with a rounded focal lucency, bounded by a thin wall (<1mm)
Bleb	Small (size<1cm) gas-containing space within the visceral pleura or in the subpleural lung
Pneumatocele	A thin-walled, gas-filled space in the lung, caused by infection, trauma, aspiration of hydrocarbon fluid

Radiology 2008; 246 : 697-722
Am J Respir Crit Care Med 2015; 191: 1354-1366

Mechanisms of cyst formation

- Proposed mechanisms

  1) check-valve obstruction with distal over-inflation

  : follicular bronchiolitis(FB), metastatic neoplasm, pneumatocele, LAM, PLCH

  2) ischemia

  : terminal bronchiole에 공급되는 small vv.의 obstruction에 의해 small airway의 necrosis, ischemic dilatation 야기

  3) remodeling induced by MMPs, matrix-degradation enzymes

  : LAM, PLCH, LCDD

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Radiological evaluation

- Distribution : diffuse/random (LAM, LIP, FB, Amyloidosis),
  upper/middle zone(PLCH),
  basilar/peripheral/subpleural (BHD)
- Size
- Shape : round, bizarre, lentiform
- Wall thickness
- Presence of internal structures : FB, LIP, BHD
- Rate of development, progression
- Pleural effusion, nodule, GGA 동반 여부

Am J Respir Crit Care Med 2015; 191: 1354-1366

Pathological evaluation

- True cysts have an epithelial cell lining
- Distribution : intraparenchymal/ basilar(BHD)
  apical/centrilobular (Emphysema)
- Abnormal cellular proliferation
  : LAM, PLCH, neoplasm
- Chronic inflammatory infiltration/fibrosis
  : CHP, CTD-ILD
- Abnormal protein deposit in amyloidosis, LCDD
  HMB-45(+) in LAM, CD1a(+) in PLCH

Am J Respir Crit Care Med 2015; 191: 1354-1366

Classification

- Neoplastic : LAM, PLCH
- Genetic : BHD (Birt-Hogg-Dube syndrome)
- Lymphoproliferative : LIP, FB, Amyloidosis
- Infectious : PCP, Staphylococcus, fungal, paragonimiasis
- ILD : HP, DIP, RB-ILD
- Other

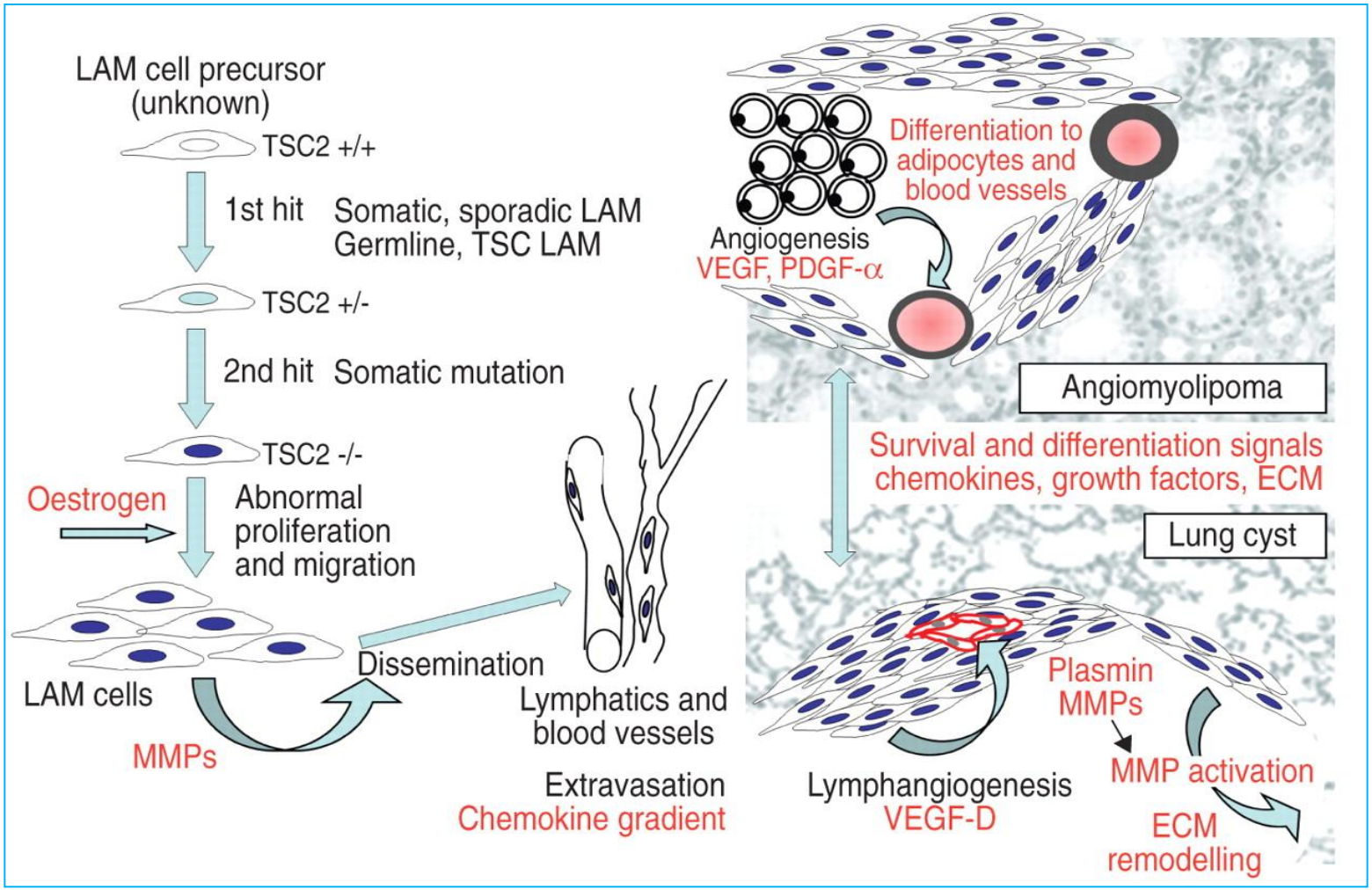
Am J Respir Crit Care Med 2015; 191: 1354-1366

LAM(Lymphagioleimyomatosis)-1

- Rare disease of the lungs and lymphatics
- Almost exclusively in females
  childbearing age(≈35yrs), usually before menopause
- Sporadic vs. autosomal dominant (Tuberous sclerosis complex, TSC)
  ➔ both associated with mutations in TS genes
- Abnormal growth of atypical smooth m.-like LAM cells
  in lungs & axial lymphatics
- Recurrent PNX, chylous effusion, respiratory failure
  angiomyolipoma

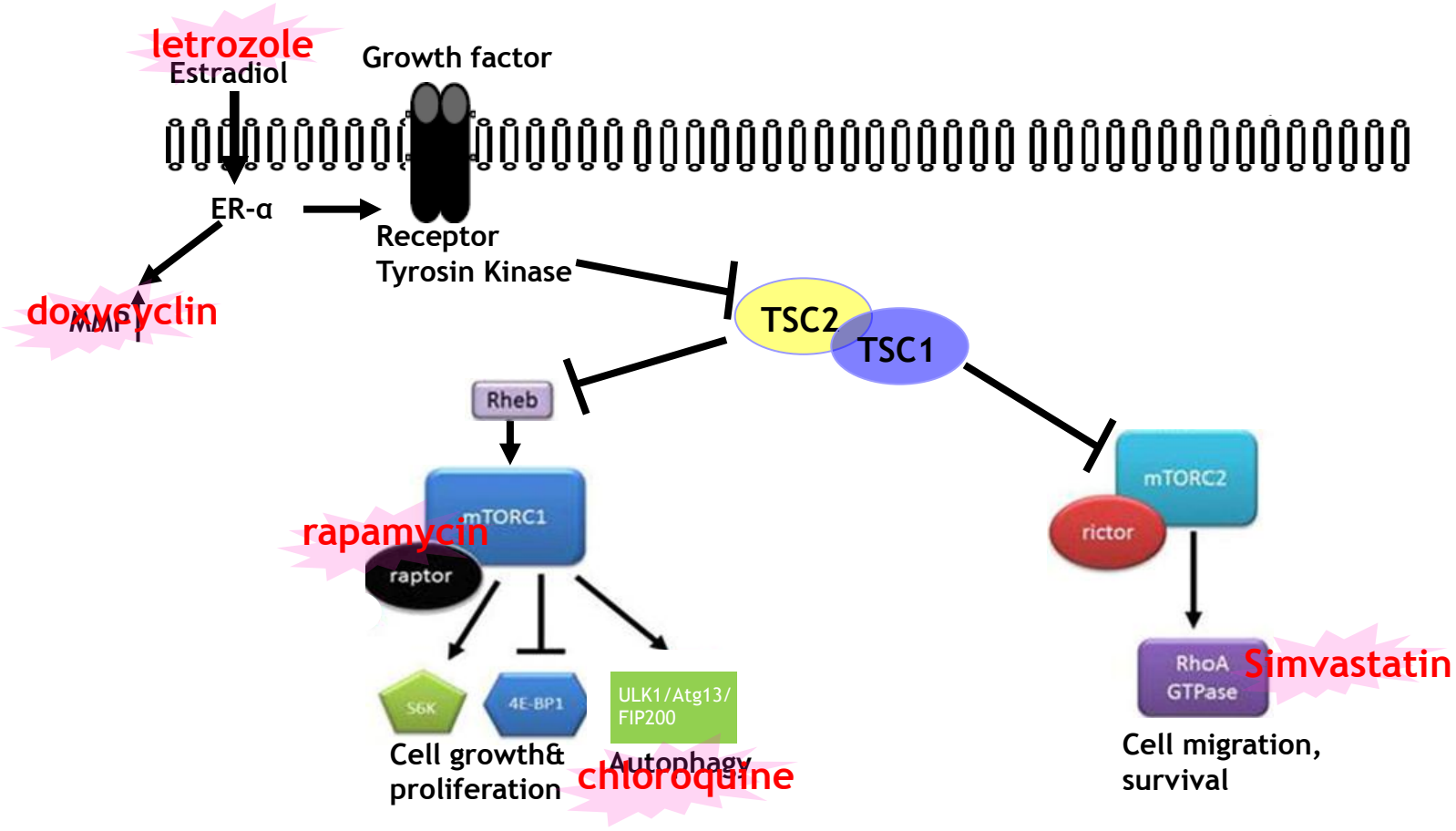
Eur Respir Mon 2009; 46; 176-207

LAM(Lymphagioleimyomatosis)-2



Eur Respir Mon 2009; 46 : 176-207
J Cell Biochem 2008; 103-369-382

LAM(Lymphagioleimyomatosis)-3



HORM CANC 2013; 4 : 70-77
Pharmacology & Therapeutics 2016; 158:114-124

LAM(Lymphagioleimyomatosis)-4

Definite LAM
1) characteristic or compatible lung HRCT
and
lung biopsy fitting the pathological criteria for LAM
or
2) characteristic lung HRCT plus any of the following:
angiomyolipoma (kd) #
thoracic or abdominal chylous effusion†
lymphangioleiomyoma or LN involved by LAM‡
TSC
Probable LAM
1) characteristic HRCT and compatible clinical historyf
or
2) compatible lung HRCT plus any of the following:
angiomyolipoma(kd) #
thoracic or abdominal chylous effusion†
Possible LAM
characteristic or compatible lung HRCT

#
: diagnosed by characteristic CT features and/or pathologic examination

†
: based on visual and/or biochemical characteristics of the effusion

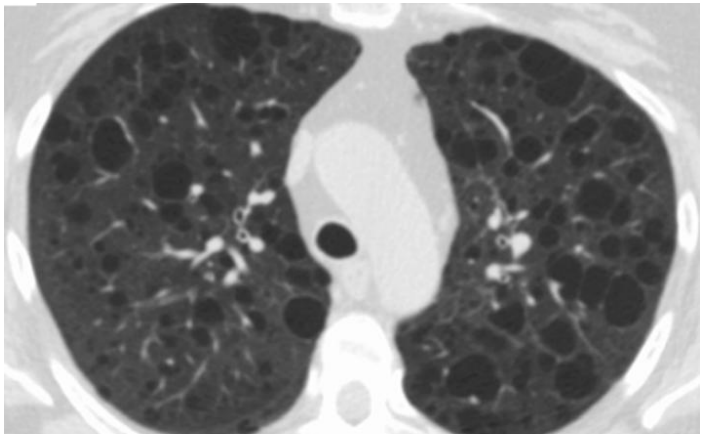
‡
: confirmed by tissue biopsy

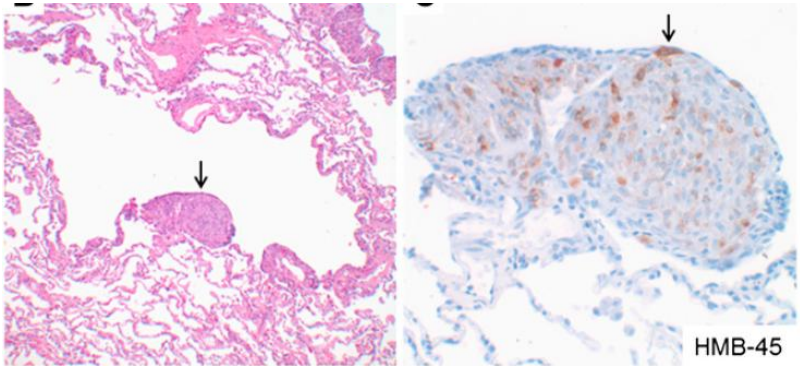
f
: PNX(especially multiple/bilateral) and/or altered lung function test

This criteria is only for females.
➔ 남자의 경우에는 characteristic or compatible HRCT & typical pathological features on lung Bx 가 필요

European Respiratory Monograph 46, December 2009
Eur Respir J 2010;35: 14-26

LAM(Lymphagioleimyomatosis)-5





- Cysts on CT

  +TSC, angiomyolipoma, LAPs,
  chylothorax,
  serum VEGF-D > 800 pg/ml,
  or Bx

Am J Respir Crit Care Med 2015; 191: 1354-1366
Semin Respir Crit Care Med 2012; 33: 486-497

LAM(Lymphagioleimyomatosis)-6

- Mx
  1) Angiomyolipomas > 4cm : embolization or mTOR Inhibitor
  2) Airflow obstruction : bronchodilator
  3) PNX : pleurodesis
  4) Lung transplantation
  5) Sirolimus : FEV_1 < 70%에서 placebo에 비해 stable lung function, improved QoL, improved functional performance
     chylous effusion, lymphangiomyoma에서도 effect(+)
     -- Optimal dose? Duration? S/E?

Am J Respir Crit Care Med 2015; 191: 1354-1366

LAM(Lymphagioleimyomatosis)-7

Prognostic clinical characteristic in LAM
Worse Px Dyspnea as presenting feature Wt loss Supplemental O_2 therapy Reversible airflow obstruction High VEGF-D
Better Px Pneumothorax as presenting feature Older age at diagnosis Higher FEV_1, DL_{CO} at diagnosis

Eur Respir J 2015; 46: 243-249

PLCH(Pulmonary Langerhans Cell Histiocytosis)-1

- Young adult smokers (F=M)
- aSx~ shortness of breath, cough, wt loss, fever, PNX(15%), skin rash, DI
- Langerhans cell: epithelial-associated dendritic cell
- Pathogenesis

  : cigarette smoking

  → cytokines(GM-CSF, TGF-ß, TNF-α), osteopontin release

  → Langerhans cell accumulation/activation

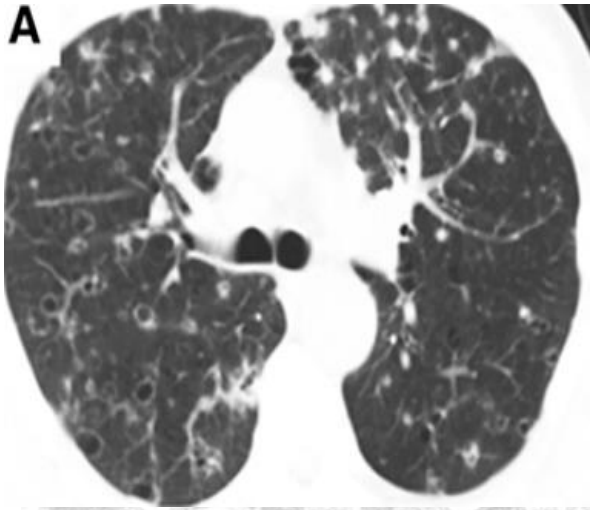
  → formation of nodules, airway remodeling, cystic change

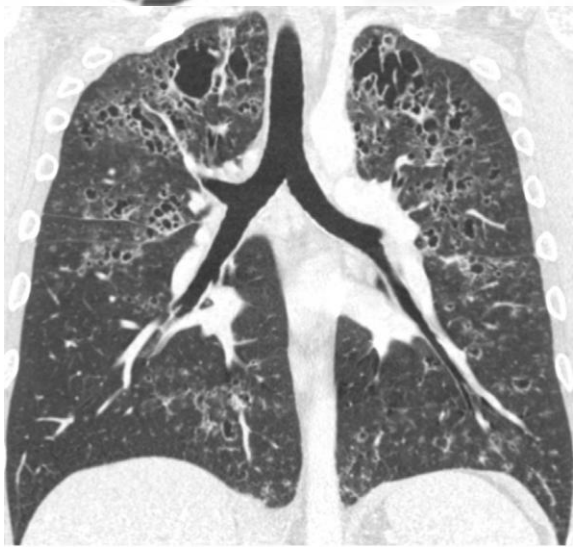
  or

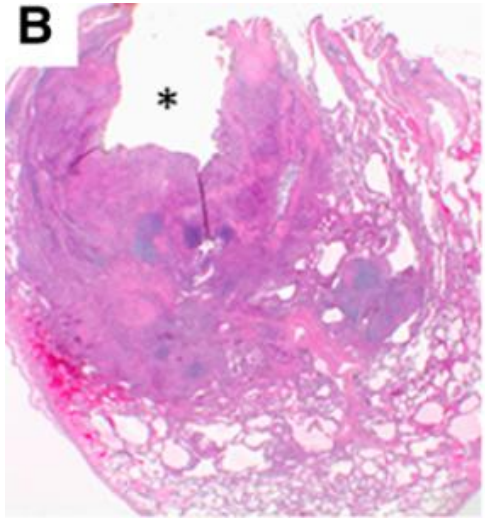
  clonal proliferative process: BRAF/ARAF/MAP2K1

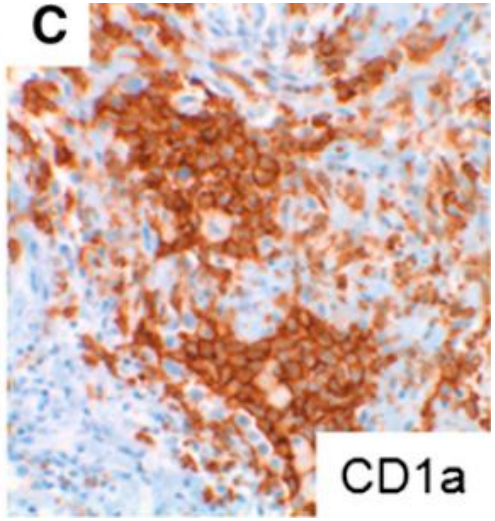
Am J Respir Crit Care Med 2015; 191: 1354-1366
J Clin Pathol 2013; 66: 904-908

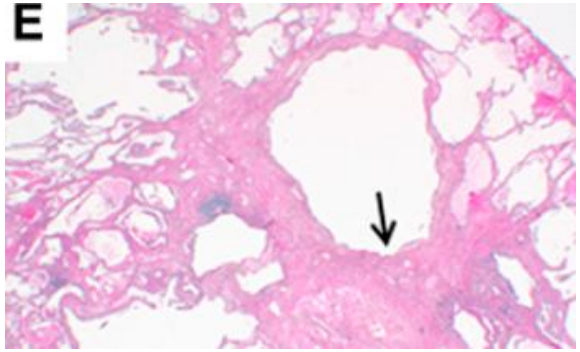
PLCH(Pulmonary Langerhans Cell Histiocytosis)-2











Am J Respir Crit Care Med 2015; 191: 1354-1366
Curr Probl Diagn Radiol 2014; 43: 115-127

PLCH(Pulmonary Langerhans Cell Histiocytosis)-3

- PFT: normal / restrictive → obstructive
  → PFT q 3-6months
- Tx
  1) smoking cessation
  2) pharmacotherapy: impaired lung function시 고려
     steroid ± vinblastine
     cladribine
     azathioprine, MTX
     BRAF inhibitor
  3) Cx: vasodilator for pul HTN, pleurodesis for PNX,
     lung transplantation

Am J Respir Crit Care Med 2015; 191: 1354-1366

BHD(Birt-Hogg-Dube syndrome)-1

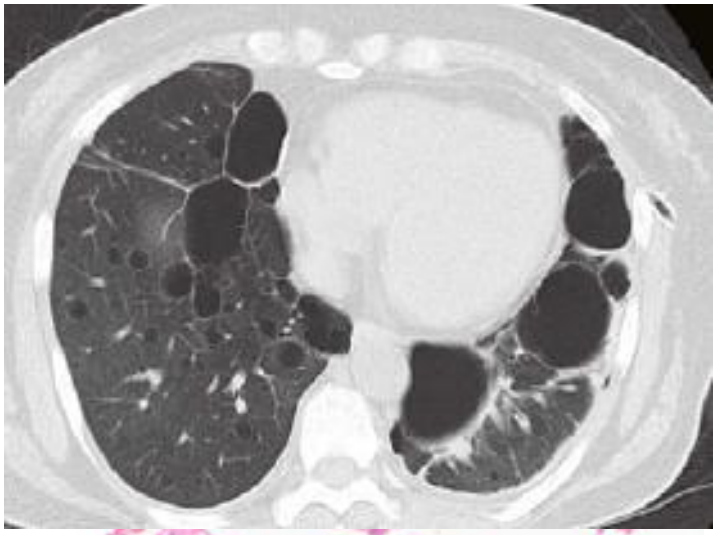
- Rare, autosomal-dominant
- Hair follicle tumor, renal neoplasm, pulmonary cysts

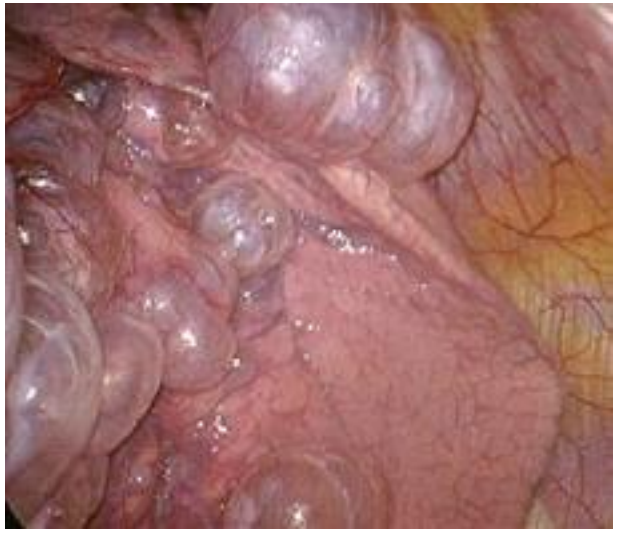
- 30-40대, PNX (75% recur)

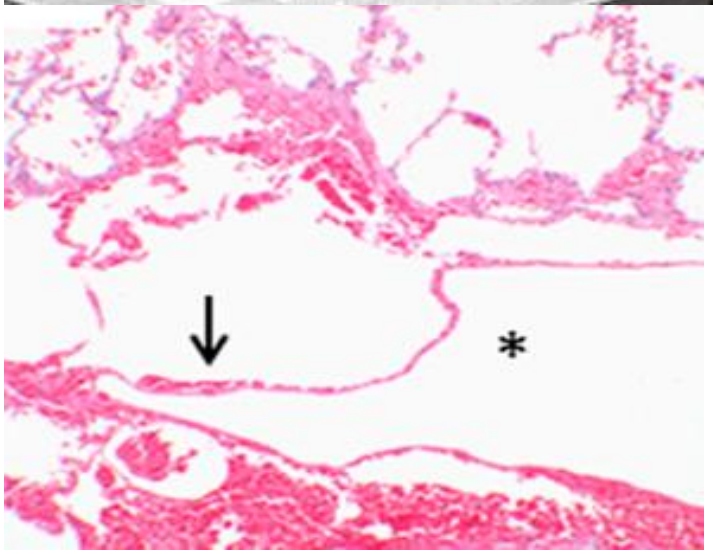
- Pathogenesis
  : FLCN(folliculin) gene mutation
  → 1) mTOR signaling 이상 야기
  2) tumor suppression 장애 (TGF-β/DENN protein)

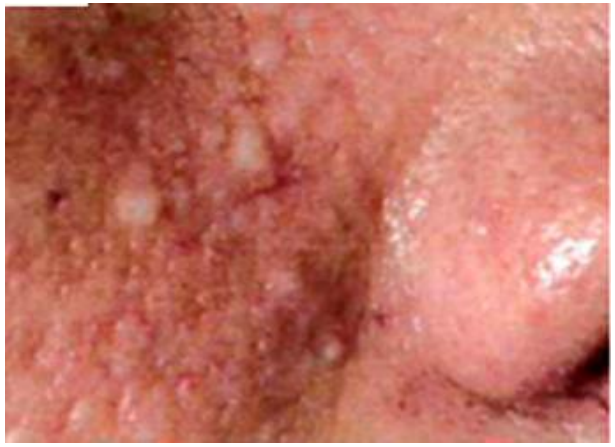
Am J Respir Crit Care Med 2015; 191: 1354-1366

BHD(Birt-Hogg-Dube syndrome)-2









Am J Respir Crit Care Med 2015; 191: 1354-1366
Int J Urol 2016; 23: 204-210

BHD(Birt-Hogg-Dube syndrome)-3

Proposed diagnostic criteria

Definite pulmonary BHD

1. Characteristic or compatible lung HR CT & skin Bx (fibrofolliculoma / trichodiscoma)
2. Characteristic or compatible lung HR CT & confirmed FHx of BHD(1^{st}/2^{nd} degree family)
3. Characteristic or compatible lung HR CT & renal Bx (chromophobe adenoma / oncocytoma)
4. Characteristic or compatible lung HR CT & genetic testing (+)

Probable pulmonary BHD

1. Characteristic HR CT, exclusion of TSC and LAM, & personal /FHx of PNX
2. Compatible HR CT, exclusion of TSC and LAM, and any of the following
   : a. personal of FHx of renal tumors
   b. skin angiofibroma
   c. renal angiomyolipoma

Possible pulmonary BHD

Characteristic lung HR CT findings

: multiple thin-walled round, elliptical or lentiform well-defined air-filled cysts, without internal structure, in a basilar, medial and subpleural predominant distribution, with preserved or increased lung volume, and no other significant pulmonary involvement (no ILD)

Compatible HR CT findings

: Thin walled cysts without the more typical elliptical shape or subpleural distribution

Fam Cancer 2013; 12: 387-396

BHD(Birt-Hogg-Dube syndrome)-4

- Rate of progression?

- PFT: preserved PFT/mild reduction of DL_{CO}
- Pleurodesis for PNX (75% recur)
- Renal tumor: begin screening at 20 yrs. q 3 yr

  → size>3cm시 nephrone-sparing resection

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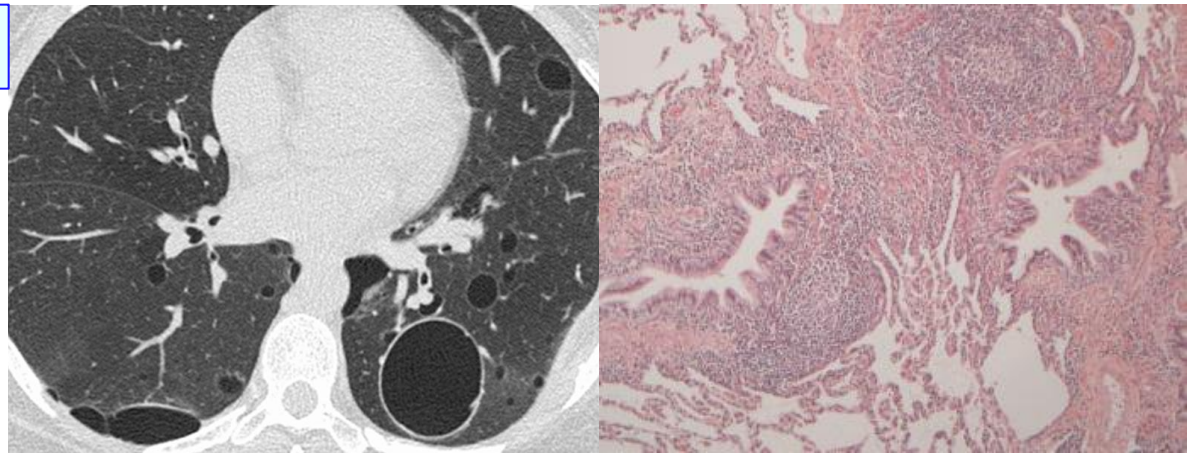
LIP/FP(Lymphocytic IP/Follicular Bronchiolitis)-1

- LIP : diffuse involvement of parenchyma by reactive lymphoid tissue
- FB : lymphoid follicular hyperplasia centered
  on airway, vv, interboluar septa (lymphatic distribution)

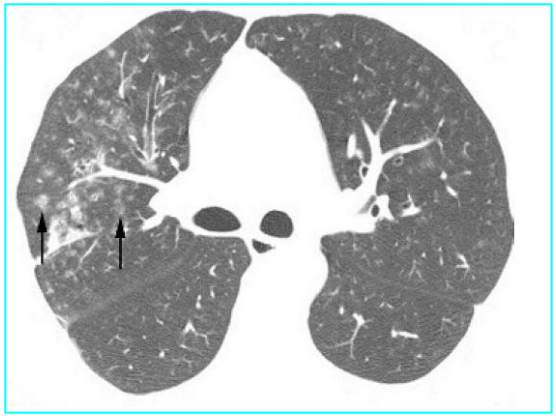
➔ idiopathic vs 2ndary (Sjogren syndrome(SS), RA, SLE, HIV..)

FB

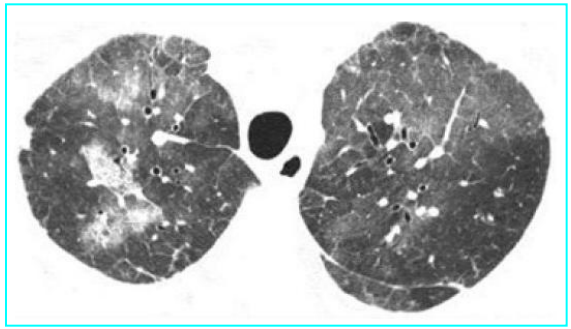


Am J Respir Crit Care Med 2015; 191: 1354-1366
Semin Respir Crit Care Med 2012; 33: 450-461

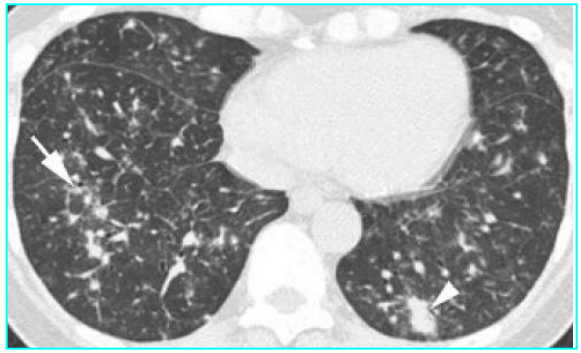
LIP/FP(Lymphocytic IP/Follicular Bronchiolitis)-2



Centrilobular GGO nodules

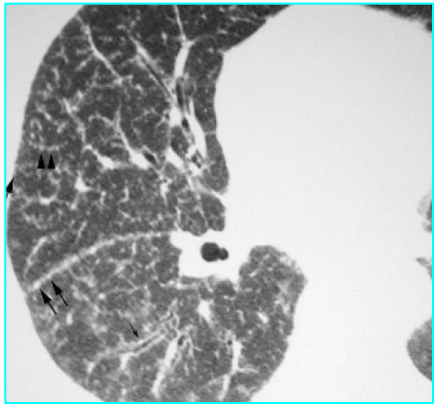


Multifocal GGO& consolidation



Peribronchovascular nodules, mild interlobular septal thickening, peribronchiolar consolidation

LIP

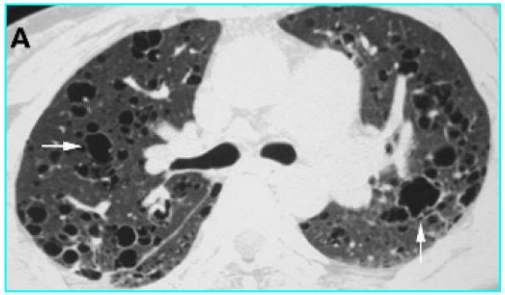


Costal/ fissual pleural nodules

Lymphatic distribution along peribronchovascular, interstitial septum.

Cyst- size from 1~ 30 mm

(아마도 d/t bronchial obstruction & air trapping)



Several thin-walled cyst

Thorax 2007;62: 546-553

LIP/FP(Lymphocytic IP/Follicular Bronchiolitis)-3

- CT: cyst - random distributed/ internal structure(+)
  16mm (3-52mm)
  GGO, centrilobular nodules, septal thickening
- PFT: LIP - restrictive
  FB – obstructive
- Natural Hx?
- Efficacy of steroid for cystic LIP/FB ?

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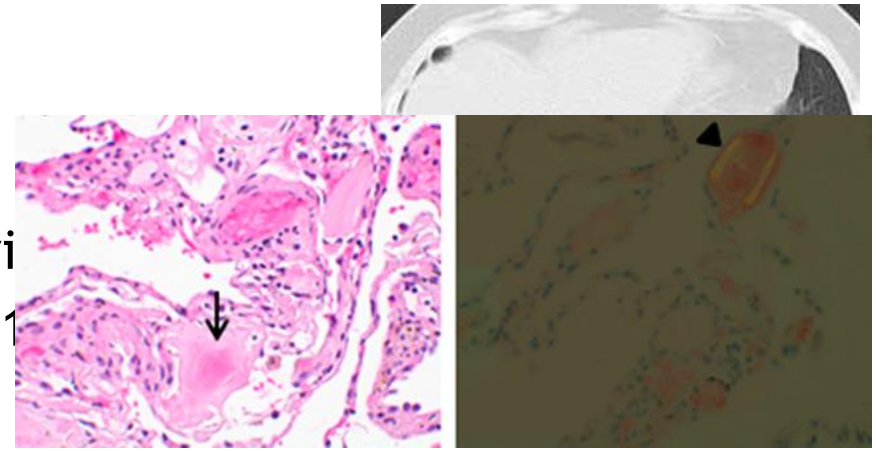
Amyloidosis-1

- Heterogeneous group of disorders
- Characterized by extracellular deposition of proteins in an abnormal fibrillary fashion

  → SS, MALT lymphoma..



- CT: Multiple nodules that may cavi

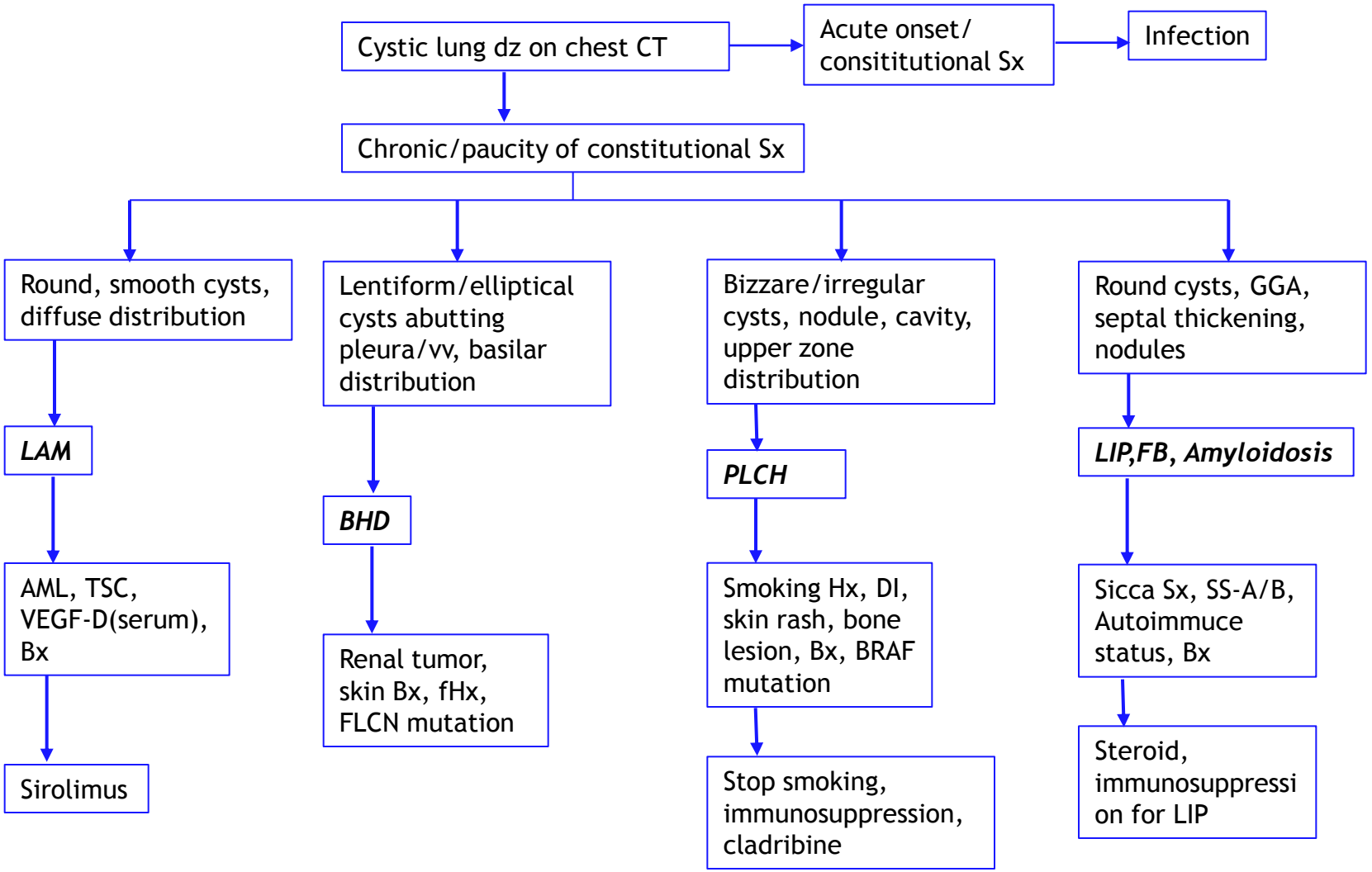
  4-45mm, majority larger than 1
- Bx: fibrillary deposits

  (apple-green birefringence (Congo red stained))

- Tx?

Am J Respir Crit Care Med 2015; 191: 1354-1366
Cleve Clin J Med 2015; 82: 115-157

Summary



Am J Respir Crit Care Med 2015; 191: 1354-1366

경청해 주셔서 감사합니다