Pulmonary Langerhans Cell Histiocytosis

What's the News ?

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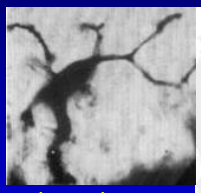
Outline - PLCH

- Introduction
- Diagnosis
  - Clinical findings
  - Histologic features, IHC
  - Role of biopsy in diagnosis
- Pulmonary hypertension
- Outcome and treatment
- Pathogenesis
- Summary

Paul Langerhans (1847-1888)

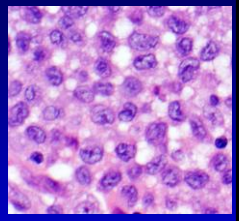
- German pathologist, physiologist, biologist
- Langerhans cells in the skin
- Islets of Langerhans in pancreas



Sholles J. J Clin Pathol. 2002;55:243.

Langerhans Cell Histiocytosis

- Rare histiocytic disorder with Langerhans cell (LC) phenotype
- LC = Dendritic cells in skin, mucosa (S100+, CD1a+, Langerin+, BG)



- Skin LC ≠ cell of origin for LCH (molecular)
- Myeloid DC = cell of origin (expresses same antigens as skin LC)

Pulmonary vs Systemic LCH

LCH	Pulmonary	Systemic
Incidence	4-5% of bxs for diffuse lung disease	3-5/Mio/year (children)
Age	Adults 2^{nd}-4^{th} decade	Children (1-3 y.o.) but any age
Sex	No predilection	?male
Smoking	>90%	Present / absent

PLCH - Clinical Presentation

- Incidental finding on chest radiograph
- Respiratory and/or constitutional symptoms
- Spontaneous pneumothorax (15%)
- Symptoms due to extra-pulmonary disease (polyuria, polydipsia, pain, skin rash) (10-15%)
- Hemoptysis uncommon (other diagnosis?)

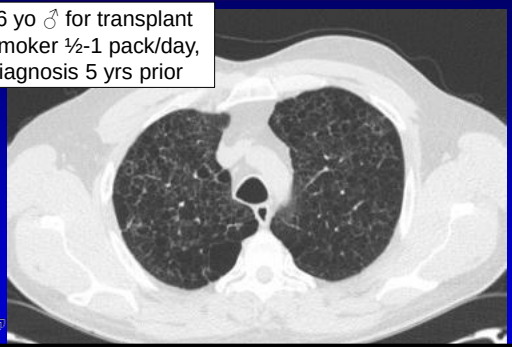
HR-CT

- Bronchiolocentric lesions in upper-middle lungs; relative sparing of lung bases
- Early: Bronchiolocentric nodules +/- GGO
- Advanced: - Cysts
  - Paracicatricial emphysema
- End stage: Fibrocystic
- FDG-PET uptake in 45% of patients (early)

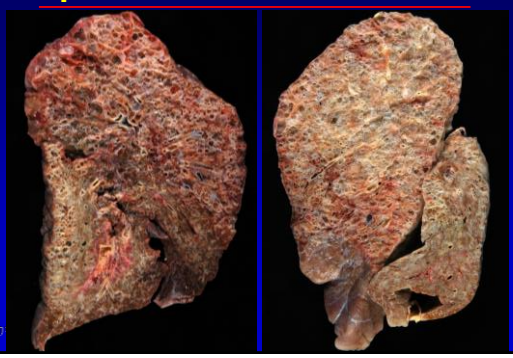
Castoldi MC et al. Insights Imaging 2014;5:483-92.

HRCT-Scan – Advanced PLCH

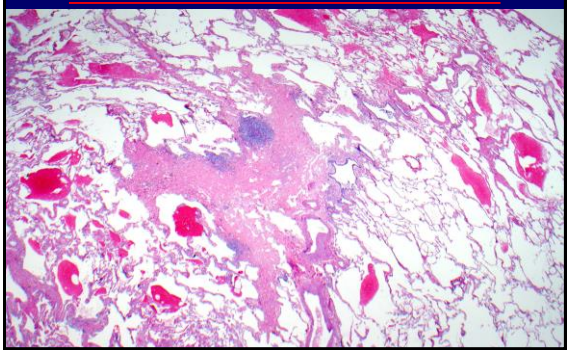
46 yo ♂ for transplant
Smoker ½-1 pack/day,
Diagnosis 5 yrs prior



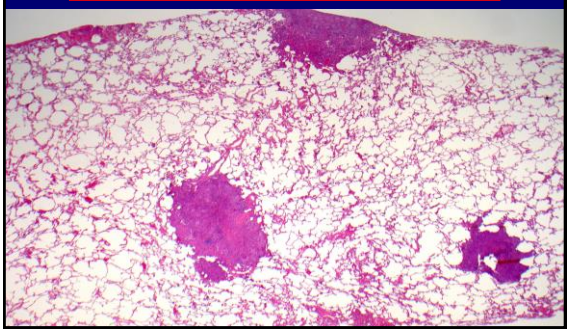
Explants for Advanced PLCH



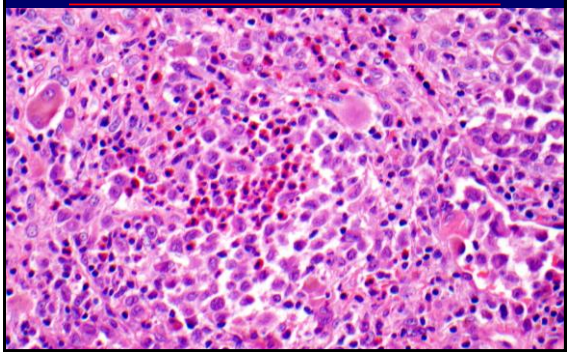
Morphology – Advanced PLCH



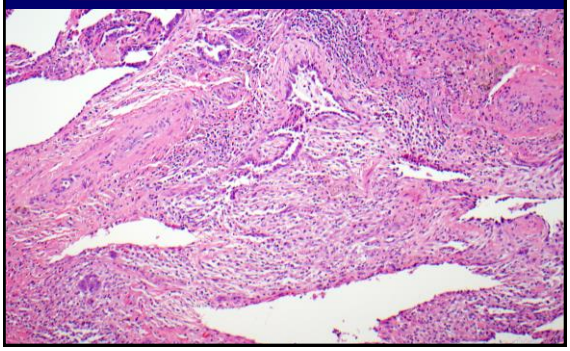
Early Disease – Bronchiolocentric Nodules



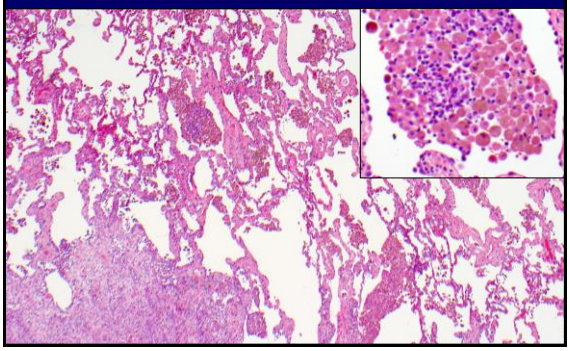
LC-nodules with inflammation



Destructive Bronchiolitis



Smoking-related changes

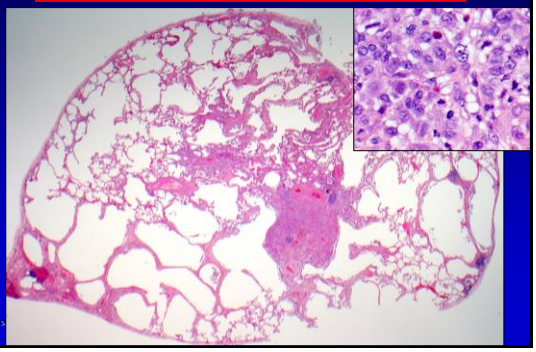


Role of Bx in diagnosis of PLCH

- 38 patients with PLCH
- Diagnosis established by
  - 50% - TBBx
  - 45% - Surgical lung biopsy (all had prior non-diagnostic TBBx)
  - 11% - Bx of extrapulm site and/or
  - 8% - BAL

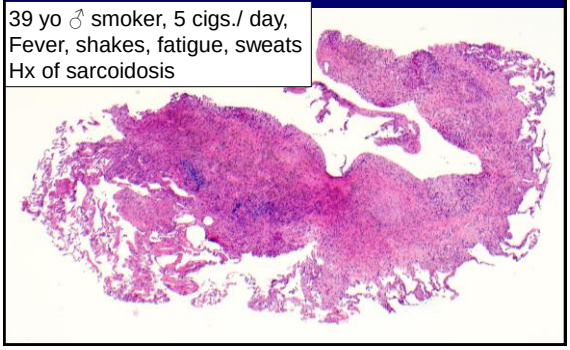
Baqir m et al. J Bronchol Intervent Pulmonol. 2013;20:309-12

Surgical Bx → Def. Diagnosis



TBBx → Diagnostic in 17-50%

39 yo ♂ smoker, 5 cigs./ day,
Fever, shakes, fatigue, sweats
Hx of sarcoidosis



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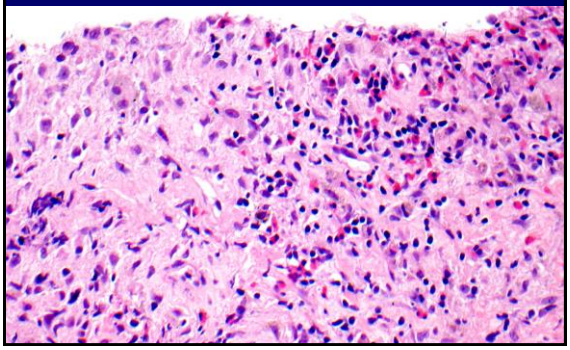

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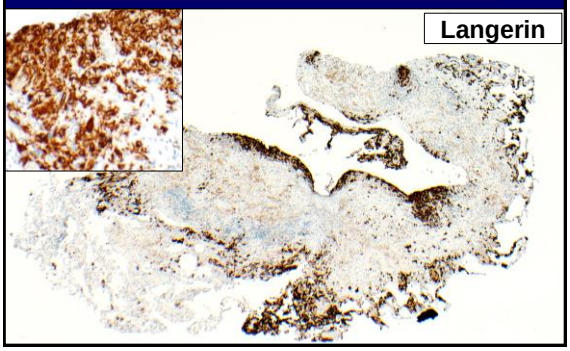


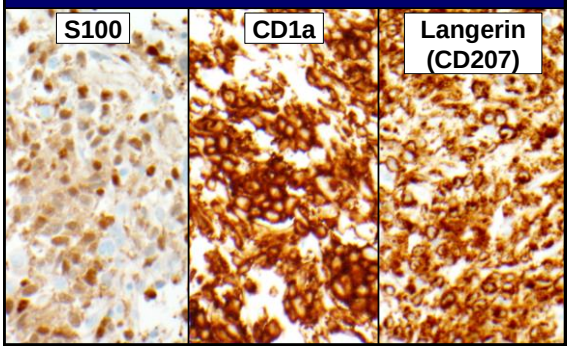
BAL in diagnosis of PLCH

- ≥ 5% CD1a+ cells = probably diagnostic but infrequent
- Can be difficult in practice (infrequent use → problems with associated costs and quality assurance)

Cryobiopsies – might be promising

- More to come

Immunohistochemistry of LCs



IHC of LCs

Diagnosis	S100	CD1a	Langerin
(n=10)	Mean # Cells per HPF		
PLCH, lesion	> 100 (39->100)	> 100 (37->100)	> 100 (37->100)
Uninvolved lung	12 (4-50)	7 (4-40)	9 (4-25)

Sholl L et al. Am J Surg Pathol. 2007;31:947-52

IHC of LCs

- Langerin - LC-specific, initiates Birbeck granule formation
- CD1a, Langerin – more specific than S100

- CD1a: 94 – 100% sensitivity in comparison to Langerin in PLCH

Sholl L et al. Am J Surg Pathol. 2007;31:947-52
Lau SK et al. Am J Surg Pathol. 2008; 32:615-9.
www.derm101.com

Pulmonary Hypertension in PLCH

- Common & severe, no predictors for PHT
- Echo study: 15/17 pts - PASP >35 mmHg
- 92%–100% in advanced PLCH-patients
- Associated with ↑ mortality
- Severity not correlated with lung function
- Severe PHT - not limited to end-stage PLCH

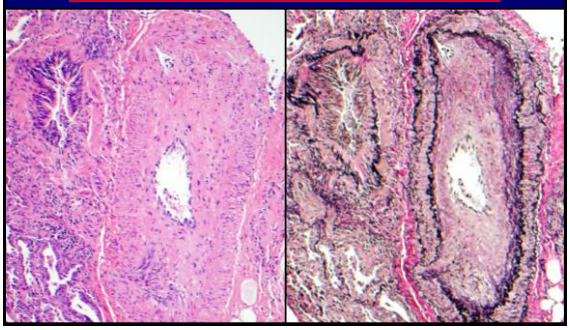
Lahm T et al. Clin Chest Med. 2013. 34:753-778.
Chaowalit N et al. Mayo Clin Proc 2004;79:1269-75.
Dauriat G et al. Transplantation. 2006; 81:746-50
Fartoukh M et al. Respir Crit Care Med. 2000; 161:216-23.

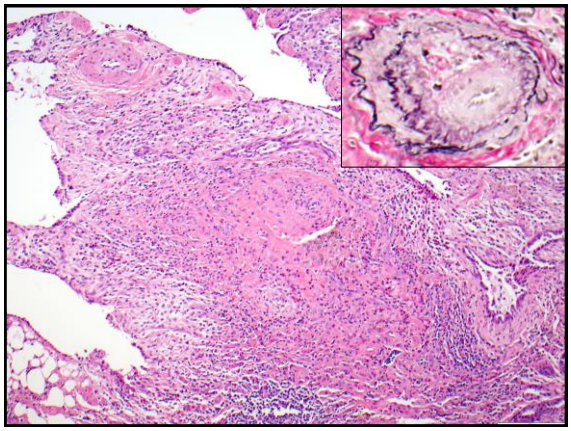
5th World Symposium – 2013
Current Classification of PHT

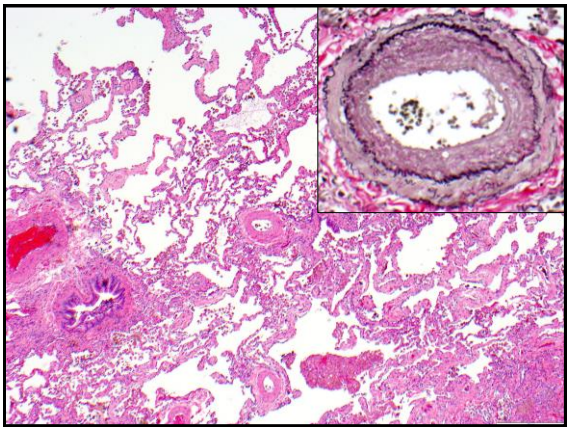
1. Pulmonary arterial hypertension (PAH)
1' PVOD and/or PCH
1'' Persistent PHT of the newborn
2. PHT due to left heart disease
3. PHT due to lung diseases and/or hypoxia
4. Chronic thromboembolic PHT
5. PHT with unclear multifactorial mechanisms

Simonneau G et al. 2013. J Am Coll Cardiol. 62. D34-41.

PA with intimal fibrosis & medial hypertrophy







PHT in PLCH

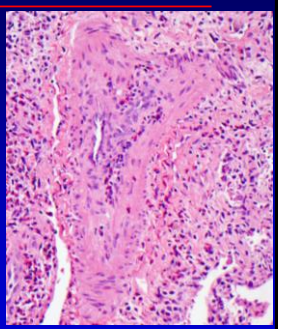
- Pulmonary arterial and venous changes
- PA - Diffuse medial hypertrophy
  - Intimal fibrosis and/or proliferation
- PV - Intimal fibrosis, muscularization
- PVOD-like disease in 1/3 of specimens
- Vascular changes also frequently in regions not affected by PLCH lesions

Fartoukh M et al. Am J Respir Crit Care Med. 2000. 161:210-23.

Pathogenesis of PHT in PLCH

- Not well understood.
- LCs infiltrate walls of small & medium-sized PAs in prominent PLCH nodules

→ Specific pulmonary vasculopathy?



Lahm T et al. Clin Chest Med. 2013. 34:753-778.

Pathogenesis of PHT in PLCH

- Cytokines, growth factors released by PLCH nodules (IL-1, IL-6, TGFβ, PDGF)
  → Diffuse pulmonary vascular remodeling
- No correlation PFT and hemodynamics
  → PHT unlikely due to hypoxemia, or cystic destruction.
- Cigarette smoke - known inducer of pulmonary vascular remodeling

Lahm T et al. Clin Chest Med. 2013. 34:753-778.

Treatment of PLCH

Smoking cessation

Corticosteroids, cyclophosphamide, MTX-limited value

Cladribine (2-chlorodeoxy-adenosine)

Transplantation

Prognosis of PLCH

- Progressive, stable or resolve – unpredictable even after smoking cessation
- 5-yr survival estimate ≥73%
- Recurrent pneumothorax (15-25%)
- 1/3-1/2 of death due to respiratory failure
- No markers to predict prognosis or behavior
- ↑ Secondary malignancies (hematologic, lung Ca, carcinoid tumor)

Pathogenesis - PLCH

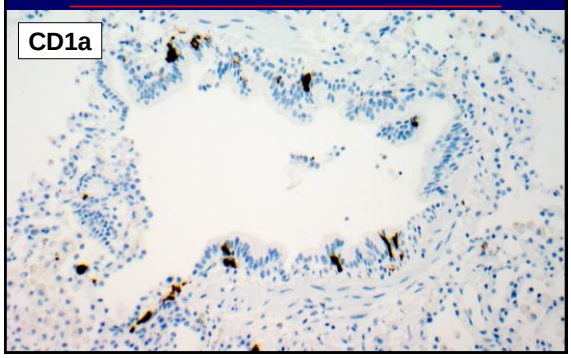
Largely unknown

Langerhans cells = sub-population of DCs

- Mucosa of tracheobronchial tree
- Primary line of defense, survey inhaled antigens
- Danger signals (Toll-like receptors on infectious pathogens; factors released by injured or necrotic cells) → Activation of LC

Suri HS et al. Orphanet J Rare Dis. 2012;7:16

LC in Bronchiolar Submucosa

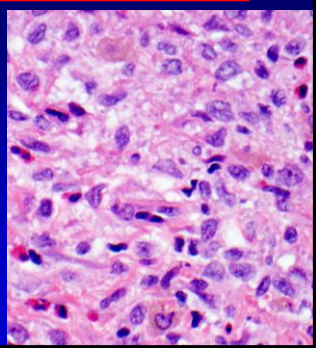


Pathogenesis - PLCH

Immune modulated?

LC nodules with inflammatory cells (eos, T_{reg}, activated macrophages)

Abnormalities in systemic immune function



Suri HS et al. Orphanet J Rare Dis. 2012;7:16

Cigarette Smoking & PLCH

- ↑ Bombesin-like peptide
  - Chemotactic for monocytes
  - Stimulate cytokine secretion
- ↑ Osteopontin
  - Chemotactic LCs & DCs
- Tobacco glycoprotein (in tobacco)
  - Induces lymphocyte differentiation and lymphokine production

Suri HS et al. Orphanet J Rare Dis. 2012;7:16

Cigarette Smoking & PLCH

- May alter turnover of DC in lung or facilitate recruitment of LC and DC precursors
  - ↑ LCs in other lung diseases of smokers (COPD, certain ILDs, lung Ca)
- Might promote DC and LC differentiation, activation and survival by
  - ↑ Cytokines for recruitment and activation of LC & DC
  - ↑ Anti-apoptotic Bcl-xL

Suri HS et al. Orphanet J Rare Dis. 2012;7:16

Pathogenesis of PLCH

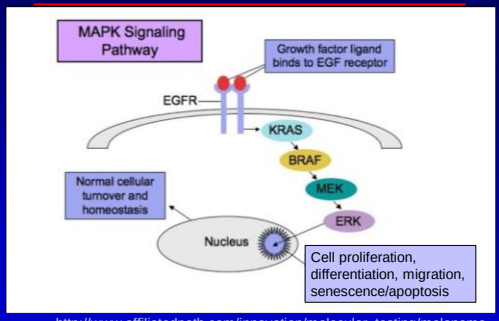
- Only a few smokers develop PLCH
  - Second hit by host factors
  - Exogenous factors /insult (virus) ?
  - Failure of anti-inflammatory reaction ?
- Clinical spectrum of PLCH seems diverse
  - Many have favorable prognosis +/- smoking cessation
  - Subset has poor prognosis

PLCH-Reactive or Neoplastic ?

- PLCH thought to be smoking-related, non-neoplastic
- Systemic LCH – no inciting agent identified
- Systemic LCH - Clonality of LCs described in 1994
- *BRAF* V600E mutations in 38-57% of systemic LCH by PCR → at least subset of LCH might be myeloid neoplasm

Willman CL et al. N Engl J Med. 1994;331:154-60
Badalian-Very G et al. Blood. 2010;116:1919-23.

BRAF



http://www.affiliatedpath.com/innovation/molecular_testing/melanoma_pathways/melanoma.html

BRAF

- *BRAF* Mutations – malignant (melanoma, colonic & lung adenoCa, papillary thyroid carcinoma) and benign (nevi) tumors
- 22 PLCH-nodules from 5 patients, NGS
  - *BRAF* V600E mutation in all nodules from 2 (of 5, 40%) pts
  - no mutations in any nodule of 3 pts

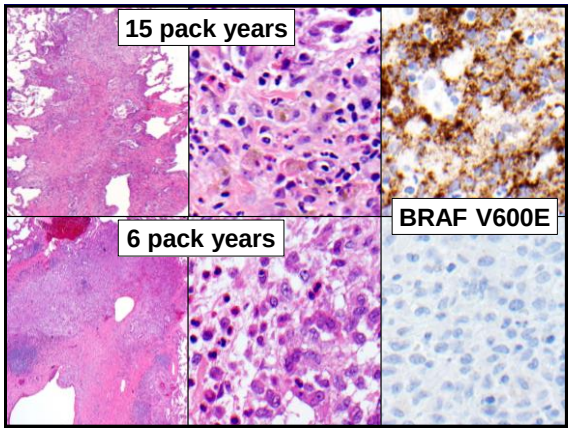
→ PLCH - clonal process ?

Yousem SA et al. 2013. Chest;143:1679-84.

BRAF-Expression in PLCH

BRAF V600E Expression	PLCH (n=25)	Extrapulmonary LCH (n=54)
% positive cases	28	35
Mean Pack Years of Smoking		
BRAF positive cases	48.3	8.9
BRAF negative cases	23.7 P=0.012	11.3 P=0.867

MAYO CLINIC Roden AC et al. 2014. Am J Surg. Pathol;38:548-51.



BRAF Mutations in PLCH

- PCR (mutation) vs IHC (protein expression) – discordant in n=3 (of 68, 4.4%):
  - 2 bone bxs: PCR positive, IHC negative;
  - 1 PLCH bx: PCR wt, IHC positive

→ IHC correlates with mutation status in most cases

MAYO CLINIC Roden AC et al. 2014. Am J Surg. Pathol;38:548-51.

PLCH – What's New ?

- CD1a & Langerin are good markers
- PHT – common and severe
- Pathogenesis of PLCH - related to host and smoking-related immune modulation ?
- A subset of PLCH might be clonal
- BRAF expression associated with smoking
- BRAF targeted therapy might be useful

MAYO CLINIC