
Pulmonary Langerhans Cell Histiocytosis

Morphology • smoking association • molecular biology • clinical course

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Why this pulmonary disorder deserves recognition

Distinctive histology

Focal Langerhans cell collections, sometimes with eosinophils.

Structural injury

Progressive scarring damages airways and alveoli, producing irregular cysts.

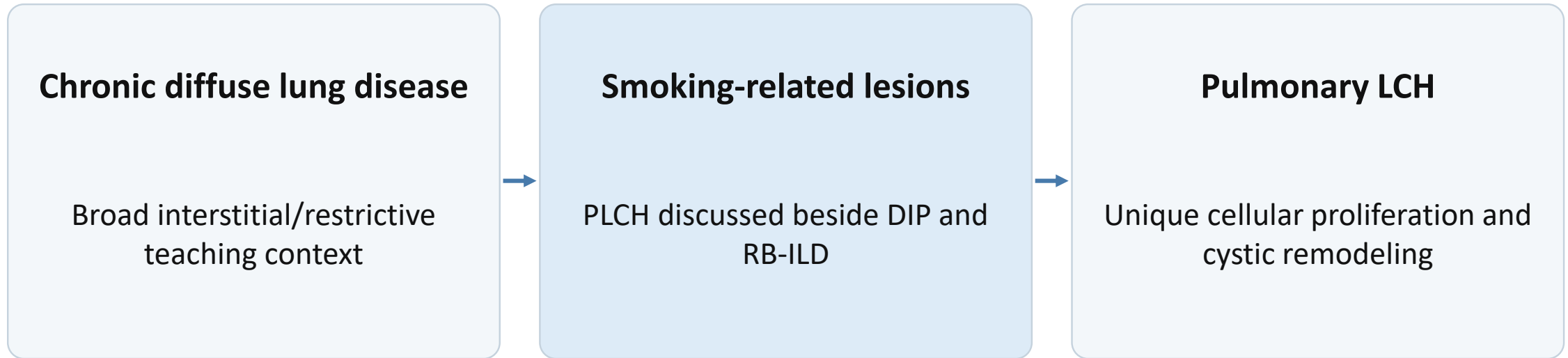
Biologic duality

Smoking responsiveness coexists with evidence of BRAF-driven neoplasia.

Learning objectives

- Recognize the defining cellular population and supportive morphologic features.
- Explain the link between cellular lesions, fibrosis, airway damage, and cyst formation.
- Interpret the smoking association and BRAF mutations without conflating them.
- Differentiate PLCH from adjacent smoking-related interstitial diseases.
- Integrate clinicopathologic evidence and the variable natural history.

Place within diffuse pulmonary diseases



Conceptual schematic — editable PowerPoint geometry

PLCH is a pulmonary phenotype of LCH

Pulmonary presentation

Disease usually discussed in the setting of adult cigarette smoking; Lung injury and cystic remodeling dominate.

Wider LCH spectrum

Histiocytoses are clonal proliferations of dendritic-lineage cells, with several extrapulmonary patterns.

What the term “histiocytosis” encompasses

Reactive disorders

Some histiocytic proliferations are entirely non-neoplastic.

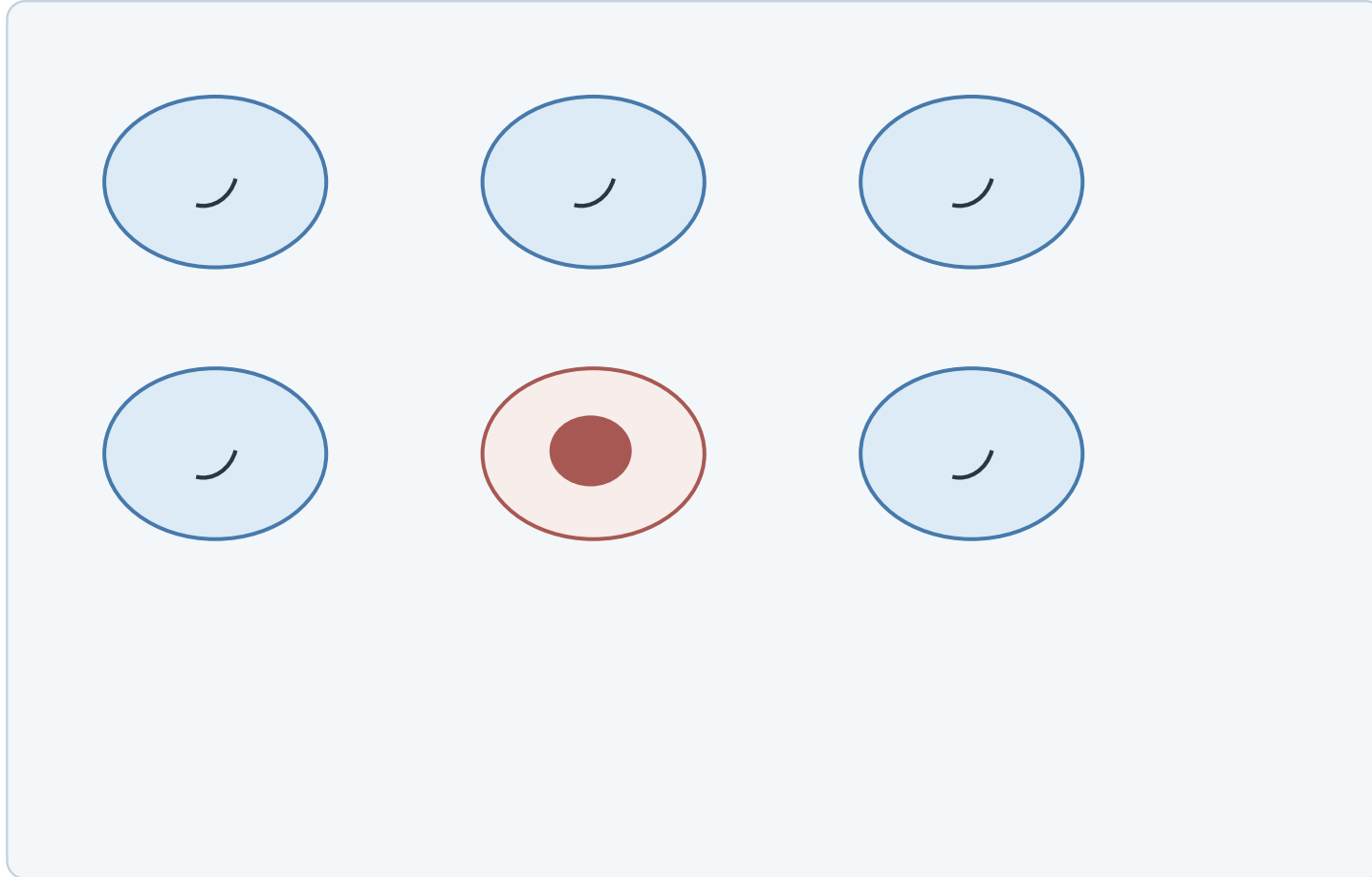
Langerhans cell histiocytosis

Clonal disorders of Langerhans-type immature dendritic cells.

Aggressive entities

Other histiocytic/dendritic tumors can have high-grade malignant behavior.

Cell of interest: The Langerhans cell



Langerhans cells

Pale cytoplasm and nuclear folds support cellular recognition.

Eosinophils

May be admixed; They do not define the proliferating cell lineage.

Why pulmonary LCH is biologically distinctive

Smoking-linked phenotype

Most affected adults are smokers or former smokers, with frequent benefit from smoking cessation.

Driver-mutated subset

Activating BRAF changes demonstrate that a subset belongs in the spectrum of neoplasia.

Pulmonary disease is rare

Rare, but pattern-forming

The importance is not prevalence: A recognizable combination of Langerhans cells, nodules, cysts, and smoking exposure makes the entity distinctive.

Strong epidemiologic association with smoking

>90%

**Current or former
smokers**

More than 90% of affected patients as relatively young adult smokers or ex-smokers. This is a case-series description of disease association, not a quantified causal risk among smokers.

Association does not establish an exclusive cause

- A strong smoking association does not imply that every exposed individual develops PLCH.
- Smoking status is supportive clinical context, not histologic proof of Langerhans cell proliferation.
- The biologic behavior cannot be predicted from smoking exposure alone.

Smoking cessation is biologically informative

~50%

Improve after cessation

Among affected smokers, about half show improvement after smoking cessation in the Robbins account. Improvement is compatible with an exposure-responsive component, but does not establish a non-neoplastic mechanism in every patient.

Two interpretations can coexist

Exposure-responsive inflammation

Lesions may improve after removing cigarette smoke, supporting an inflammatory/reactive contribution in some cases.

Clonal neoplasia

Other lesions contain activating BRAF mutations; This molecular finding supports neoplastic proliferation.

Why the reactive–neoplastic contrast is not a binary test

- Clinical regression and neoplastic driver mutations address different aspects of biology.
- A lesion with a driver mutation need not progress relentlessly.
- A lesion that improves with cessation is not automatically demonstrated to lack a driver mutation.
- Avoid inferring molecular status solely from clinical behavior.

BRAF: A molecular clue to clonality



Conceptual schematic — editable PowerPoint geometry

Pulmonary-specific BRAF frequency

40%

**BRAF-mutated
pulmonary LCH**

Chapter 13 reports BRAF mutations in approximately 40% of pulmonary lesions. This pulmonary-specific figure must not be replaced by the higher figures reported for LCH overall.

Genetics of the wider LCH spectrum

RAS signaling

More than 85% of general LCH cases have a driver in components of RAS signaling.

BRAF V600E

A common activating variant in the wider LCH spectrum; General LCH frequency is 55–60%.

MAPK1

Encodes a kinase downstream of BRAF and can be mutated in general LCH.

Do not transplant general LCH rates into PLCH

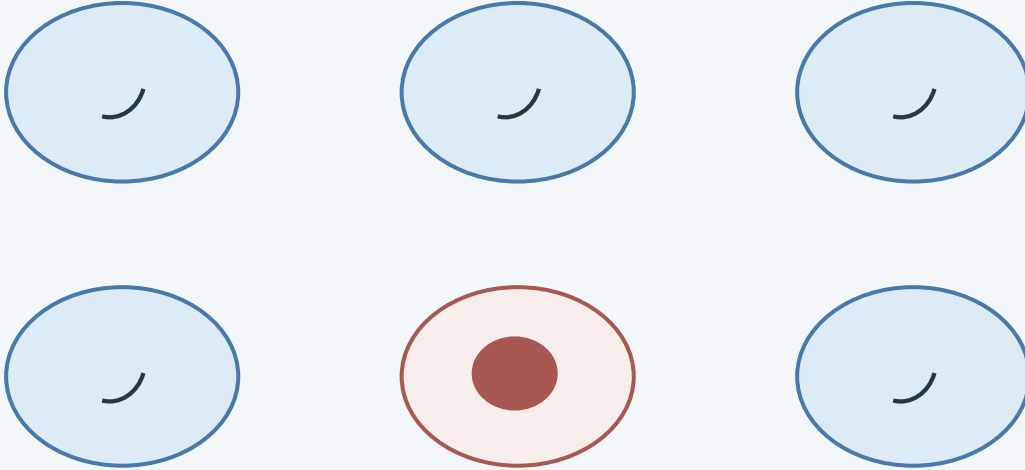
General LCH

BRAF alterations in 55–60%, within a broader group of RAS-signaling drivers.

Pulmonary LCH

The same textbook separately states a BRAF mutation frequency of about 40% in pulmonary disease.

What establishes the basic lung lesion?



Langerhans cells

Pale cytoplasm and nuclear folds support cellular recognition.

Eosinophils

May be admixed; They do not define the proliferating cell lineage.

Eosinophils accompany—but do not define—the lesion

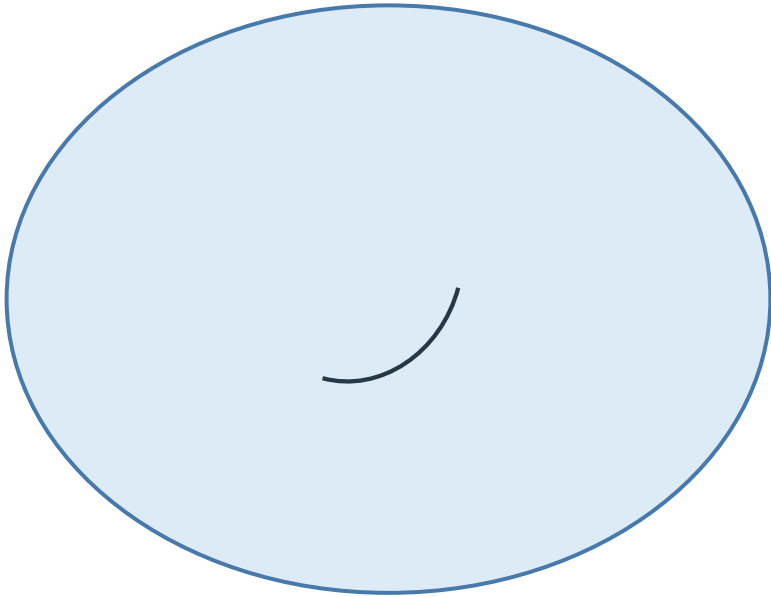
Defining component

Focal accumulation of Langerhans cells is central to the pulmonary entity.

Variable accompaniment

Eosinophils are often present; Their presence alone cannot establish Langerhans cell identity.

Cytologic recognition: Nuclear grooves and folds



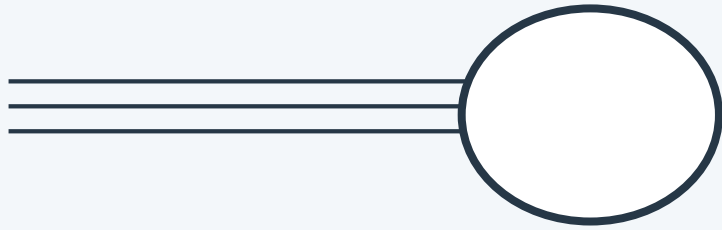
Nuclear grooves or folds

Morphologic clue in Langerhans cell proliferations; Interpreted with other features.

Cytoplasm: Pale and sometimes vacuolated

- Proliferating Langerhans cells have abundant cytoplasm in the general LCH description.
- The cytoplasm may appear vacuolated.
- Cell shape and nuclear contours are useful morphologic clues rather than stand-alone molecular evidence.

Birbeck granules: Ultrastructural signature



Birbeck granule — stylized

Pentalaminar tubule with terminal dilatation

A characteristic ultrastructural feature containing langerin; The “tennis-racket” analogy describes its profile.

Characteristic immunophenotype in general LCH

CD1a

Typical expression supports Langerhans cell differentiation.

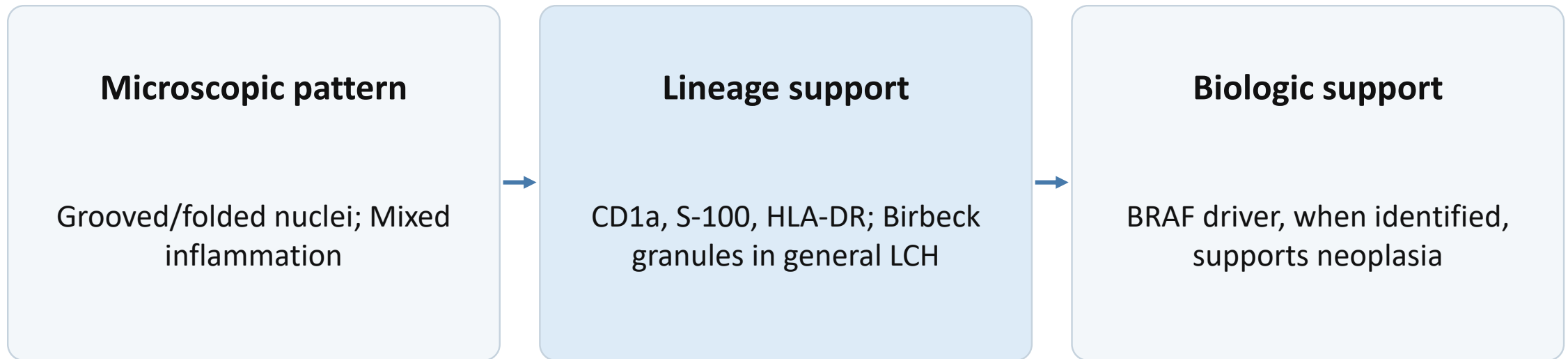
S-100

Frequently expressed;
Interpreted within the wider lineage panel.

HLA-DR

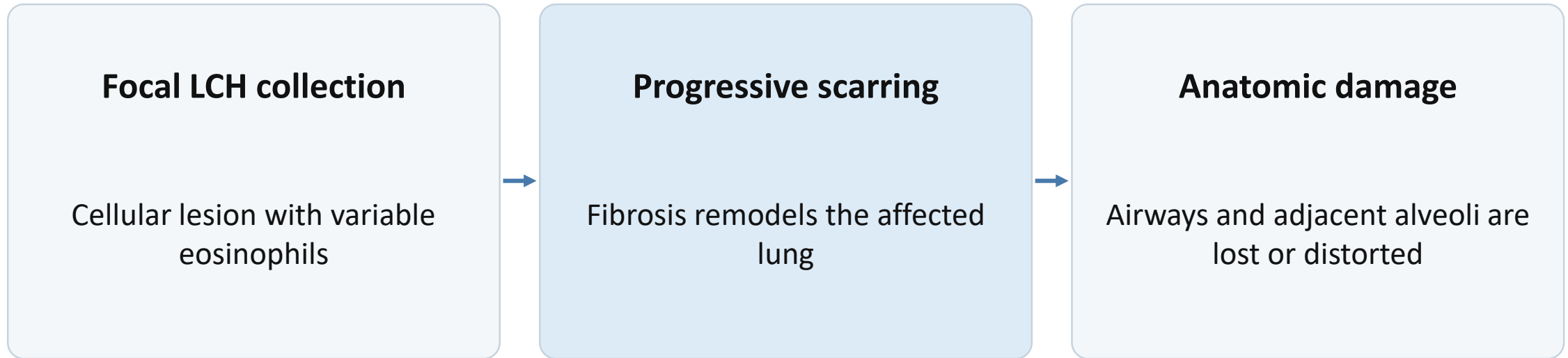
Another typical marker'
LCH morphology section.

Histology, phenotype, and mutation are complementary



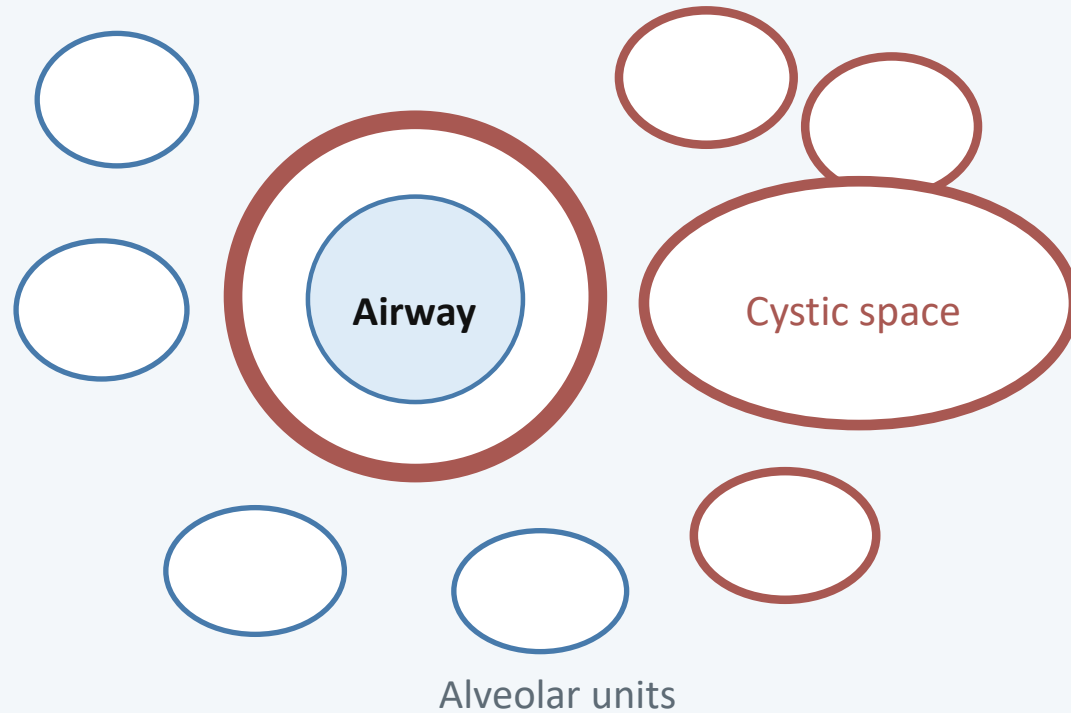
Conceptual schematic — editable PowerPoint geometry

Evolution: Cellular lesions can become fibrotic



Conceptual schematic — editable PowerPoint geometry

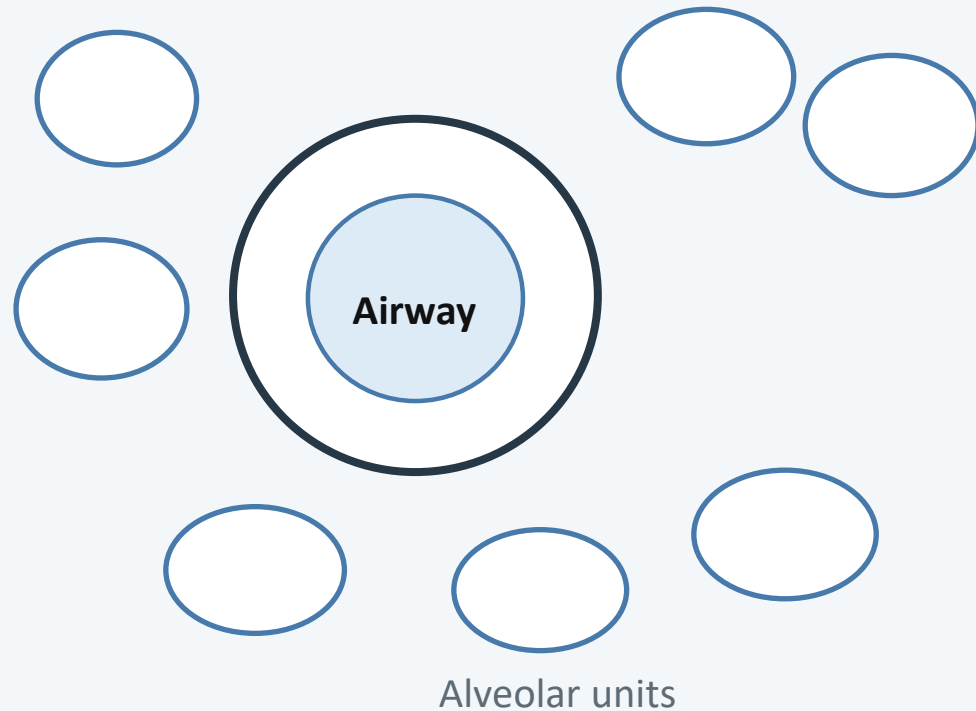
The airway is a target of destructive remodeling



Scarring changes geometry

Fibrosis damages airways and neighboring alveolar tissue; Progressive tissue destruction may leave irregular cystic spaces.

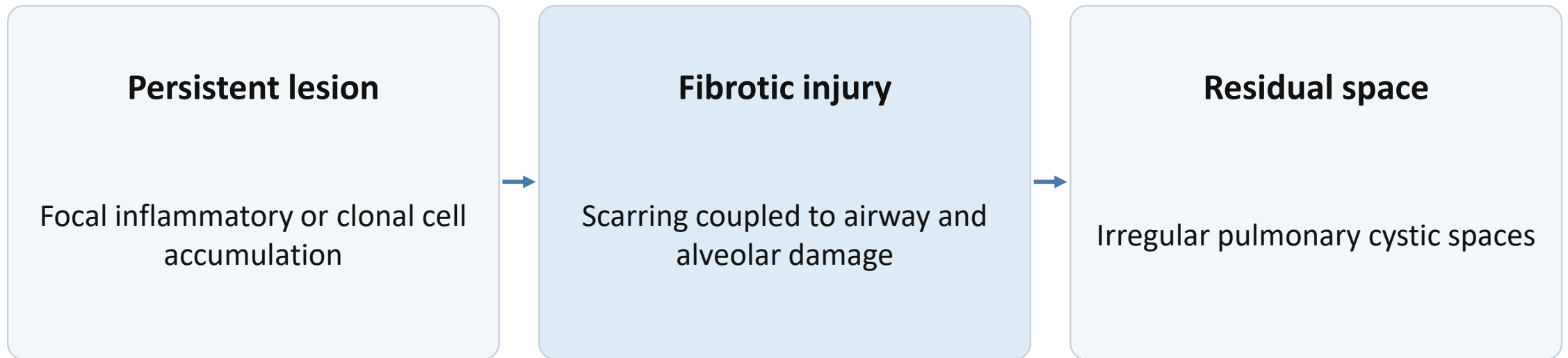
Alveolar injury contributes to architecture loss



Functional lung architecture

An airway and adjacent alveoli form a connected unit; Changes in either compartment can affect lung architecture.

How irregular cystic spaces arise



Conceptual schematic — editable PowerPoint geometry

Why “irregular cysts” matters morphologically

Cysts reflect destruction

In PLCH, the source links cystic change to scarring, airway destruction, and alveolar injury. A pulmonary cyst is thus a structural consequence, not simply a diagnostic label.

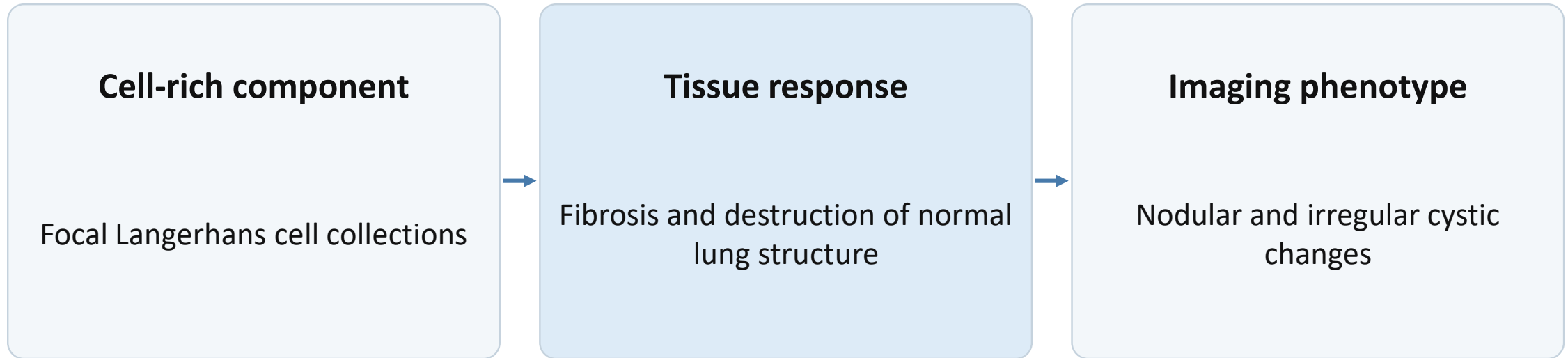
Imaging clue: Nodular abnormalities

- Nodular abnormalities among the characteristic imaging findings.
- Nodules are concordant with a disease containing focal cellular lesions.
- Imaging pattern should be integrated with smoking history and tissue findings when available.

Imaging clue: Cystic abnormalities

- The chest imaging phenotype includes cystic abnormalities.
- These are structurally intelligible because lesions may scar and destroy airways and adjacent alveoli.
- The textbook passage does not establish a cyst-size threshold or zonal distribution criterion.

Nodules plus cysts: An integrated reading



Conceptual schematic — editable PowerPoint geometry

A single lung can display different lesion states

Cellular emphasis

More conspicuous collections of Langerhans cells with inflammatory admixture.

Scarred emphasis

Progressive parenchymal and airway destruction leaves irregular cystic spaces.

Why imaging cannot determine lineage alone

- Cystic or nodular appearances describe lung architecture, not a specific cell marker.
- A Langerhans cell lesion is fundamentally a cellular and lineage diagnosis.
- Image interpretation gains specificity from clinical context and, when obtained, pathologic examination.

DIP: A distinct smoking-related morphology

Primary cell

Pigment-containing smoker's macrophages fill alveolar airspaces.

Septal response

Mild inflammatory thickening; Fibrosis usually limited.

Clinical setting

Current or former smokers;
Often improve with cessation and therapy.

RB-ILD: Bronchiolar smoker's macrophages

Localization

Dusty brown macrophages within respiratory bronchioles.

Tissue reaction

Chronic inflammation and mild peribronchiolar fibrosis.

Clinical threshold

RB-ILD implies clinically significant symptoms and functional or imaging findings.

PLCH versus DIP: Cellular target differs

Pulmonary LCH

Focal Langerhans cell proliferation;
Eosinophils may accompany it; Scarring
can destroy architecture.

DIP

Predominantly diffuse intraalveolar
pigmented macrophages with relatively
mild septal thickening.

PLCH versus RB-ILD: The lesion differs

Pulmonary LCH

Langerhans cell foci that can evolve toward destructive fibrotic cysts.

RB-ILD

Pigmented smoker's macrophages concentrate in bronchioles with mild peribronchiolar injury.

Morphologic comparison across smoking-related lung disease

Feature	PLCH	DIP	RB-ILD
Dominant cells	Langerhans cells	Pigmented macrophages	Pigmented macrophages
Primary pattern	Focal collections	Alveolar airspaces	Respiratory bronchioles
Fibrosis	Can destroy airways	Usually mild	Mild peribronchiolar
Distinctive clue	Irregular cysts	Macrophage-rich alveoli	Bronchiolar localization

The same smoking history can mask different pathology

Exposure ≠ diagnosis

PLCH, DIP, and RB-ILD can all occur in smokers, but the dominant cell type, tissue compartment, and downstream structural effect are different.

Pulmonary alveolar proteinosis is a useful contrast

PLCH

Focal proliferation of Langerhans cells;
Scarring and tissue destruction may
produce cysts.

PAP

Surfactant accumulates in alveolar
spaces because of impaired GM-CSF-
dependent macrophage function.

General LCH has several clinicopathologic settings

Pulmonary special category

Frequently associated with adult smoking and can regress after cessation.

Unisystem disease

May present in bone or other single-organ locations.

Multisystem disease

Can involve skin, bone, lymph nodes, liver/spleen and marrow.

Unifocal LCH beyond the lung

- The general LCH spectrum includes unifocal lesions, particularly in bone.
- Langerhans cell proliferations may be admixed with eosinophils, lymphocytes, plasma cells, or neutrophils.
- Some unifocal lesions follow an indolent course and may heal spontaneously.

Multisystem LCH is clinically different

- General multisystem LCH often affects very young children, unlike typical smoking-associated PLCH.
- Skin lesions, bone destruction, lymphadenopathy and hepatosplenomegaly may occur.
- Bone marrow involvement may cause cytopenias in extensive disease.

Do not equate pulmonary disease with systemic disease

Pulmonary phenotype

Smoking-associated lesions may occur predominantly in the lung.

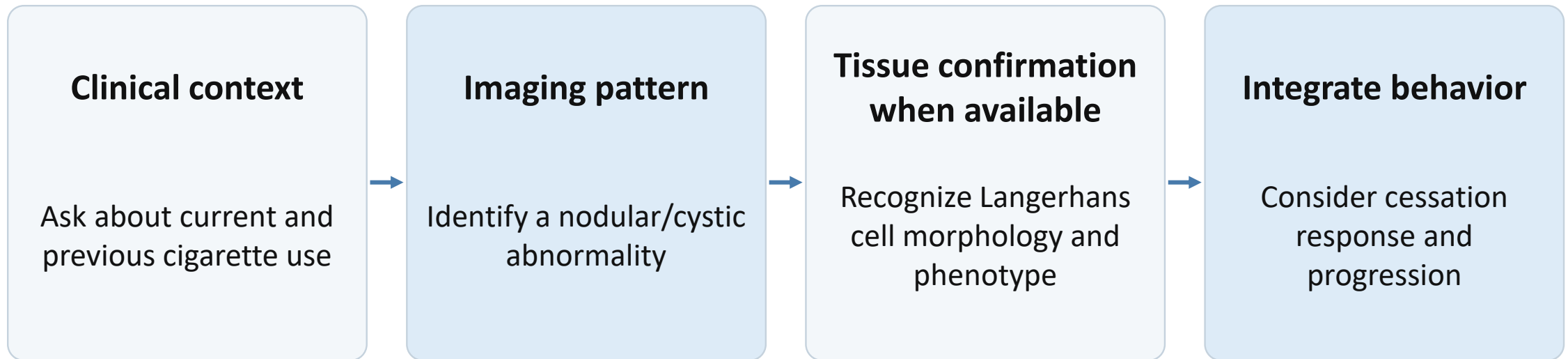
Systemic phenotype

Additional tissue involvement belongs to wider LCH clinicopathology and requires separate clinical evidence.

Age and organ pattern are diagnostic context

Clinical clue	Pulmonary LCH	Multisystem LCH
Typical setting	Relatively young adult smoker	Often early childhood
Dominant emphasis	Lung nodules/cysts	Several organ systems
Biologic issue	Smoking response plus BRAF subset	Clonal systemic disease
Diagnostic caution	Do not infer systemic spread	Do not infer cigarette link

A reasoned approach to suspected PLCH



Conceptual schematic — editable PowerPoint geometry

A pathology report should describe what is seen

- Identify the Langerhans-type cell population and characteristic nuclear contours.
- Describe eosinophilic and other inflammatory accompaniment, if present.
- Record scarring, airway damage, and cystic architectural change where sampled.
- Distinguish observed findings from causal interpretation.

Lineage immunophenotype: Correct evidentiary role

- CD1a, S-100 and HLA-DR are typical of LCH Chapter 13.
- Marker expression supports cellular identity when correlated with morphology.
- A molecular driver and immunophenotype answer different questions: Biology versus lineage.

BRAF result: What it can—and cannot—show

Positive BRAF driver

Provides evidence that the population has neoplastic molecular features.

Negative or unavailable result

Does not itself establish a purely reactive process or exclude PLCH.

Prognosis: Favourable is not universal

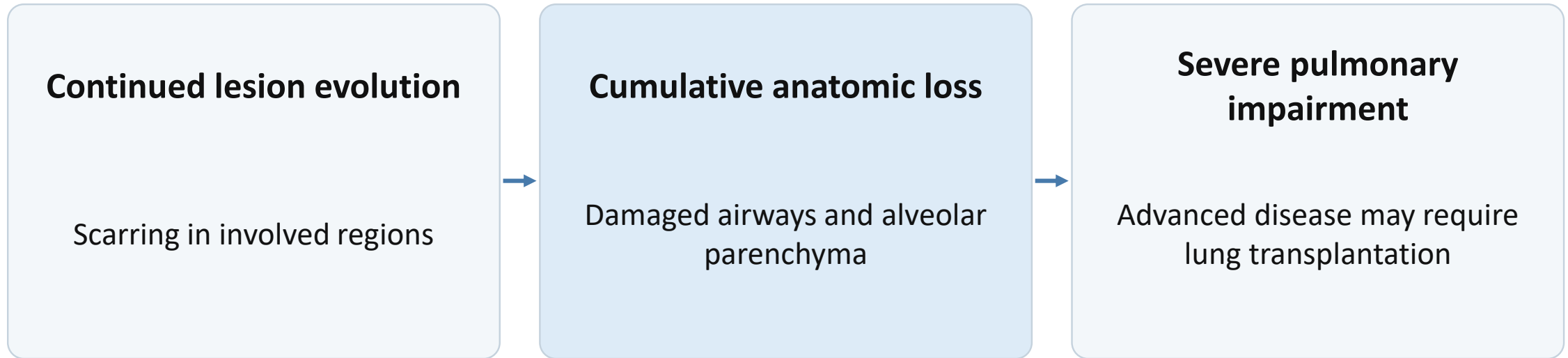
Most cases

Robbins characterizes the usual prognosis as excellent.

Progressive subset

Some patients develop substantial progression despite the favourable overall description.

Why a progressive case can become severe



Conceptual schematic — editable PowerPoint geometry

Smoking cessation is central to the disease narrative

Exposure removal

Directly addresses the dominant associated exposure.

Clinical response

Approximately half improve in the account.

Continued assessment

Other patients progress;
Cessation does not eliminate uncertainty.

Lung transplantation marks the severe end of PLCH

An uncommon, serious outcome

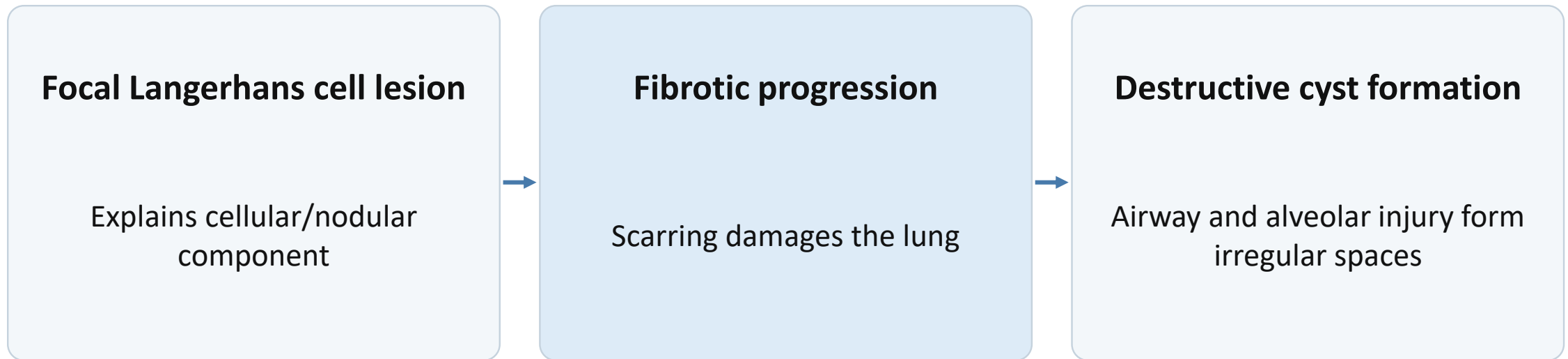
Although the overall prognosis is often excellent, some patients develop progressive lung damage severe enough to require transplantation.

Applied case 1: Smoker with nodules and cysts

A relatively young adult smoker has both pulmonary nodular and irregular cystic abnormalities.

Question: Which tissue mechanism unifies the paired radiologic findings,?

Applied case 1: Mechanistic interpretation



Conceptual schematic — editable PowerPoint geometry

Applied case 2: Cells with grooved nuclei

A pulmonary infiltrate contains pale cells with nuclear folds and admixed eosinophils.

Question: Which lineage features from general LCH can support identification of these cells?

Applied case 2: Morphologic and immunophenotypic answer

Morphology

Abundant pale/vacuolated cytoplasm and grooved or folded nuclei.

Immunophenotype

Typical CD1a, S-100 and HLA-DR expression in general LCH.

Ultrastructure

Characteristic langerin-containing Birbeck granules.

Applied case 3: Response to smoking cessation

A smoker with pulmonary LCH improves after stopping cigarettes.

Question: Does improvement prove that the original lesion was non-neoplastic?
Explain the logic.

Applied case 3: Response does not settle clonality

Observation

Improvement after cessation is consistent with an exposure-responsive component.

Molecular principle

Some lesions harbor activating BRAF mutations; Clinical improvement is not a molecular assay.

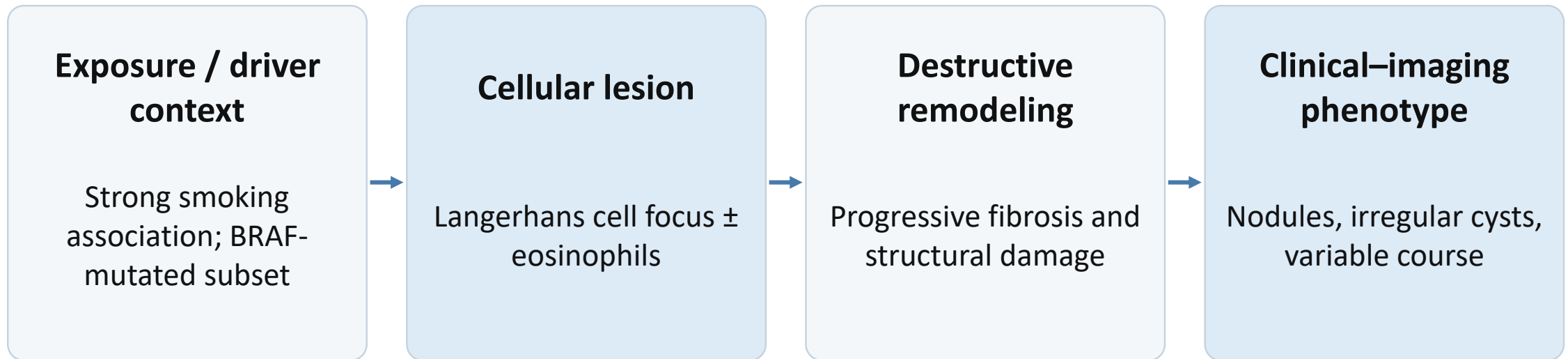
Four discriminators worth retaining

Question	Finding to prioritize
Who is affected?	Predominantly young adult smokers / ex-smokers
Which cells?	Langerhans cells with possible eosinophils
What injury?	Scarring → airway and alveolar destruction → cysts
What biology?	Cessation-responsive cases plus BRAF-mutated subset

What is directly established versus inferred

Directly stated	Reasonable teaching synthesis
Focal Langerhans cell collections	A cell-rich focus can explain nodularity
Scarring damages airways/alveoli	Different lesions can show differing activity
Characteristic nodules and cysts	Imaging is supportive, not cell-lineage proof
BRAF mutations in pulmonary subset	Regression does not determine mutation status

Integrated mechanism of pulmonary LCH



Conceptual schematic — editable PowerPoint geometry

Final synthesis: Four essential statements

- PLCH is a rare lung disease defined by focal collections of Langerhans cells, often with eosinophils.
- Progressive scarring damages airways and alveoli, explaining irregular cystic spaces.
- Smoking is strongly associated; Cessation benefits about half of affected smokers.
- BRAF mutations support neoplasia in a subset, and a minority experience clinically severe progression.

Textbook references and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 15, “The Lung,” p. 637.
- Chapter 13, “Langerhans Cell Histiocytosis,” pp. 571–572, supplies morphology, immunophenotype, general classification, and mutation context.
- Smoking-related interstitial disease comparisons are drawn from Chapter 15, p. 637.
- Histology, ultrastructure, and imaging shown schematically only; original published diagnostic images were not available for licensed reuse.