

Langerhans Cell Histiocytosis

Pathogenesis • morphology • clinicopathologic patterns

A pathology teaching lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain why LCH is considered a clonal myeloid neoplasm.
- Link driver mutations and chemokine receptors to biological behavior.
- Identify characteristic cellular features and immunophenotype.
- Distinguish the major clinical patterns and their consequences.

Histiocytosis is an umbrella designation

- The term encompasses proliferations of dendritic cells or macrophages.
- Its biological range extends from reactive to frankly malignant processes.
- LCH occupies an unusual intermediate position on this spectrum.

Reactive

Benign macrophage proliferation

LCH

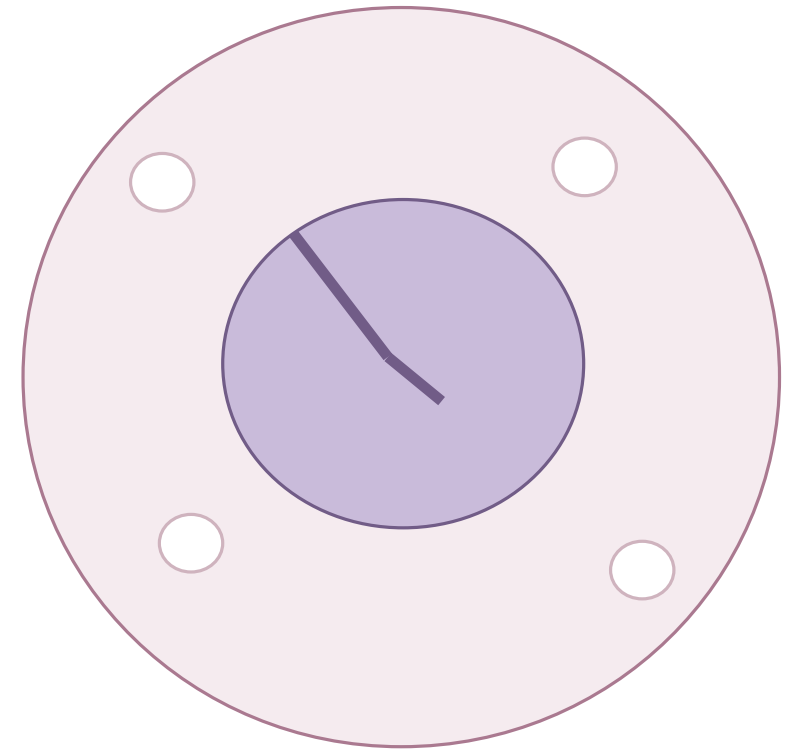
Clonal dendritic-cell disorder

Highly malignant

Histiocytic sarcoma / BPDCN

LCH arises from an immature dendritic-cell lineage

- The proliferating cell resembles the specialized Langerhans dendritic cell.
- Langerhans cells belong to the innate immune system.
- The defining process is clonal proliferation rather than ordinary inflammation.



Clonal Langerhans-type cell (schematic)

Schematic — not a histologic specimen

Why LCH is grouped with myeloid neoplasms

- Dendritic lineage links the lesional cell to the innate immune compartment.
- Recurrent oncogenic driver mutations support neoplastic biology.
- Clonal lineage and clinical behavior must be distinguished.

Lineage

Innate immune / dendritic

Genomics

Driver mutations are common

Clinical behavior

Ranges from regression to dissemination

Clonality does not imply uniformly aggressive behavior

- Most cases harbor cancer-associated driver mutations.
- Spontaneous remission is nevertheless a recognized feature.
- Biological classification and individual clinical prognosis are not equivalent.

NEOPLASM

Somatic clonal
driver mutations

CLINICAL COURSE

May regress, remain
localized, or
disseminate

RAS-pathway mutations predominate

- RAS signaling-pathway driver mutations in over 85% of cases.
- Mutation of pathway components provides a mechanistic basis for cell proliferation.
- This frequency describes the overall LCH population, not every individual lesion.

>85%

Pathway-associated drivers

Reported across LCH cases in the cited
Robbins edition

BRAF V600E is the most frequent driver

- A valine-to-glutamate substitution occurs at BRAF codon 600.
- The substitution activates BRAF signaling.
- BRAF V600E in approximately 55%–60% of cases.

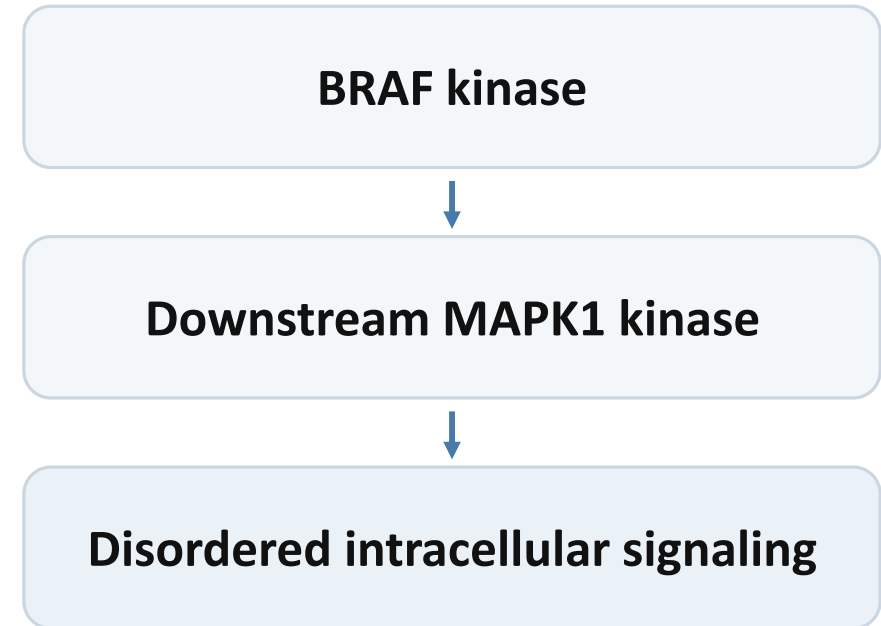
55–60%

BRAF V600E

Share of LCH cases reported in the
primary textbook

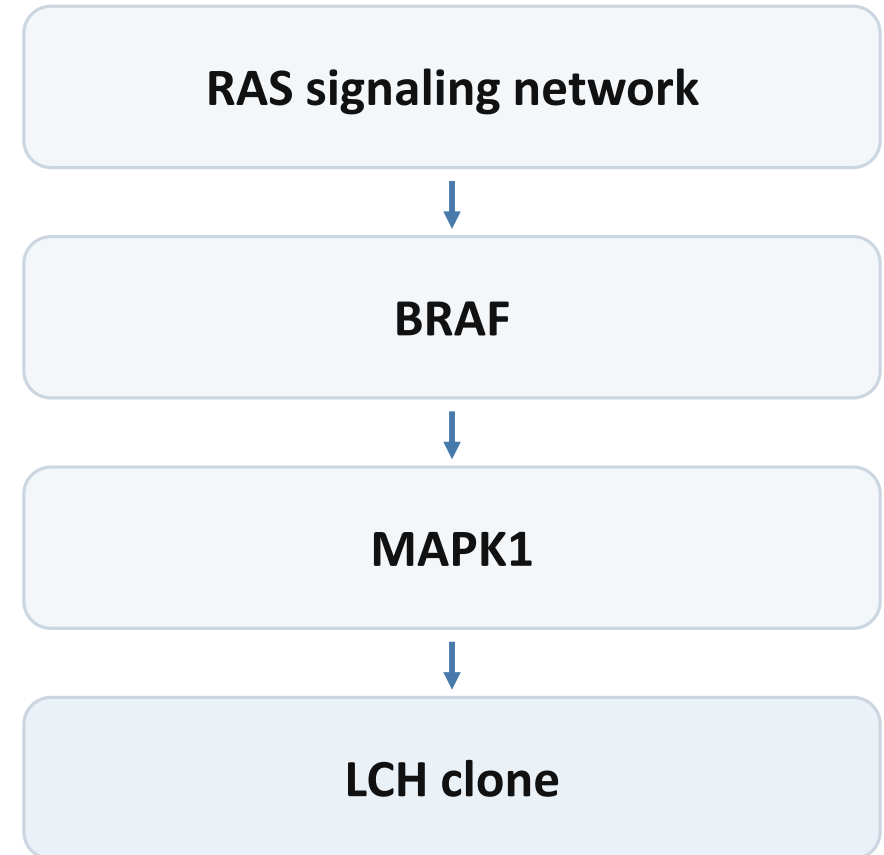
MAPK1 is another recurrently mutated gene

- MAPK1 encodes a kinase acting downstream of BRAF.
- MAPK1 as the next most commonly mutated gene.
- The shared theme is aberrant signaling within one growth-control network.



Mutations converge on a signaling network

- Different mutated genes can affect components of one RAS pathway.
- Pathway convergence is more informative than treating every mutation separately.
- The diagram is a simplified relationship—not a complete molecular cascade.



The molecular paradox of LCH

- Oncogenic mutations establish a neoplastic framework.
- A driver mutation alone does not dictate disseminated disease.
- Some lesions undergo spontaneous regression despite clonality.

Mutation

Shared neoplastic mechanism

Distribution

One lesion or multiple systems

Outcome

Regression or progression

Tissue homing depends on chemokine receptors

- Lesional cells express receptors that recognize tissue chemokines.
- Chemokine–receptor pairing provides a route to tissue-selective migration.
- This explains localization beyond intrinsic proliferative signals.

Receptor expression



Tissue chemokine ligand



Migration / tissue homing

Normal epidermal Langerhans cells express CCR6

- CCR6 is expressed by normal epidermal Langerhans cells.
- The chemokine CCL20 serves as a CCR6 ligand.
- Receptor expression contributes to tissue-directed cell trafficking.

Normal epidermal Langerhans cell



Ligand-directed tissue homing (schematic)

Neoplastic cells coexpress CCR6 and CCR7

- LCH cells aberrantly express both CCR6 and CCR7.
- The additional receptor expands the repertoire of tissue destinations.
- Receptor coexpression contributes to the disease's distribution pattern.

NORMAL

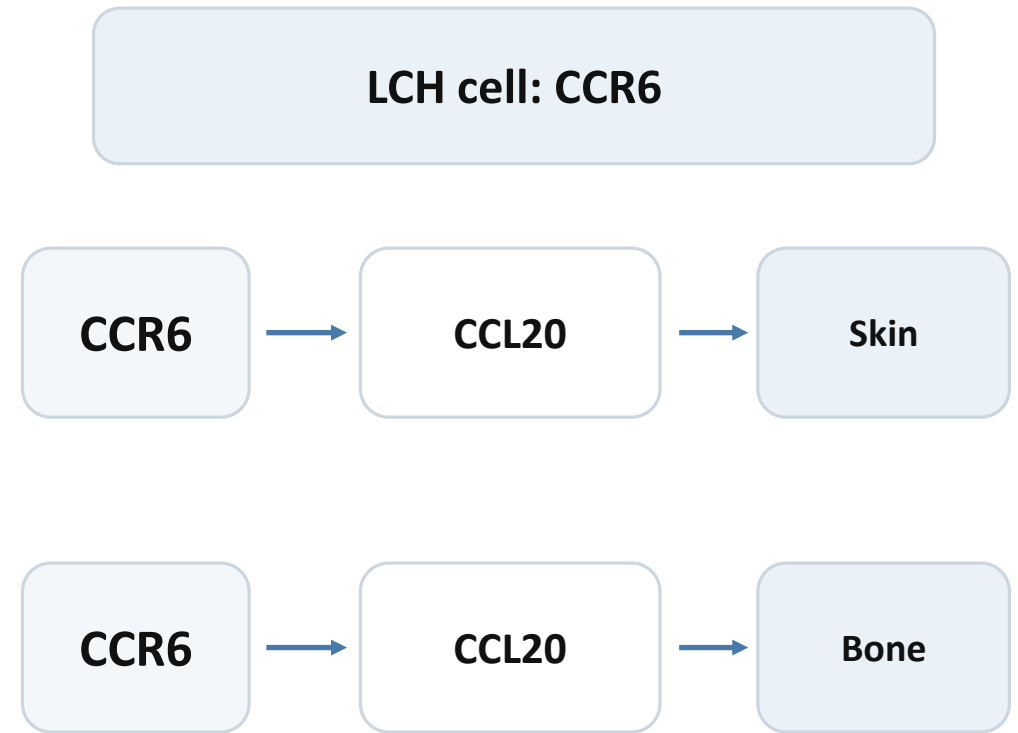
CCR6 expression

NEOPLASTIC

CCR6 + CCR7
expression

The CCR6–CCL20 axis directs skin and bone homing

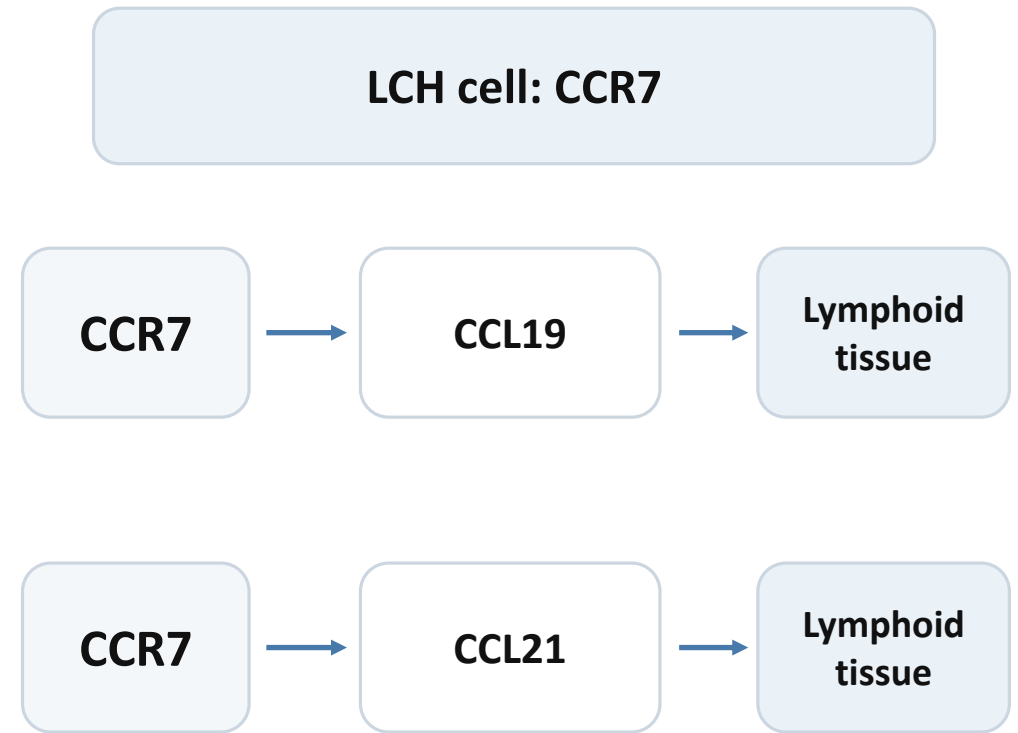
- CCL20 is present in skin and bone marrow.
- CCL20 is a ligand for CCR6.
- The pairing supports migration of neoplastic Langerhans cells to these sites.



Ligand-directed tissue homing (schematic)

The CCR7 axis supports lymphoid organ homing

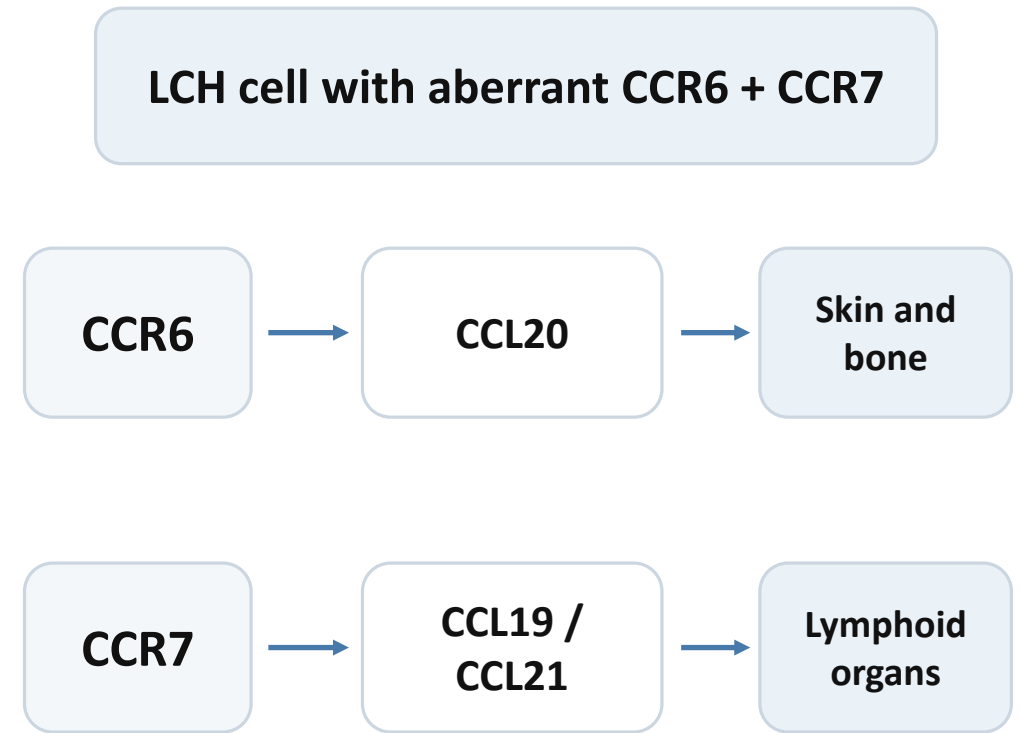
- CCL19 and CCL21 are ligands for CCR7.
- These ligands guide lesional cells toward lymphoid sites.
- Aberrant CCR7 expression helps explain lymphoid involvement.



Ligand-directed tissue homing (schematic)

Receptors connect genotype to organ distribution

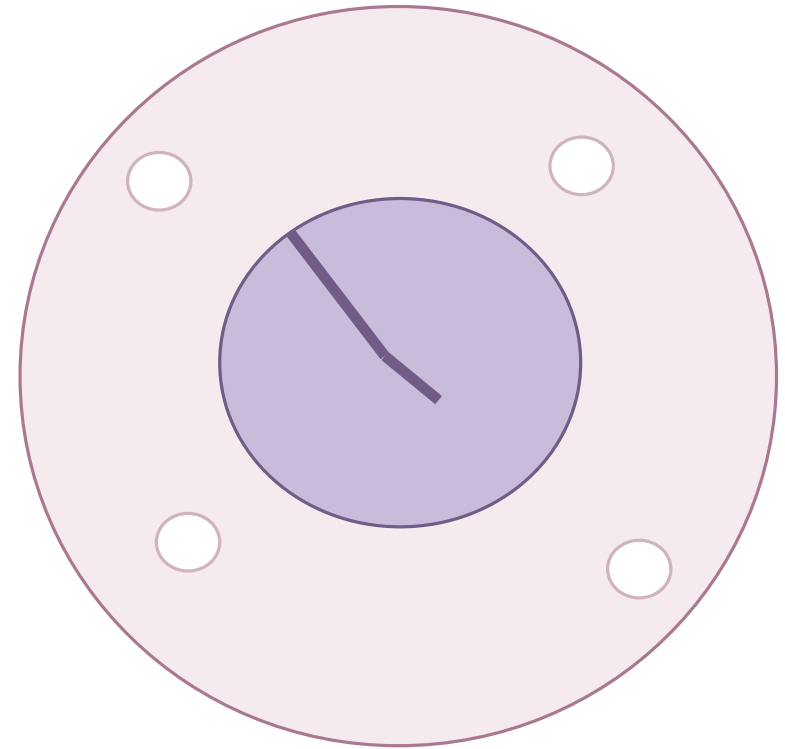
- Proliferative signals and tissue migration are different biological functions.
- BRAF/MAPK1 alterations explain pathway dysregulation.
- CCR6/CCR7 expression helps explain the organ sites of infiltration.



Ligand-directed tissue homing (schematic)

The defining cytology is recognizable across patterns

- Lesional cells have abundant cytoplasm, sometimes vacuolated.
- Nuclei are vesicular and typically contain grooves or folds.
- These features apply regardless of the extent of clinical involvement.

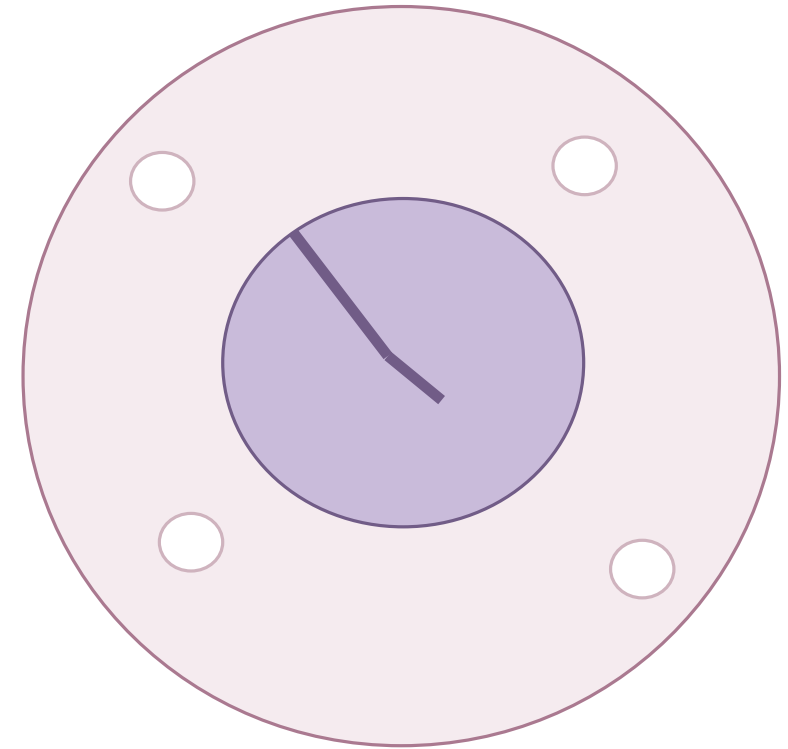


Cellular morphology (schematic)

Schematic — not a histologic specimen

Nuclear grooves are a primary recognition clue

- Nuclei may show longitudinal linear grooves.
- Folding creates irregular or reniform nuclear contours.
- The finding must be interpreted with the cellular and immunophenotypic context.

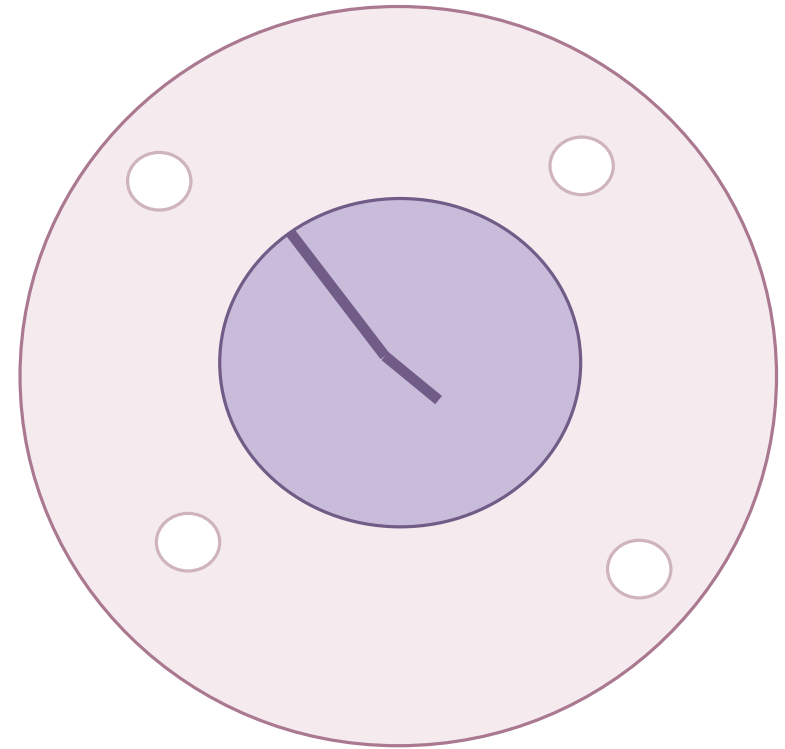


Grooved / folded nucleus

Schematic — not a histologic specimen

Cytoplasmic abundance is characteristic

- LCH cells show moderately abundant or abundant pale cytoplasm.
- Vacuoles may be present in the cytoplasm.
- Morphology alone should not be mistaken for a complete diagnostic test.



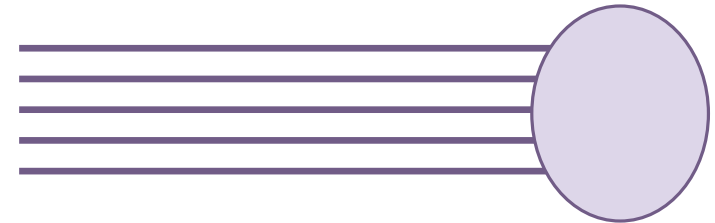
Pale, sometimes vacuolated cytoplasm

Schematic — not a histologic specimen

Birbeck granules are characteristic ultrastructures

- Characteristic granules lie within the lesional cell cytoplasm.
- They are pentalaminar tubular structures.
- This ultrastructural feature links morphology to Langerhans differentiation.

Birbeck granule



Pentalaminar tubular structure

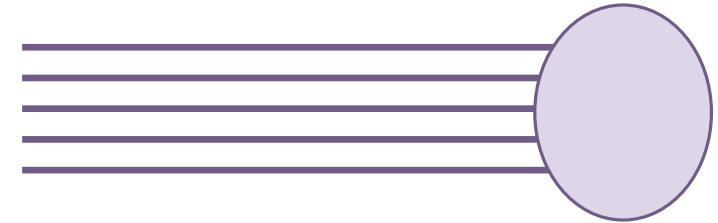
Dilated terminal end → “tennis racket” profile

Schematic — not electron microscopy

The tennis-racket profile comes from terminal dilation

- Birbeck granules commonly have a rod-like profile.
- A dilated terminal end creates the classic “tennis racket” appearance.
- This is an electron-microscopic feature; The drawing is explanatory only.

Birbeck granule



Pentalaminar tubular structure

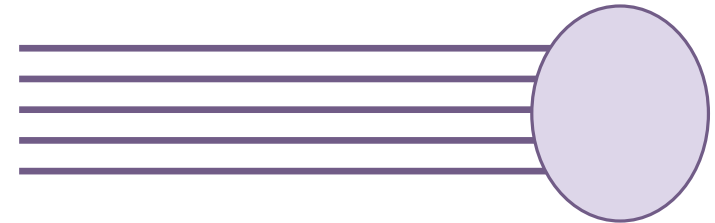
Dilated terminal end → “tennis racket” profile

Schematic — not electron microscopy

Langerin is present in Birbeck granules

- The granules contain the protein langerin.
- This connects an ultrastructural hallmark with a molecular cell marker.
- Granule morphology and immunophenotype are complementary levels of evidence.

Birbeck granule



Pentalaminar tubular structure

Dilated terminal end → “tennis racket” profile

Schematic — not electron microscopy

The textbook immunophenotypic profile

- The lesional cells typically express CD1a.
- S-100 and HLA-DR are also typically expressed.
- Langerin is linked to the characteristic Birbeck granules.

CD1a

Typical lesional
marker

S-100

Typical lesional
marker

HLA-DR

Typical lesional
marker

Langerin

Granule-associated
protein

Morphology and immunophenotype should be integrated

- Grooved nuclei and pale cytoplasm suggest the lesional cell phenotype.
- Typical markers provide corroborating cell-lineage evidence.
- No single descriptive feature should be used in isolation.

Compatible cell morphology



CD1a / S-100 / HLA-DR profile



**Integrated pathological
interpretation**

The inflammatory background is variable

- Lesional cells may be mixed with eosinophils, lymphocytes, and plasma cells.
- Neutrophils can also be part of the admixture.
- The reactive-cell population modifies the lesion's appearance.

LCH cells

Neoplastic
component

Eosinophils

Variable prominence

Lymphocytes

Background
population

Others

Plasma cells /
neutrophils

Eosinophils are common—but not required

- Eosinophils often stand out in unisystem lesions.
- The number of eosinophils is variable.
- An eosinophil-poor lesion is not excluded by this single feature.

EOSINOPHIL-RICH

Prominent
associated
eosinophils

EOSINOPHIL- POOR

Compatible LCH
cells may still be
present

One cellular morphology, multiple clinical settings

- The characteristic Langerhans cell morphology persists across presentations.
- The clinical category reflects lesion number and distribution.
- Organ infiltration determines the main symptoms and consequences.

LCH: Clinical patterns

Multifocal multisystem

Unifocal / multifocal unisystem

Pulmonary

LCH is clinically heterogeneous

- Multisystem, single-system, and pulmonary presentations.
- Single-system disease can be unifocal or multifocal.
- Extent of organ involvement—not a different cell phenotype—separates these groups.

LCH: Clinical patterns

```
graph TD; A[LCH: Clinical patterns] --- B[Multifocal multisystem]; B --- C[Unifocal / multifocal unisystem]; C --- D[Pulmonary];
```

Multifocal multisystem

Unifocal / multifocal unisystem

Pulmonary

Age and disease distribution often correlate

Pattern	Typical age	Clinical distribution
Multisystem	Usually <2 years	Several organs
Multifocal unisystem	Peak 2–10 years	Multiple lesions, one system
Unifocal	Older children / adults	Usually bone

Letterer–Siwe pattern: Multisystem LCH

- The multisystem form often begins in infancy.
- Disease can involve skin, lymph nodes, liver, spleen, lungs, bone, and marrow.
- Its severity reflects widespread organ infiltration.

Skin

Seborrheic eruption

Reticuloendothelial

Liver / spleen / nodes

Lung / bone

Pulmonary and lytic lesions

Marrow

Cytopenias / infections

The characteristic skin eruption mimics seborrhea

- Cutaneous lesions resemble a seborrheic eruption.
- Infiltrating LCH cells affect scalp and anterior/posterior trunk.
- The skin finding may be an early clue to multisystem disease.

Scalp

Seborrheic-like eruption

Front of trunk

Infiltrative eruption

Back of trunk

Infiltrative eruption

Systemic clues

Check organ distribution

Hepatosplenomegaly and lymphadenopathy reflect infiltration

- Hepatomegaly and splenomegaly occur in multisystem disease.
- Lymphadenopathy is also common in that clinical pattern.
- These findings indicate disease beyond a single localized lesion.

Neoplastic tissue infiltration



Enlarged liver / spleen / nodes



Multisystem disease recognition

Pulmonary and osteolytic lesions add tissue injury

- Pulmonary lesions may accompany other systemic manifestations.
- Destructive osteolytic bone lesions can develop over time.
- Bone destruction explains pain and susceptibility to fracture.

LUNG

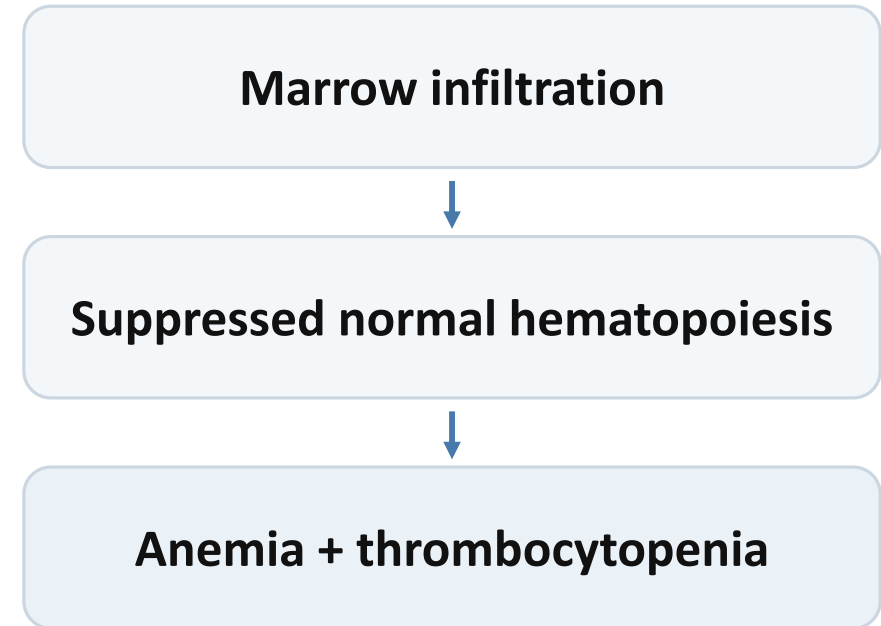
Pulmonary lesions in multisystem disease

BONE

Progressive destructive osteolytic lesions

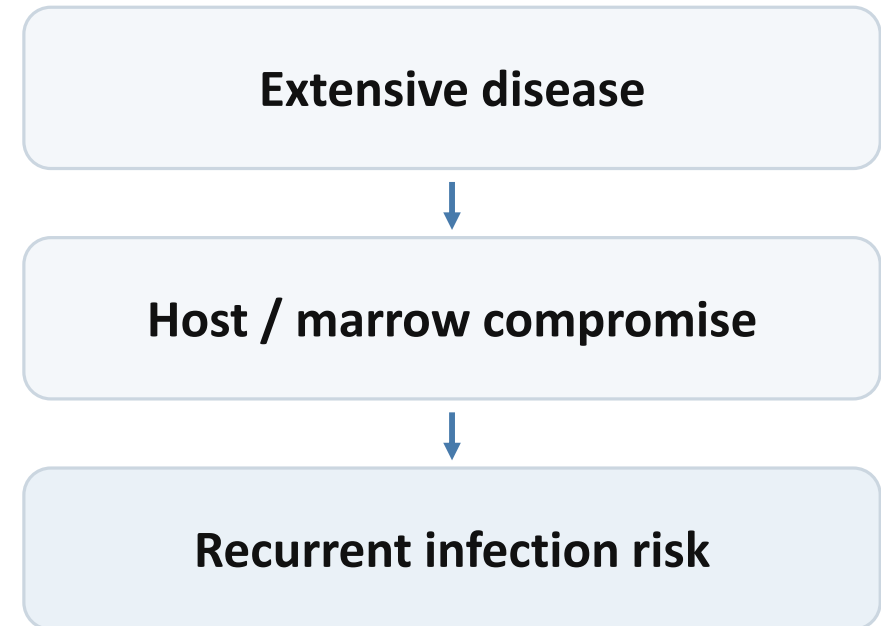
Marrow infiltration produces cytopenias

- Extensive marrow infiltration impairs normal blood-cell production.
- Anemia and thrombocytopenia may result.
- This mechanism links pathological infiltration to systemic risk.



Infections can complicate multisystem disease

- Widespread disease predisposes to recurrent infections.
- Otitis media and mastoiditis are specifically described.
- Infection susceptibility is part of the clinical burden of marrow/systemic disease.



Anaplastic proliferations may be labeled sarcoma

- Some proliferations show striking anaplasia.
- The term “Langerhans cell sarcoma” for such cases.
- This must be distinguished from the usual LCH cellular phenotype.

USUAL LCH

Recognizable
grooved nuclei and
clinical variability

ANAPLASTIC FORM

Markedly atypical
cells; Sarcoma
designation in
source

Multisystem disease has the greatest severity

- The untreated multisystem pattern may be rapidly fatal.
- Approximately 50% five-year survival with chemotherapy.
- That textbook figure should not be treated as a current risk-stratified estimate.

~50%

**5-year survival with
chemotherapy**

Historical textbook estimate for the
disseminated Letterer–Siwe pattern;
Not contemporary individualized
prognosis

Unisystem LCH has one-system distribution

- Single-system LCH may consist of one or multiple lesions.
- The bone marrow cavities are frequent sites of localized disease.
- Identical histology is possible in skin, lung, or stomach.

LCH: Clinical patterns

```
graph TD; A[LCH: Clinical patterns] --> B[Unifocal single-system]; A --> C[Multifocal single-system]; A --> D[Less commonly: Non-bone single-system];
```

Unifocal single-system

Multifocal single-system

Less commonly: Non-bone single-system

The common skeletal sites are recognizable

- The calvaria is a common site.
- Ribs and femur are also frequent locations.
- Bone lesions characteristically arise within medullary cavities.

Calvaria

Common skeletal site

Ribs

Common skeletal site

Femur

Common skeletal site

Medullary cavity

Typical anatomic
setting

Unifocal bone disease is often called eosinophilic granuloma

- “Eosinophilic granuloma” is the older designation.
- This form often affects older children and adults.
- The name reflects a frequent inflammatory component, not a separate cell of origin.

HISTORICAL NAME

Eosinophilic
granuloma

CURRENT PATHOLOGIC IDENTITY

Unifocal Langerhans
cell histiocytosis

Bone lesions can be silent or symptomatic

- Some unifocal lesions are incidentally asymptomatic.
- Others cause localized bone pain and tenderness.
- The symptom profile depends on lesion location and tissue damage.

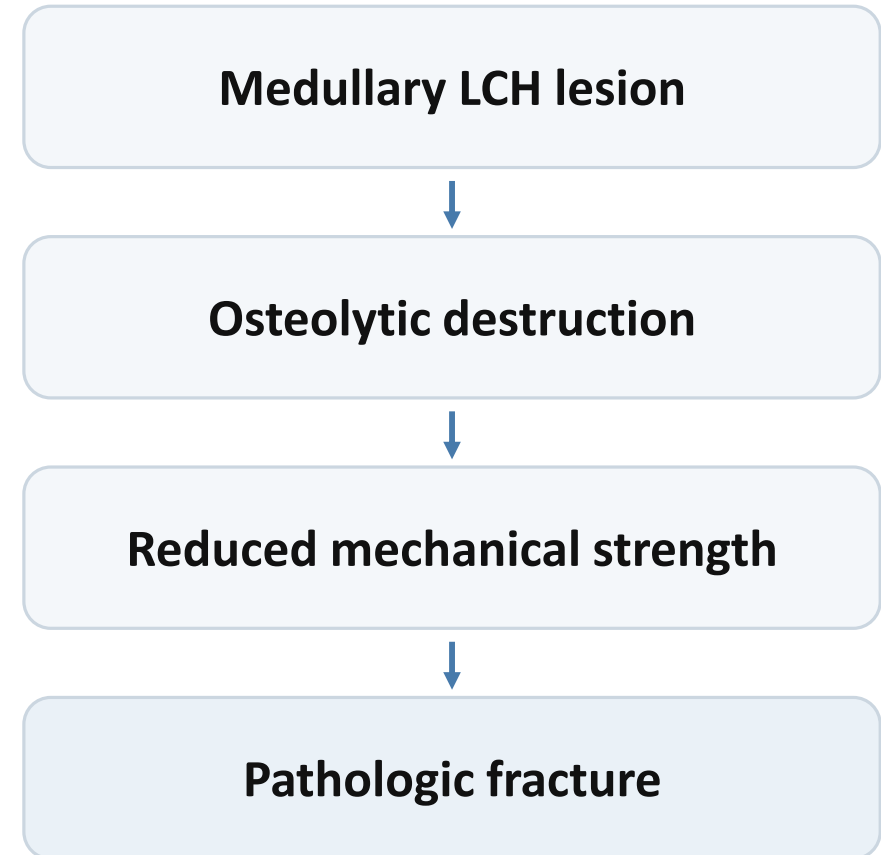
Silent lesion No overt symptoms

Symptomatic lesion Local pain and tenderness

Structural damage Possible fracture

Osteolysis can culminate in pathologic fracture

- Destructive lesions erode normal bone substance.
- Loss of structural integrity predisposes to fracture.
- A fracture in this setting is a consequence of focal tissue destruction.



Unifocal disease is commonly indolent

- The localized form may heal spontaneously.
- When needed, local excision or irradiation may be curative.
- This course contrasts with untreated disseminated disease.

Natural history

May spontaneously heal

Local therapy

Excision or irradiation

Clinical implication

Often favorable localized course

Multifocal unisystem disease peaks at ages 2–10

- Multiple lesions remain within a single involved organ system.
- Young children are most often affected.
- Peak onset between 2 and 10 years.

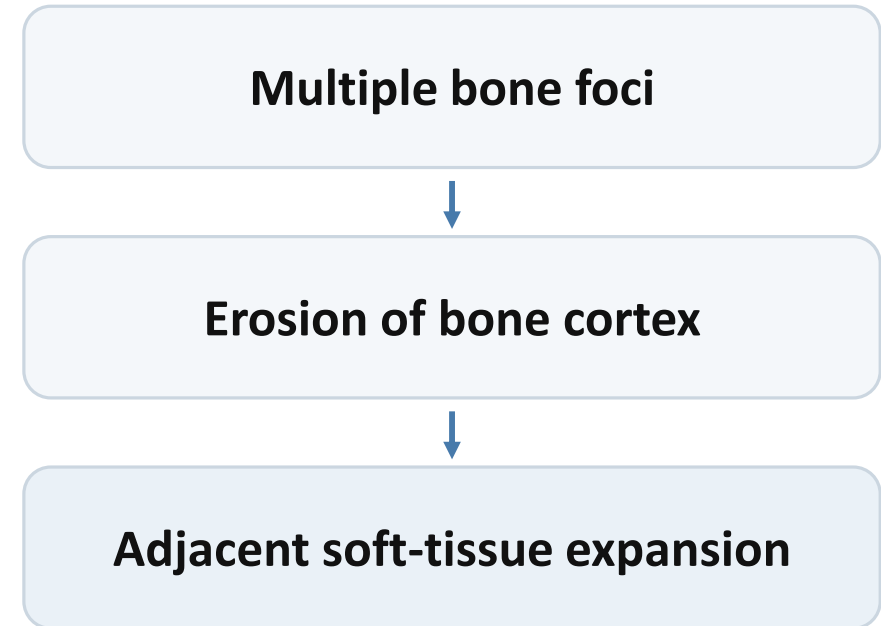
2–10

Years: Peak onset

Multifocal single-system LCH in the
primary source

Multifocal bone lesions can expand into soft tissue

- The lesions appear as multiple erosive bony masses.
- Some extend beyond bone into adjacent soft tissue.
- Local extension should not be confused with involvement of another organ system.



Pituitary-stalk infiltration explains diabetes insipidus

- The posterior pituitary stalk may be involved in childhood disease.
- This involvement produces diabetes insipidus.
- Diabetes insipidus in about 50% of multifocal cases.

Posterior pituitary stalk lesion



Posterior pituitary disruption



Diabetes insipidus

The Hand–Schüller–Christian triad

- Calvarial bone defects.
- Diabetes insipidus.
- Exophthalmos.

Calvaria

Destructive skull defects

Pituitary stalk

Diabetes insipidus

Orbit

Exophthalmos

Pattern

Classic historical triad

Multifocal disease may regress or require therapy

- Many patients experience spontaneous regression.
- Other patients can be treated successfully with chemotherapy.
- Clinical monitoring must reflect lesion location and disease extent.

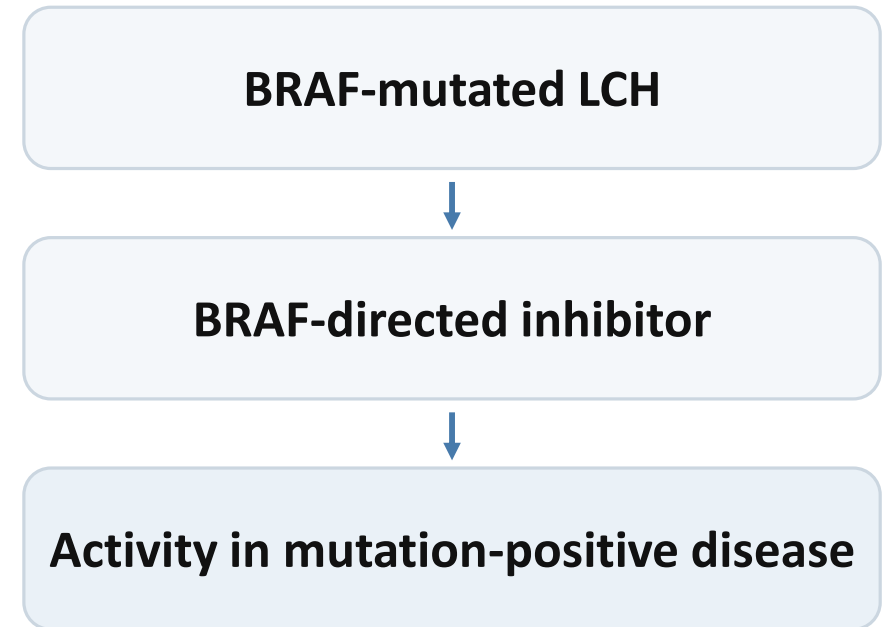
Regression Possible without therapy

Persistent disease May need systemic therapy

Organ-specific risk Depends on sites involved

BRAF-mutated LCH has a targeted-treatment option

- Activity of BRAF inhibitors in BRAF-mutated disease.
- Mutation status connects a molecular lesion to a therapeutic mechanism.
- Do not infer drug selection, dosing, or universal benefit from this statement.



Pulmonary LCH is a special clinical category

- Pulmonary LCH is most often described in adult smokers.
- Its clinical context differs from infantile disseminated LCH.
- Smoking is a distinctive contextual factor for this presentation.

PULMONARY LCH

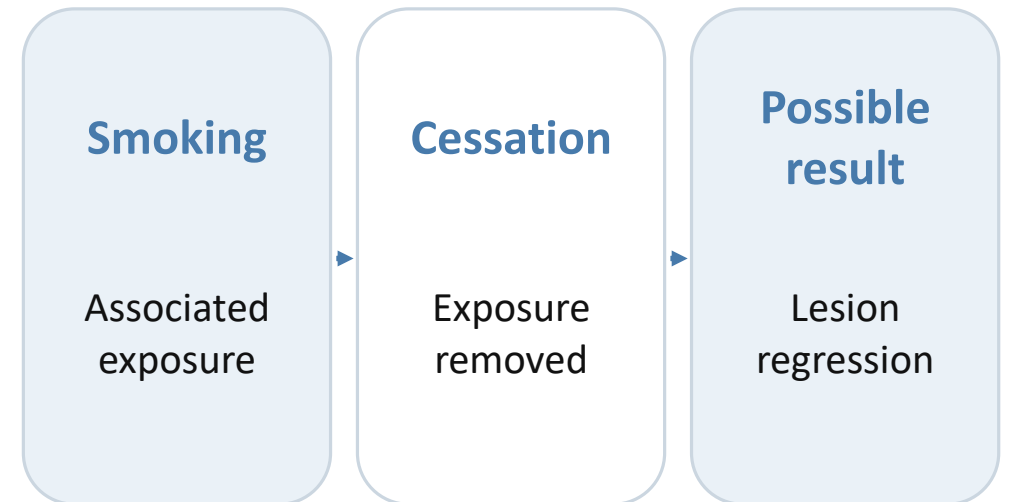
Commonly in adult smokers

MULTISYSTEM LCH

Frequent infancy onset; Several organs

Smoking cessation may lead to pulmonary regression

- Pulmonary lesions can regress spontaneously after smoking cessation.
- The smoking association does not exclude a neoplastic component.
- Course and intervention can therefore differ from other LCH patterns.



Regression is possible, not guaranteed

Pulmonary lesions may also harbor BRAF mutations

- BRAF mutations in about 40% of pulmonary LCH cases.
- This supports a neoplastic component in some lesions.
- The source contrasts this with earlier descriptions of reactive proliferation.

~40%

BRAF-mutated pulmonary LCH

Textbook frequency; Separate from the overall 55%–60% BRAF V600E estimate

How the major patterns compare

Pattern	Distinguishing context	Typical consequence
Multisystem	Infant; several organs	Organ infiltration, cytopenias
Unifocal unisystem	Usually solitary bone lesion	Pain or pathologic fracture
Multifocal unisystem	Child; multiple bony lesions	Erosion, possible DI
Pulmonary	Frequently adult smoker	Pulmonary disease, possible regression after cessation

LCH and other histiocytic disorders are not synonymous

- Reactive macrophage proliferation is not inherently clonal LCH.
- Highly malignant histiocytic and dendritic tumors are distinct categories.
- LCH should be interpreted using lineage, morphology, and biological context.

Reactive

Non-neoplastic macrophage increase

LCH

Clonal immature dendritic-cell tumor

Other neoplasms

Sarcoma / dendritic-cell malignancy

Case 1: An infant with a persistent scalp eruption

- An infant has seborrheic-like scalp and truncal lesions
- Hepatosplenomegaly and enlarged lymph nodes coexist
- Biopsy shows grooved-nucleus dendritic cells.

PATTERN RECOGNITION

Scalp + trunk eruption
Hepatosplenomegaly
Lymphadenopathy

INTERPRETATION

Multifocal multisystem LCH (Letterer–Siwe pattern)

Case 2: A solitary femoral lytic lesion

- An older child has focal femoral pain.
- Imaging describes one osteolytic lesion.
- Pathology shows characteristic LCH cells with an eos

PATTERN RECOGNITION

Localized femoral pain
Single destructive bone focus
LCH-like histology

INTERPRETATION

**Unifocal single-system LCH (formerly
eosinophilic granuloma)**

Case 3: Bone lesions and polydipsia

- A child has several calvarial defects.
- A posterior pituitary-stalk lesion causes diabetes insipidus.
- Exophthalmos accompanies the skeletal lesions.

PATTERN RECOGNITION

Calvarial defects
Diabetes insipidus
Exophthalmos

INTERPRETATION

Classic Hand–Schüller–Christian triad

Case 4: Adult smoking-associated pulmonary disease

- An adult smoker has an LCH-type pulmonary lesion.
- Other organ-system findings are not described.
- Smoking cessation may be followed by disease regression.

PATTERN RECOGNITION

Adult smoker

Pulmonary involvement

Potential regression on cessation

INTERPRETATION

**Pulmonary Langerhans cell
histiocytosis**

Diagnostic reasoning: Integrate three evidence streams

- Cellular findings: Nuclear grooves, pale cytoplasm, variable eosinophils.
- Cell markers: CD1a, S-100, HLA-DR; Langerin/Birbeck connection.
- Clinical pattern: Lesion distribution and organ-specific consequences.

Morphologic pattern



Supporting immunophenotype



Clinical distribution



Coherent LCH interpretation

Core concepts to retain

- LCH is a clonal dendritic-cell neoplasm with heterogeneous clinical outcomes.
- RAS-pathway drivers and CCR6/CCR7-mediated homing explain different aspects of biology.
- Grooved nuclei, Birbeck granules, and typical markers identify the cell phenotype.
- The distinction between localized, multisystem, and pulmonary disease matters clinically.

Primary reference

Robbins, Cotran & Kumar

Pathologic Basis of Disease

11th edition (2026)

Section: Langerhans Cell Histiocytosis

Photomicrographs are not reproduced in this deck; cell/granule drawings are editable schematics.