

Granulomatous Diseases

Sarcoidosis and hypersensitivity pneumonitis

Mechanisms • morphology • clinicopathologic diagnosis

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Learning objectives

- Describe immune-mediated granuloma formation in pulmonary disease.
- Recognize characteristic morphology and organ distribution in sarcoidosis.
- Relate inhaled-antigen exposure to hypersensitivity pneumonitis.
- Compare granulomatous patterns, clinical manifestations and outcomes.
- Apply source-supported diagnostic reasoning to short clinical cases.

Two different granulomatous disorders

Sarcoidosis

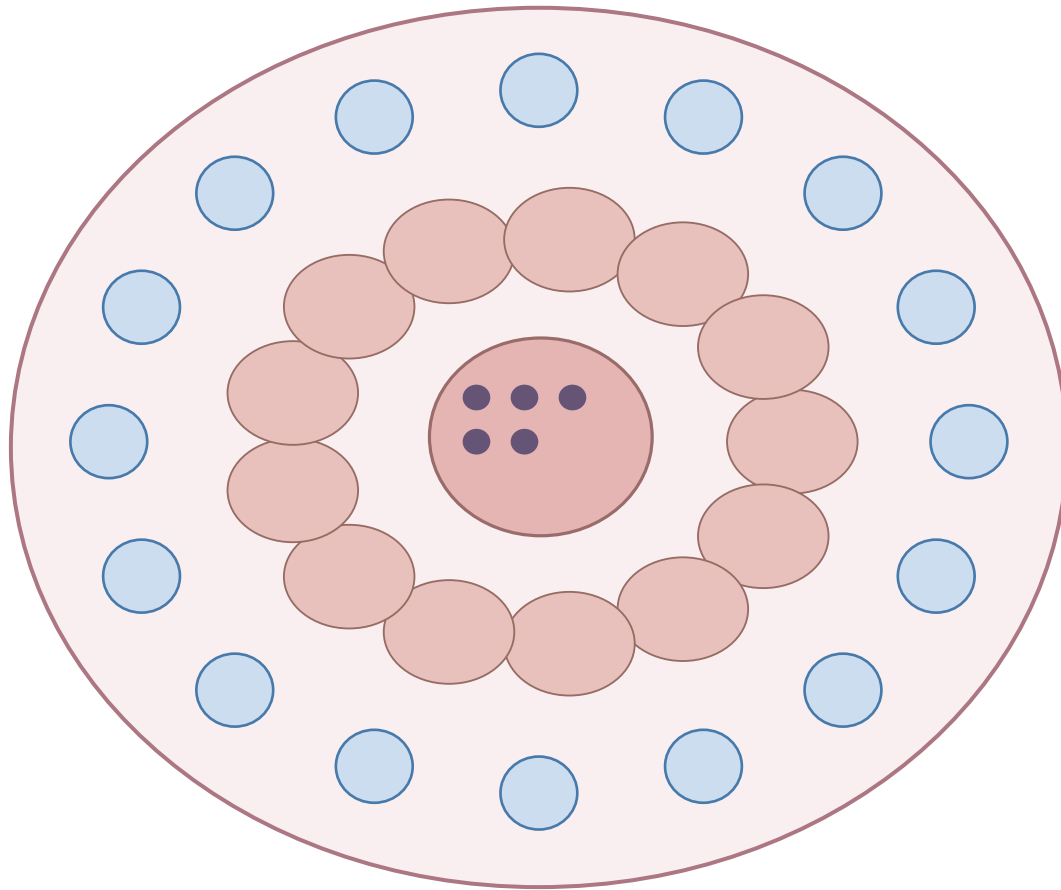
- Multisystem granulomatous condition of unknown cause
- Often involves lung and thoracic nodes
- Well-formed nonnecrotizing granulomas

Hypersensitivity pneumonitis

- Immune reaction to inhaled antigenic material
- Predominantly interstitial / bronchiolocentric injury
- Often poorly formed nonnecrotizing granulomas

A nonnecrotizing granuloma: Cellular architecture

Original schematic — not a histologic specimen



Tightly clustered epithelioid macrophages

Activated macrophages form the core of the lesion.

Multinucleated giant cells

May occur centrally; Not essential for diagnosis.

Peripheral lymphocytes surround the core.

What granuloma morphology does—and does not—prove

- Epithelioid macrophage aggregates reflect a sustained cellular immune response.
- Giant cells may be present within granulomas.
- Absence of necrosis is an important morphologic descriptor, not an etiologic diagnosis.
- Clinical exposure, organ distribution and competing causes remain essential.

Nonnecrotizing granulomas are not specific to sarcoidosis

Possible cause	Clinical discriminator	Interpretive caution
Sarcoidosis	Typical systemic / pulmonary pattern	Diagnosis of exclusion
Mycobacterial disease	Infectious context	May have nonnecrotizing lesions
Fungal infection	Infectious exposure or risk	Organisms must be considered
Beryllium-associated disease	Occupational exposure	May mimic sarcoidosis

Sarcoidosis: Defining features

- Multisystem granulomatous disease with no established causative agent.
- Lung parenchyma and hilar lymph nodes are most frequently affected.
- Ocular, cutaneous and other systemic lesions are common patterns.
- Well-formed nonnecrotizing granulomas are the histopathologic hallmark.

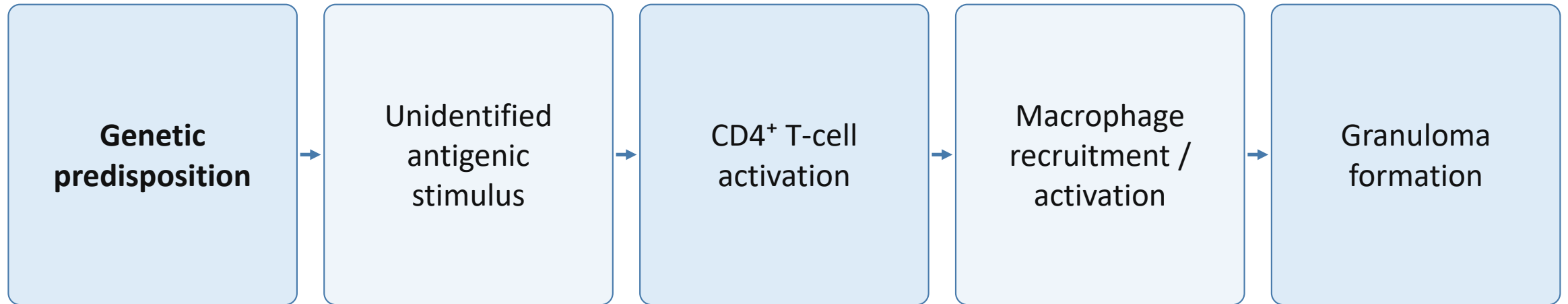
Sarcoidosis: Where disease is found

- Pulmonary or bilateral hilar nodal involvement occurs in about 90% of cases.
- Eye and skin manifestations are next in clinical frequency.
- Lymph nodes, spleen, liver and bone marrow may harbor granulomas.
- Heart, central nervous system and endocrine tissues may also be affected.

Sarcoidosis: Epidemiologic context

- Often presents in adults younger than 40 years; Any age can be affected.
- Overall frequency is higher among females description.
- Prevalence and patterns of organ involvement differ across populations.
- Epidemiology raises or lowers suspicion but does not establish diagnosis.

Sarcoidosis: Proposed immune pathogenesis



Causal antigen is unproven; This is an evidence-based working model.

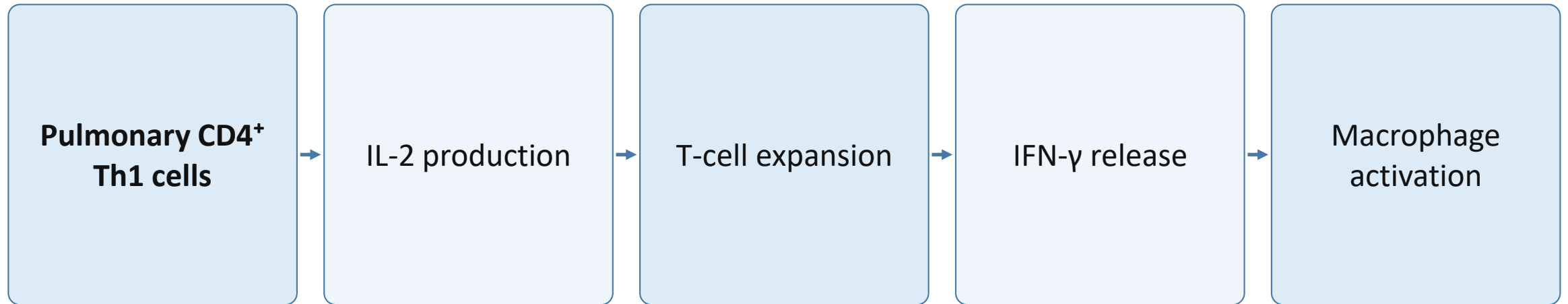
Pulmonary CD4⁺ T-cell enrichment

- Sarcoid lungs accumulate CD4⁺ T cells in alveolar and interstitial spaces.
- Textbook CD4:CD8 ratios in the local infiltrate range from 5:1 to 15:1.
- The enrichment implicates helper T-cell responses in granuloma formation.
- These observations do not by themselves identify an etiologic antigen.

Oligoclonal T-cell expansion: Evidence of antigen drive

- Rearrangement analyses show expansion of selected T-cell clones.
- Oligoclonality is consistent with antigen-driven proliferation.
- The responsible antigen has not been established.
- Interpret immune clonality as a mechanistic clue, not proof of one trigger.

Th1 cytokines connect T cells to macrophages



Distinct cytokine effects are illustrated in a simplified teaching sequence.

Chemokines and TNF amplify the granuloma

- Activated macrophages release TNF in the local pulmonary environment.
- IL-8 and macrophage inflammatory protein-1 α facilitate leukocyte recruitment.
- Incoming T cells and monocytes enlarge and sustain granulomatous foci.
- The text associates elevated bronchoalveolar TNF with disease activity.

Sarcoidosis: Local immunity versus systemic tests

Local pulmonary response

- CD4⁺ helper T-cell accumulation
- Increased Th1-related cytokine activity
- Epithelioid granuloma formation

Systemic immune abnormalities

- Anergy to common skin-test antigens
- Polyclonal hypergammaglobulinemia
- Complex rather than globally increased immunity

Genetic susceptibility is contributory, not deterministic

- Familial and population clustering suggests heritable susceptibility.
- Associations with HLA genotypes are described in the source.
- Environmental or antigenic contributions remain unidentified.
- No single HLA pattern establishes or excludes sarcoidosis.

Sarcoid granulomas: The central histologic lesion

- Compact epithelioid macrophages form well-demarcated aggregates.
- Multinucleated giant cells may occur in the lesion.
- Central necrosis is unusual.
- Lymphocytes surround lesions variably; Chronic lesions become fibrotic.

Sarcoid granuloma: Activity and remodeling

Active lesion

- Coherent clusters of epithelioid histiocytes
- Potential giant cells
- Limited or absent central necrosis

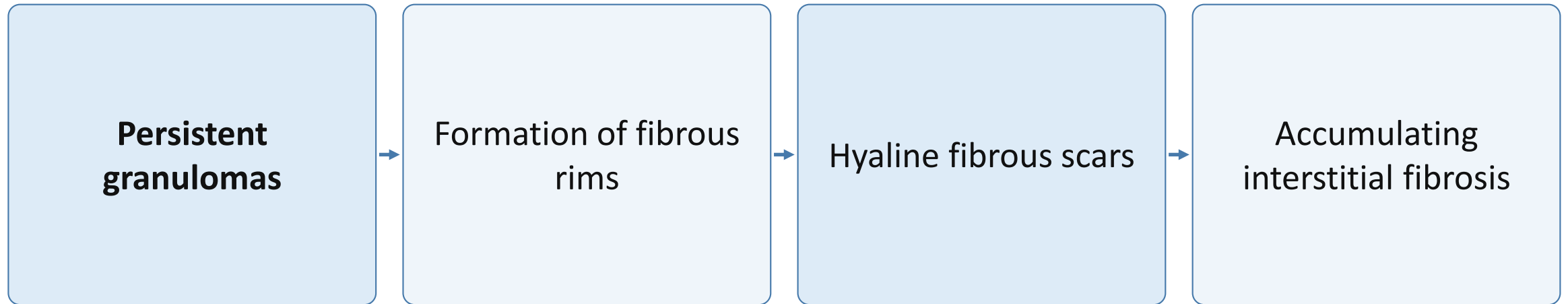
Chronic lesion

- Fibrous rims may encircle granulomas
- Progressive hyalinization may replace cellular lesion
- Late fibrotic change may impair function

Giant-cell inclusions: Schaumann and asteroid bodies

- Schaumann bodies are laminated concretions containing calcium and proteins.
- Asteroid bodies are stellate inclusions found in giant cells.
- Both are described in sarcoid granulomas.
- Neither inclusion is pathognomonic; Other granulomatous diseases can show them.

Granuloma remodeling and functional decline

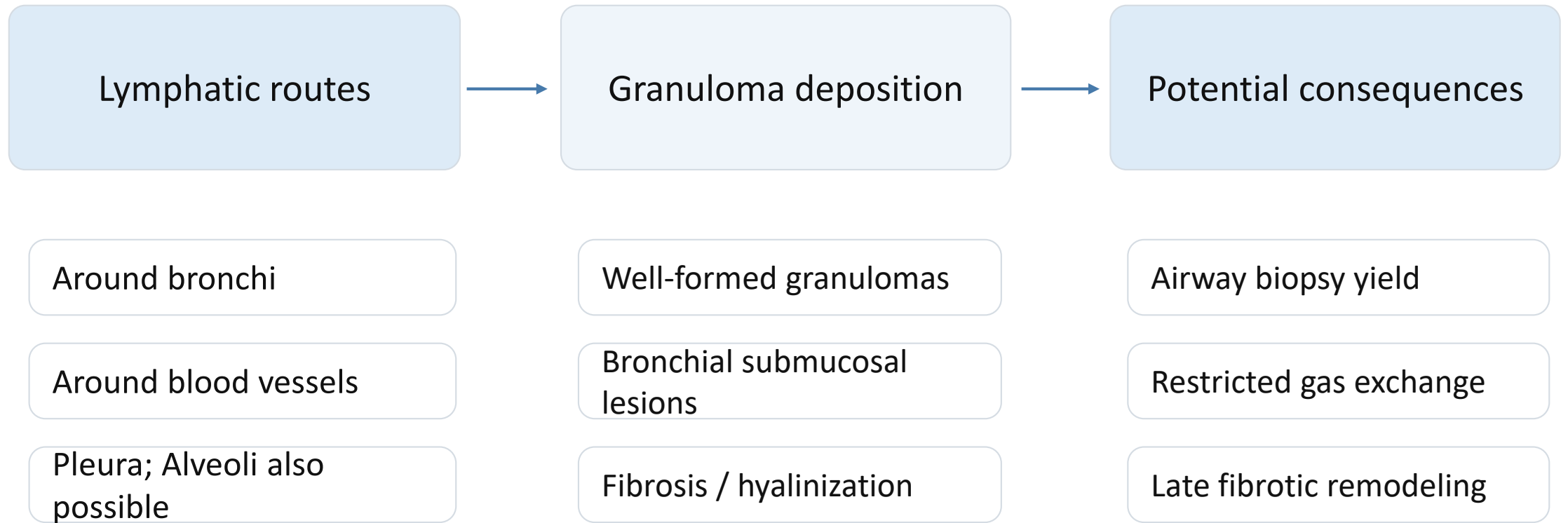


Fibrosis is a possible chronic outcome, not an inevitable consequence of each granuloma.

Pulmonary sarcoidosis: Gross appearance

- Grossly visible lung changes may be absent despite histologic granulomas.
- Advanced lesions may coalesce into firm nodules.
- Textbook describes occasional 1–2 cm noncaseating, noncavitated consolidations.
- Disease stage alters the balance between inflammatory nodules and fibrosis.

Sarcoidosis: Pulmonary compartment relationships



Why bronchoscopic sampling may be informative

- Bronchial submucosal granulomas occur frequently in pulmonary sarcoidosis.
- Endobronchial tissue can therefore demonstrate a diagnostic pattern.
- A tissue pattern must still be interpreted after exclusion of mimics.
- Sampling should be directed by the available tissue and clinical pattern.

Hilar and mediastinal lymph nodes

- Lymph-node involvement is present in almost all described cases.
- Hilar and mediastinal nodes are particularly prominent sites.
- Nodes are enlarged and discrete; Some undergo calcification.
- Nodal findings help explain the common radiographic presentation.

Spleen: Common microscopic, less common gross disease

- Granulomas can affect splenic tissue even without clinical enlargement.
- The source reports splenic involvement in about 75% of cases.
- Overt splenomegaly is described in approximately 20%.
- Coalescent granulomas occasionally produce visible splenic nodules.

Liver: Portal-predominant granulomas

- Hepatic involvement occurs somewhat less often than splenic involvement.
- Tissue typically contains scattered granulomas.
- Granulomas predominate in portal triads rather than lobules.
- Clinical enlargement may occur, but histologic involvement can be subtle.

Bone marrow and skeletal manifestations

- Marrow involvement is described in roughly one-fifth of cases.
- Phalangeal bones of hands and feet may show discrete resorption foci.
- Radiographs may demonstrate a reticulated marrow-cavity pattern.
- Bone remodeling can produce expansion or periosteal new bone formation.

Cutaneous sarcoidosis: Varied appearances

Granulomatous skin lesions

- Subcutaneous nodules
- Raised erythematous plaques
- Flat erythematous, scaling lesions

Other cutaneous presentations

- Mucosal lesions can occur
- Shin nodules may represent erythema nodosum
- Clinical appearances are not uniform

Erythema nodosum: Inflammatory skin manifestation

- Typically presents with painful erythematous nodules on the shins.
- The underlying tissue reaction is septal panniculitis.
- It is a clinical manifestation associated with sarcoidosis.
- Do not equate erythema nodosum itself with a diagnostic sarcoid granuloma.

Ocular involvement can threaten sight

- Ocular sarcoidosis frequently presents as iritis or iridocyclitis.
- Inflammation may be unilateral or bilateral.
- Complications described include corneal opacity and glaucoma.
- Untreated or progressive ocular involvement can result in visual loss.

Lacrimal and salivary gland involvement

- Inflammation of lacrimal glands can diminish tear production.
- Dry eyes are described as part of a sicca presentation.
- Parotid and other major salivary glands can be affected.
- Ocular and glandular involvement can coexist in multisystem disease.

Muscle, heart and nervous system

- Muscle granulomas can be asymptomatic; Weakness or myalgia may prompt investigation.
- Cardiac granulomas are uncommon but clinically consequential.
- Central nervous system involvement is described in a minority of cases.
- Pituitary and other endocrine involvement can occur.

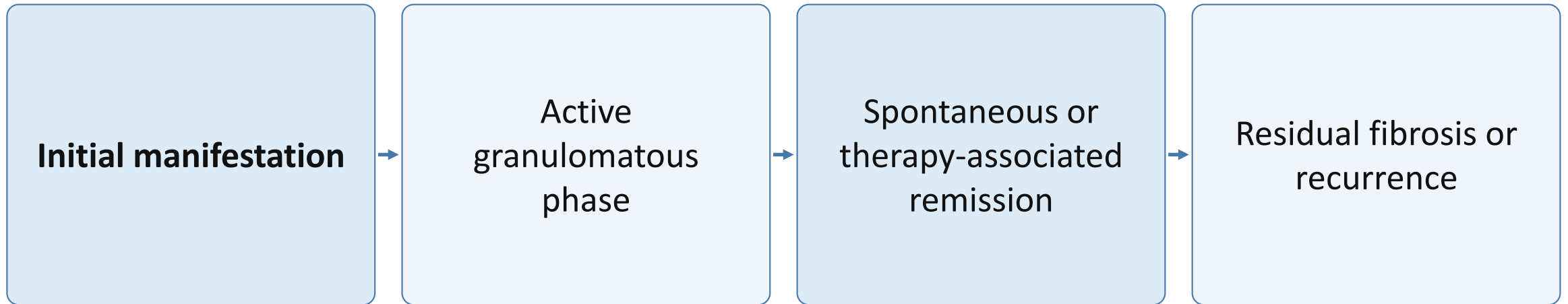
How pulmonary sarcoidosis presents

- Bilateral hilar lymphadenopathy may be found incidentally.
- Insidious dyspnea and cough often prompt evaluation.
- Chest pain and hemoptysis are also described.
- An apparently localized pulmonary syndrome may coexist with systemic lesions.

Constitutional manifestations and multisystem clues

- Fever, fatigue, weight loss and anorexia can precede diagnosis.
- Night sweats are among the reported presenting symptoms.
- Peripheral adenopathy, skin changes or ocular symptoms may dominate.
- The wide spectrum follows from variable organ distribution.

Sarcoidosis may follow several time courses



The last two possibilities are alternatives; The diagram should not be read as an inevitable linear pathway.

Sarcoidosis: Long-term clinical trajectories

65%–70%

Recovery with minimal or no residual disease

≈20%

Residual pulmonary or visual impairment

10%–15%

Severe cases; Some deaths from pulmonary, cardiac or CNS disease

Sarcoidosis: Why the diagnosis remains exclusionary

- Nonnecrotizing granulomas support but do not uniquely identify sarcoidosis.
- Mycobacterial and fungal infections can share the granulomatous pattern.
- Beryllium-associated granulomatous disease is another recognized mimic.
- A convincing diagnosis requires compatible morphology and clinical evaluation.

Sarcoidosis: Interpret the tissue in context

Observation	Supports	Does not establish
Well-formed granulomas	Granulomatous inflammation	Unique sarcoid etiology
Absent central necrosis	Nonnecrotizing morphology	Exclusion of infection
Thoracic adenopathy	Compatible organ pattern	Sarcoidosis without differential
Systemic skin/eye signs	Broader organ correlation	An antigen or molecular cause

Case 1: Bilateral hilar lymphadenopathy

A young adult has bilateral hilar lymph-node enlargement and a biopsy showing sharply formed nonnecrotizing granulomas. The patient also reports recurrent painful eye inflammation.

Interpretation tasks

- Which diagnosis is most strongly suggested?
- Why is the biopsy finding not sufficient on its own?

Case 1 interpretation

- The combination strongly suggests sarcoidosis.
- Pulmonary / hilar nodal disease with ocular inflammation fits the textbook pattern.
- Well-formed nonnecrotizing granulomas are supportive.
- Infection and relevant exposure-related granulomatous mimics must be considered.

Hypersensitivity pneumonitis: Defining mechanism

- Immune-mediated interstitial lung disease from inhaled antigenic material.
- Exposure is often intense, repeated or prolonged.
- Primary site of injury is the alveolar wall and related small airways.
- The alternate term is extrinsic allergic alveolitis.

HP: Exposure source and antigen type

Biologic antigens

- Spores of thermophilic bacteria
- Fungal material and microbial products
- Animal-derived proteins

Common exposure environments

- Warm or damp agricultural material
- Bird handling or bird-housing sites
- Contaminated humidifier / air-conditioning water

Farmer's lung: A biologically plausible exposure

- Warm, moist harvested hay can support thermophilic actinomycetes.
- Dust generated during handling carries antigenic microbial material.
- An exposed, sensitized person may develop recurrent pulmonary symptoms.
- An occupational history can link episodes to the relevant environment.

Bird fancier's lung: An animal-protein exposure

- Bird-related serum, excreta and feathers contain triggering proteins.
- Pigeon breeding is the named textbook example.
- Domestic pet-bird exposure may be missed without direct questioning.
- The diagnosis turns on a plausible exposure–illness relationship.

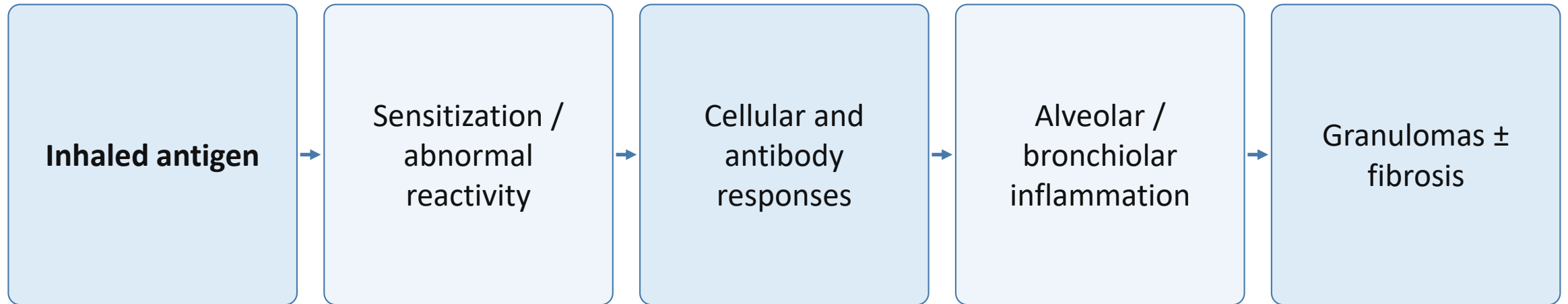
Humidifier and air-conditioner lung

- Heated water reservoirs can support thermophilic microorganisms.
- Aerosolized biologic material provides an inhalational exposure.
- The source lists humidifier and air-conditioning systems as exposure settings.
- Indoor water systems deserve attention when workplace causes are absent.

Exposure history is central in suspected HP

- Ask specifically about farming, hay and damp agricultural storage.
- Ask about domestic birds, pigeon breeding and bird-related activities.
- Enquire about humidifiers, water reservoirs and mold-prone environments.
- Relate symptoms to repeated contact, duration and removal from exposure.

Hypersensitivity pneumonitis: Immune response



The source supports humoral and cell-mediated immune evidence; The diagram is a synthesis, not a single obligatory pathway.

HP: Immune evidence from lavage

- Acute bronchoalveolar lavage may show elevated proinflammatory chemokines.
- The source names IL-8 and macrophage inflammatory protein-1 α (CCL3).
- Both CD4⁺ and CD8⁺ lymphocytes increase in lavage specimens.
- The immune profile differs from a purely bronchodilator-responsive airway disorder.

HP: Antibodies and complement

- Antibodies directed at an implicated exposure antigen are common.
- Immunoglobulin and complement deposits may be found in vessel walls.
- These observations support a humoral immune component.
- Circulating antigen-specific antibodies alone should not be treated as proof of clinical disease.

HP: Why granulomas suggest cellular immunity

- Nonnecrotizing granulomas are reported in approximately two-thirds of patients.
- The morphology supports a T-cell–mediated component of tissue injury.
- The source explicitly implicates type IV hypersensitivity mechanisms.
- Granulomas must be interpreted alongside interstitial and bronchiolar changes.

HP: Acute injury pattern

- Morphology depends on time since antigenic challenge.
- Acute alveolar injury dominates in the first hours or days.
- Inflammatory responses can accompany fever and new respiratory symptoms.
- A single biopsy cannot be interpreted without phase and exposure context.

HP: Subacute interstitial pneumonitis

- Inflammation prominently affects bronchioles and adjacent interstitium.
- Lymphocytes, plasma cells and macrophages dominate the infiltrate.
- Eosinophils are uncommon in this pattern.
- Nonnecrotizing granulomas may accompany the cellular interstitial process.

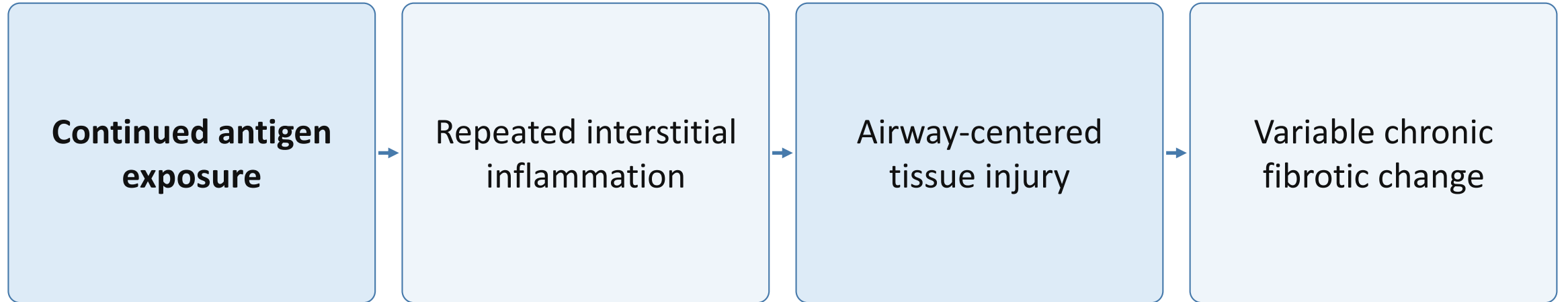
HP: Characteristic bronchiolocentric injury

- Tissue injury tends to center on bronchioles and nearby lung.
- Peribronchiolar metaplasia may involve alveolar ducts and respiratory bronchioles.
- Granulomas are often loosely organized rather than densely formed.
- This arrangement helps distinguish HP from perilymphatic sarcoidosis.

HP: Chronic fibrotic remodeling

- Persistent disease may produce interstitial fibrosis and fibroblastic foci.
- Honeycombing and obliterative bronchiolitis can coexist with granulomas.
- Fibrosis may overlap with organizing pneumonia or other interstitial patterns.
- In advanced disease, nonspecific or UIP-like fibrosis can obscure the cause.

HP: Exposure and progression



Recognizing the exposure early allows preventive antigen removal.

Acute HP: Characteristic timing

- Symptoms typically develop 4–6 hours after antigenic dust exposure.
- Fever, cough, dyspnea and leukocytosis are described.
- Attacks can last from 12 hours to several days.
- Re-exposure can reproduce the syndrome.

HP: Respiratory physiology and imaging

- The acute phase may produce a restrictive ventilatory disorder.
- Chest radiography may show micronodular interstitial infiltrates.
- Pulmonary dysfunction follows alveolar-wall and interstitial involvement.
- Findings must be integrated with exposure rather than interpreted alone.

Chronic HP: Clinical consequences

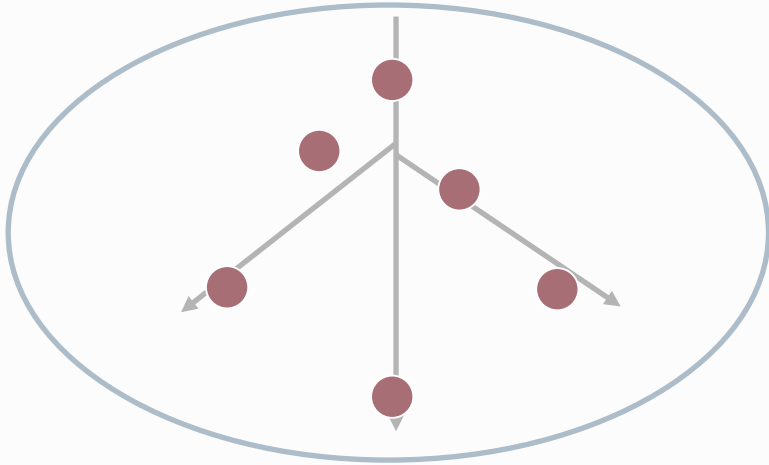
- Ongoing exposure can produce progressive fibrosis.
- Dyspnea and cyanosis may emerge with advanced interstitial disease.
- Chronic presentations resemble other fibrotic interstitial lung diseases.
- Loss of a classic granulomatous pattern complicates etiologic recognition.

Why early recognition of HP matters

- Antigen removal may prevent progression to serious chronic fibrosis.
- Exposures may be hidden in domestic, occupational or indoor environments.
- Clinical recurrence after contact is a useful contextual clue.
- Separating exposure-driven HP from sarcoidosis changes prevention strategy.

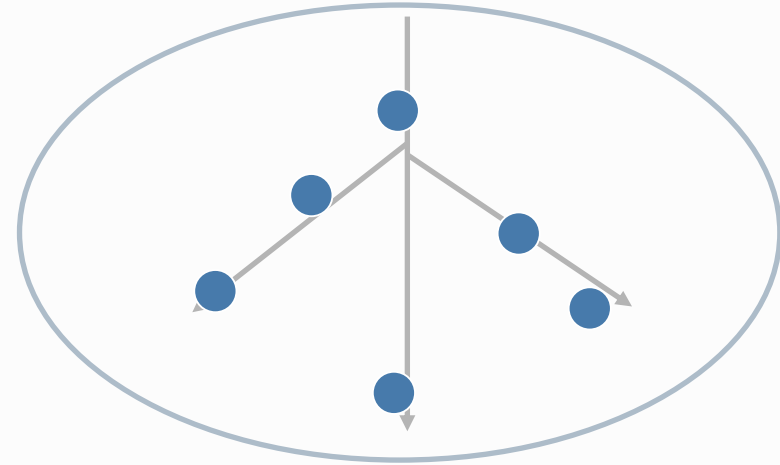
Granuloma distribution in lung: Anatomic clues

Sarcoidosis



Predominantly perilymphatic /
peribronchovascular

Hypersensitivity pneumonitis



Bronchiolocentric inflammation and granulomas

Sarcoidosis versus hypersensitivity pneumonitis

Feature	Sarcoidosis	Hypersensitivity pneumonitis
Principal context	Multisystem, cause unknown	Exposure-related interstitial disease
Granulomas	Often well-formed	Often poorly formed
Lung distribution	Perilymphatic	Bronchiolocentric
Extra clues	Thoracic nodes, eye, skin	Bird, hay, humidifier exposure
Clinical trajectory	Remissions or progression	Recurrent exposure-related episodes or fibrosis

Case 2: Fever after agricultural dust exposure

A person working with damp stored hay experiences episodes of fever, cough and breathlessness several hours after handling it. Examination during one episode suggests an interstitial restrictive disorder.

Interpretation tasks

- What exposure-associated diagnosis is suggested?
- Which tissue compartments are expected to show inflammation?

Case 2 interpretation

- An acute presentation of hypersensitivity pneumonitis is suggested.
- Damp hay can harbor thermophilic actinomyces capable of provoking HP.
- The 4–6-hour delay and recurrence after exposure are compatible features.
- Pathology, when sampled, may show alveolar-wall inflammation and bronchiolocentric changes.

Case 3: A granuloma is not a final diagnosis

Lung tissue shows a nonnecrotizing granuloma. No clinical exposure history, imaging distribution or systemic examination has been supplied.

Interpretation tasks

- Can the specimen alone establish sarcoidosis?
- Which two major categories of alternative causes require consideration?

Case 3 interpretation

- No: Granuloma morphology alone is insufficiently specific.
- Infectious granulomatous disease must be considered.
- Occupational beryllium-associated disease is another named mimic.
- Exposure context and distribution must precede a confident etiologic diagnosis.

Interpretive clues: A comparative diagnostic grid

Observation	Favors consideration of	Limitation
Well-formed granuloma, hilar nodes	Sarcoidosis	May overlap infection / berylliosis
Exposure-related recurrent fever	Hypersensitivity pneumonitis	History requires correlation
Bronchiolocentric mixed inflammation	Hypersensitivity pneumonitis	Not uniquely diagnostic
Nonnecrotizing granuloma alone	Multiple causes	No etiologic specificity

Common diagnostic reasoning errors

- Calling every nonnecrotizing granuloma “sarcoidosis.”
- Failing to ask specifically about birds, damp hay and indoor water systems.
- Ignoring distribution: Perilymphatic versus bronchiolocentric patterns.
- Assuming advanced fibrosis must retain the classic initiating morphology.

Five integrated pathology conclusions

- Sarcoidosis is systemic, commonly thoracic, and a diagnosis of exclusion.
- Local Th1-associated T-cell and macrophage activity underlies its granulomas.
- Organ-specific disease produces pulmonary, ocular, cutaneous and systemic signs.
- HP links inhaled biologic antigen exposure to interstitial / bronchiolar injury.
- Granuloma quality, distribution and exposure history guide differentiation.

Primary reading and source limitations

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Chapter 15, The Lung: “Granulomatous Diseases,” pp. 634–636.
- Scope: Sarcoidosis; Hypersensitivity Pneumonitis, with contiguous text on p. 637.
- The supplied Markdown interleaves columns; unrelated asbestosis text was excluded.
- Original chapter PDF and embedded textbook figures were not provided.