
Coccidioidomycosis

PATHOGENESIS · TISSUE MORPHOLOGY · CLINICOPATHOLOGIC INTEGRATION

An endemic dimorphic fungal infection

From inhaled arthroconidia to tissue spherules

Mechanisms • morphology • clinical distribution

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Learning objectives

- Identify the two *Coccidioides* species and the principal entry route.
- Explain innate immune evasion and the role of T-cell immunity.
- Recognize nonbudding endospore-containing spherules and tissue reactions.
- Connect host risk factors with pulmonary and disseminated disease.

The etiologic organisms

- *Coccidioides immitis* and *Coccidioides posadasii* cause the infection.
- Both belong to the group of geographically endemic fungal pathogens.
- Species-level distinction is not required to recognize the characteristic tissue spherule.

C. Immitis

Etiologic species

C. Posadasii

Etiologic species

Why this is an endemic mycosis

- Endemic mycoses arise from fungi associated with specific regions.
- They can produce systemic illness even in otherwise healthy people.
- Coccidioides infection is acquired through inhalation of environmental spores.



Simplified conceptual sequence

Geographic exposure

- The described endemic setting includes the southwestern and western United States and Mexico.
- Exposure history is therefore etiologically informative.
- A positive response to a fungal skin test is common in endemic populations description.

Region

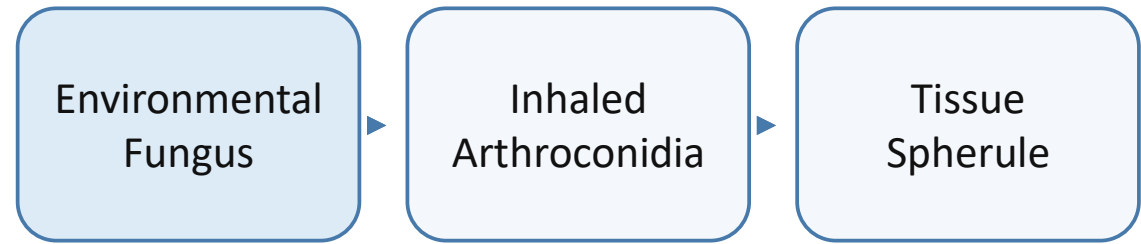
Southwestern / western
US

Region

Mexico

Fungal morphology depends on context

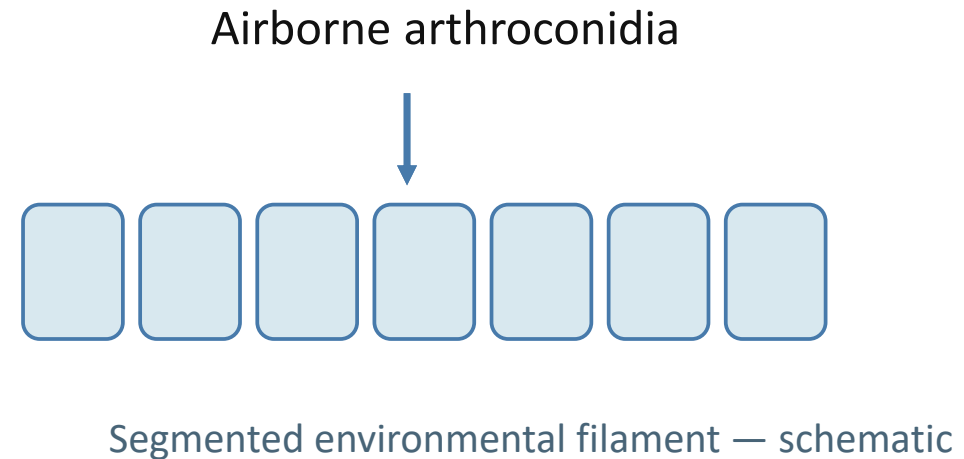
- Molds consist of hyphae and can form airborne conidia.
- Dimorphic fungi occupy different morphologic states under environmental versus host conditions.
- For *Coccidioides*, tissue diagnosis hinges on spherules—not conventional budding yeasts.



Simplified conceptual sequence

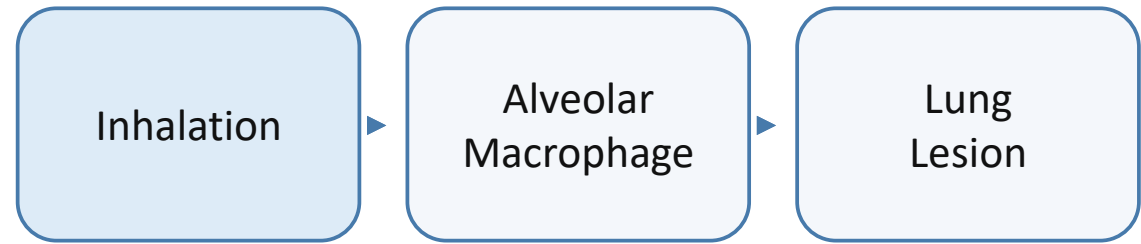
Arthroconidia: The infective form

- The infectious units inhaled from the environment are arthroconidia.
- Their small size permits access to the respiratory tract.
- Their interaction with alveolar macrophages as an early pathogenic step.



The respiratory portal of entry

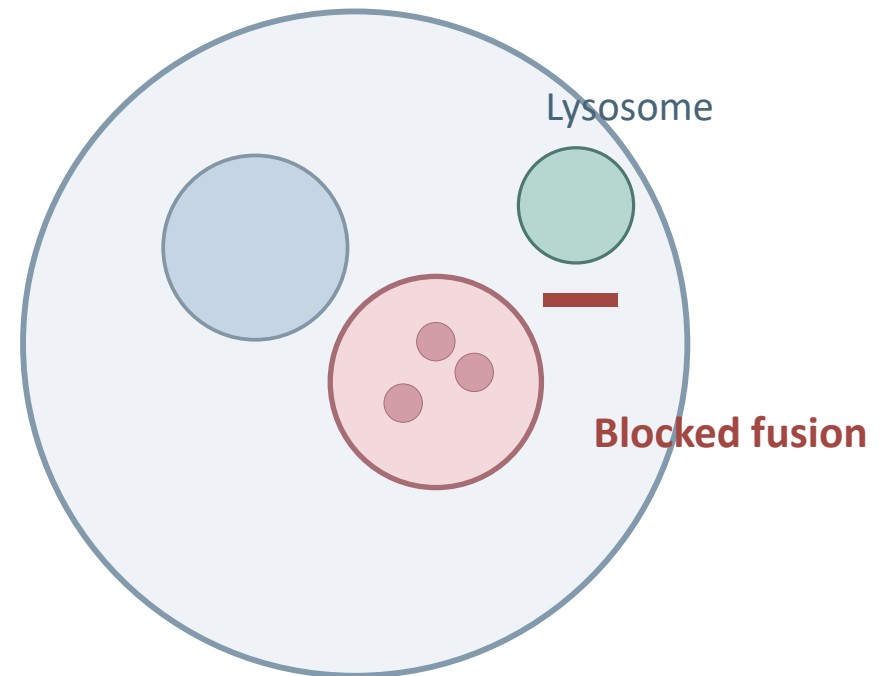
- Inhalation establishes the exposure-to-lung sequence.
- Alveolar macrophages encounter the incoming arthroconidia.
- The pulmonary lesion is the starting point for the clinicopathologic spectrum.



Simplified conceptual sequence

First-line defense: The macrophage

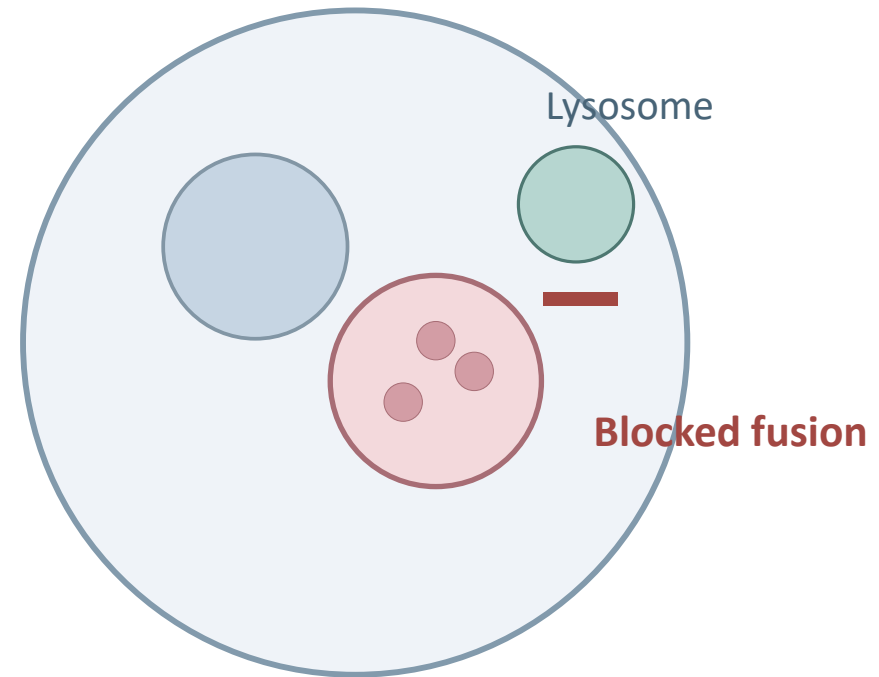
- Phagocytosis normally brings microbes into an intracellular compartment.
- That compartment ordinarily participates in the delivery of killing mechanisms.
- *Coccidioides arthroconidia* can subvert this defense step.



Schematic phagosome with arthroconidium

Phagosome–lysosome fusion is blocked

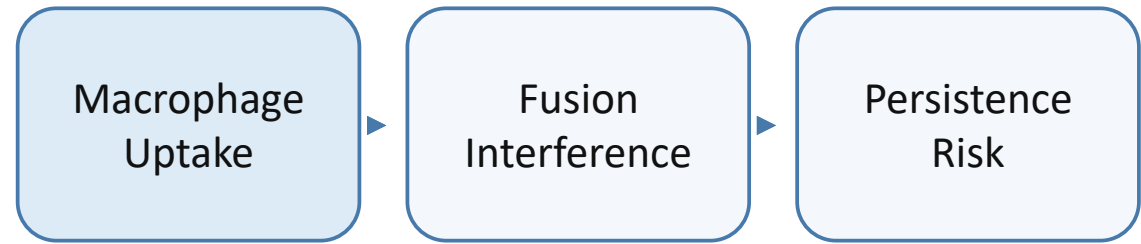
- After engulfment, infective arthroconidia impede phagosome–lysosome fusion.
- The consequence is resistance to intracellular killing.
- This mechanism helps account for the organism's infectivity.



Schematic phagosome with arthroconidium

Immune evasion changes the initial balance

- Entry and uptake do not automatically eliminate the fungus.
- Blocked fusion permits survival despite contact with a host phagocyte.
- Subsequent disease depends on the organism–host immune interaction.



Simplified conceptual sequence

Two connected immune responses

- Innate macrophage mechanisms confront inhaled fungal elements.
- Cell-mediated immunity becomes important in containing persistent fungal material.
- A delayed-type hypersensitivity response is a prominent feature of *Coccidioides* infection.

Innate

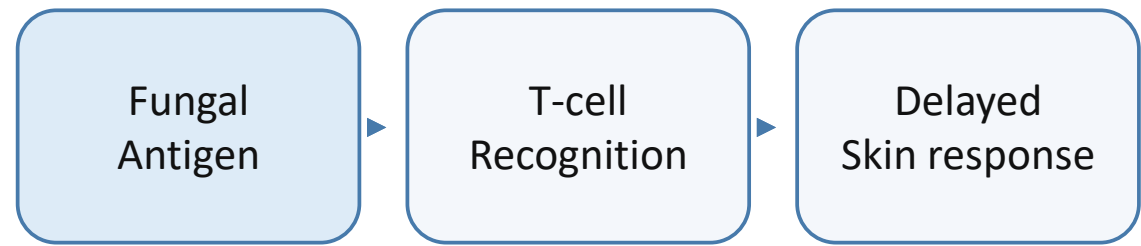
Macrophage uptake

Adaptive

T-cell / DTH response

Delayed-type hypersensitivity (DTH)

- DTH is a T-cell–mediated inflammatory response to antigen.
- Previously sensitized hosts can mount a delayed cutaneous reaction.
- This explains how an asymptomatic infected person may still have a positive skin test.



Simplified conceptual sequence

DTH is not identical to clinical disease

- An immune response indicates recognition of fungal antigen.
- Most infected people remain asymptomatic.
- Therefore a positive skin reaction should not be equated with active pulmonary or disseminated disease.

Immune evidence

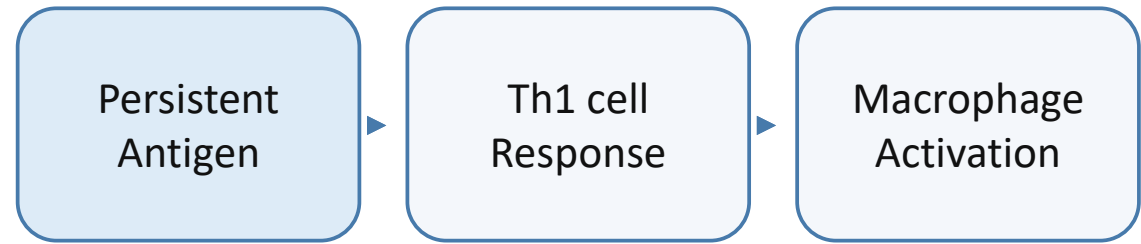
DTH / skin-test positivity

Disease evidence

Compatible pathology /
clinical lesion

Cell-mediated inflammation: The Th1 axis

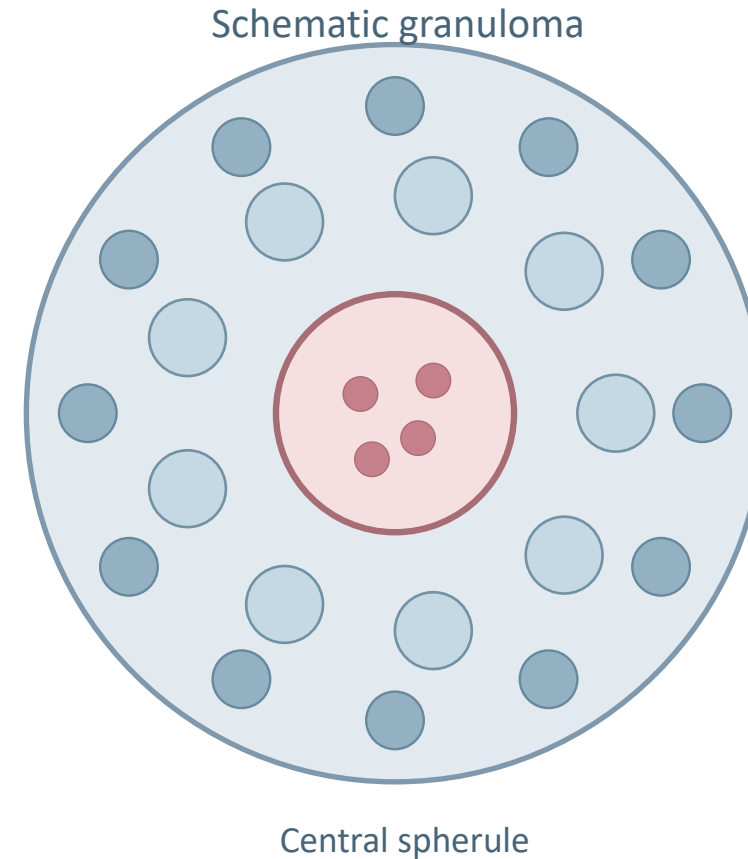
- In immune granulomas, persistent microbial antigens can stimulate T cells.
- Th1-associated cytokines, particularly interferon- γ , activate macrophages.
- Macrophage activation links antigen recognition to containment of persistent material.



Simplified conceptual sequence

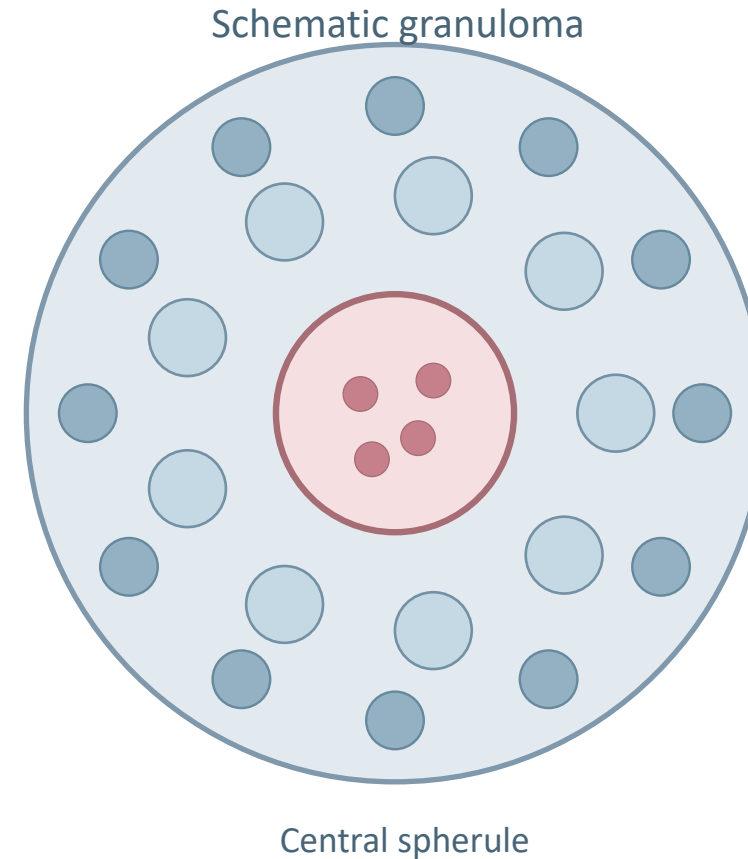
Why granulomas form

- Granulomas represent attempts to contain an agent difficult to eradicate.
- They contain aggregates of activated macrophages, often with lymphocytes.
- Macrophages may become epithelioid and fuse into giant cells.



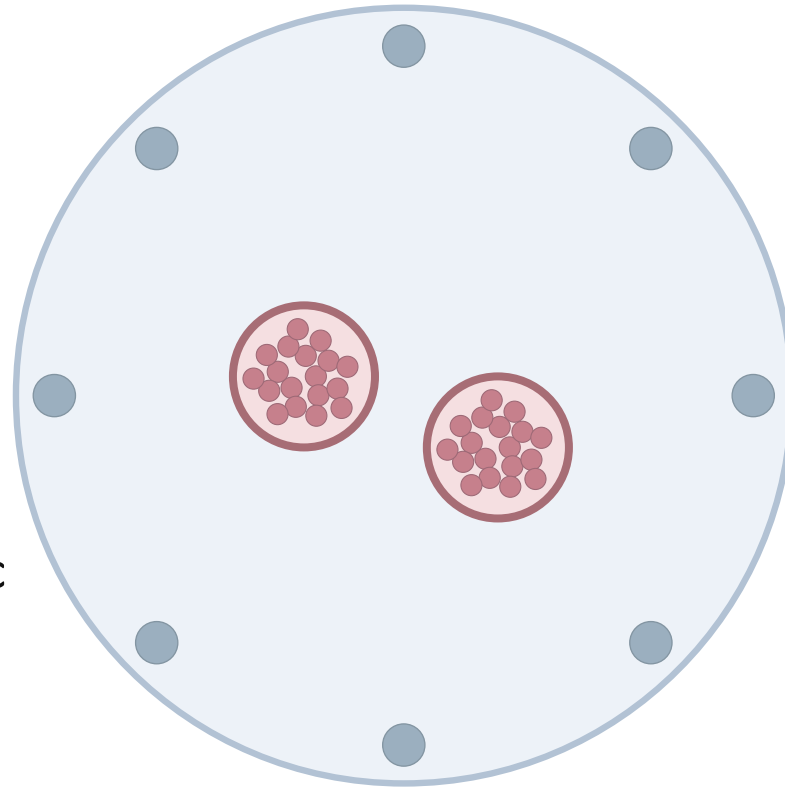
The cellular composition of a granuloma

- Epithelioid macrophages are the principal constituent.
- Multinucleated giant cells may be present.
- Peripheral T lymphocytes support the immune organization of the lesion.



What a giant cell contributes diagnostically

- A giant cell is produced by the fusion of activated macrophages.
- The Robbins coccidioidomycosis figure describes spherules within a giant cell.
- An identifiable organism supplies etiologic specificity beyond the granuloma pattern alone.



Multinucleated giant cell (schematic)

The inflammation can injure tissue

- Persistent antigen-driven macrophage activation is not harmless.
- Granulomatous inflammation can damage normal structures while containing pathogens.
- *Coccidioides* lesions may coexist with a pyogenic component.

Containment

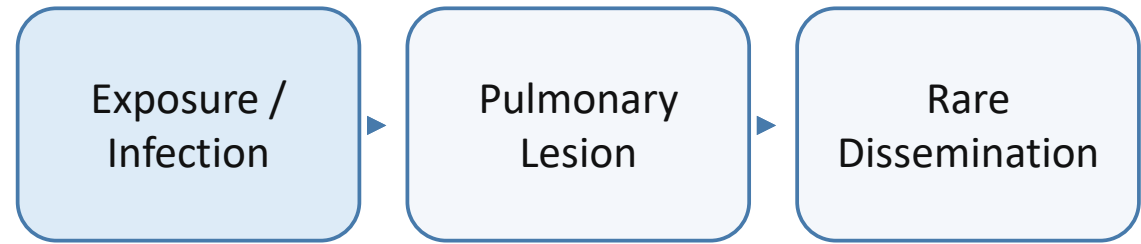
Granulomatous reaction

Injury

Pyogenic / mixed
response

Possible outcomes after inhalation

- Most infections remain clinically asymptomatic.
- A minority produces recognizable lung lesions.
- Rare progressive infection can involve multiple extrapulmonary tissues.



Simplified conceptual sequence

The relative frequencies

- Skin-test reactivity above 80% in endemic-area populations.
- It reports lung lesions in approximately 10% of infected individuals.
- It describes disseminated infection in fewer than 1% of infected individuals.

>80%

Skin-test reaction
in endemic-area
populations

~10%

Lung lesions
among infected
individuals

<1%

Disseminated
infection among
infected
individuals

Different denominators and descriptions; Not additive

How to interpret these estimates

- The three percentages use different clinical descriptions and should not be summed.
- The figures reflect the textbook's narrative estimates rather than a contemporary cohort analysis.
- Disease frequencies must be interpreted in the setting of host immunity and the population sampled.

Asymptomatic infection is common

- Infection and inflammatory sensitization may occur without illness.
- Absence of symptoms does not negate prior exposure.
- The asymptomatic majority contrasts with the much smaller group with progressive lesions.

Frequent

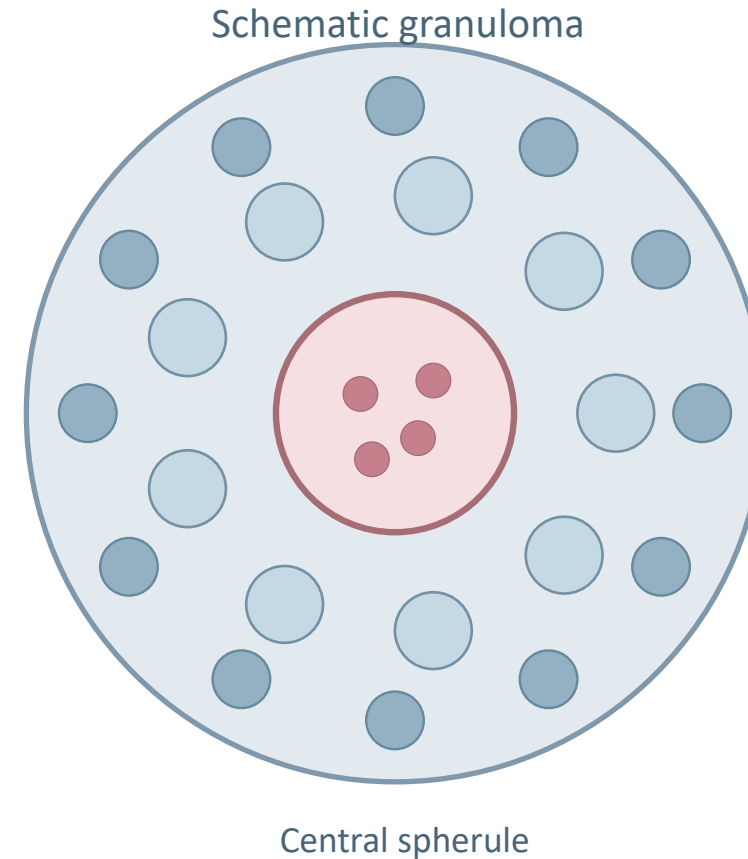
Exposure + immune
sensitization

Less frequent

Pathologically evident
disease

Pulmonary disease is the principal focus

- The lung is the initial site reached following inhalation.
- *Coccidioides* is among the causes of chronic granulomatous pneumonia listed by Robbins.
- Recognition of organisms helps distinguish fungal infection from noninfectious granulomas.



Chronic pneumonia as parent context

- Chronic pneumonia as commonly granulomatous.
- Mycobacteria and certain dimorphic fungi can produce this pattern.
- Pulmonary histology must therefore integrate inflammatory architecture with organism morphology.

Pattern

Granulomatous
pneumonia

Cause

Infectious organism
must be identified

Host immunity influences disease extent

- T-cell function supports granulomatous responses to persistent organisms.
- Suppression of T-lymphocyte immunity is a risk factor for dissemination.
- Host factors therefore affect the probability of disease progression.



Simplified conceptual sequence

Pregnancy as a dissemination risk

- Robbins specifically flags infection acquired during the second or third trimester.
- This is a host-state risk factor for disseminated infection.
- Pregnancy-related susceptibility should be considered when assessing progressive disease in an endemic setting.

Period named

Second / third trimester

Concern

Risk of dissemination

HIV-associated T-cell impairment

- HIV infection may suppress T-lymphocyte immunity.
- That impaired immunity is associated with an increased risk of dissemination.
- A disseminated presentation should be understood as an interaction between pathogen and host defenses.

Host factor

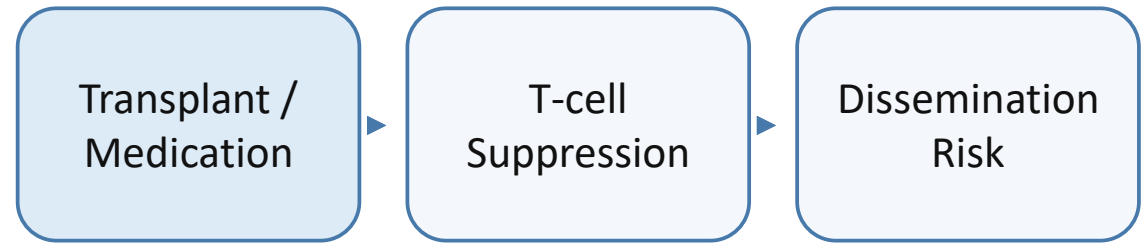
HIV / low T-cell function

Risk

Disseminated
Coccidioides

Organ transplantation and immune suppression

- Post-transplant immunosuppression is explicitly listed as a dissemination risk.
- Immunosuppressive drugs are another named risk setting.
- A history of immune-modifying treatment is essential clinicopathologic context.



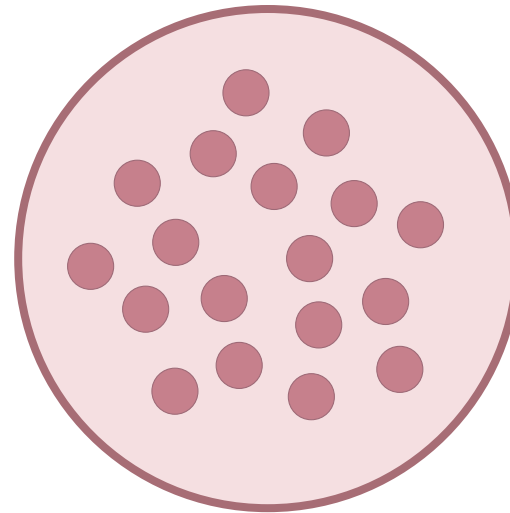
Simplified conceptual sequence

Risk factors: A unified framework

Risk setting	Mechanistic / clinical implication
Second / third trimester	Increased dissemination risk
HIV infection	T-lymphocyte immune suppression
Organ transplant treatment	Therapeutic immunosuppression
Other immunosuppressive drugs	Reduced cellular defenses

Tissue phase: A nonbudding spherule

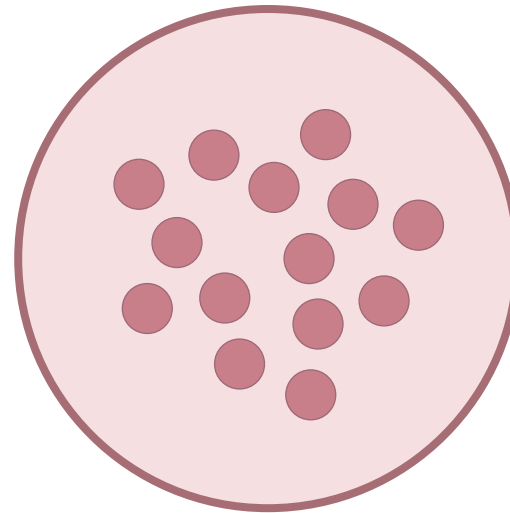
- The *Coccidioides* tissue form is a thick-walled spherule.
- It does not reproduce by the budding pattern of ordinary tissue yeasts.
- The spherule may contain numerous small endospores.



Schematic: Endospore-containing spherule

Approximate spherule diameter

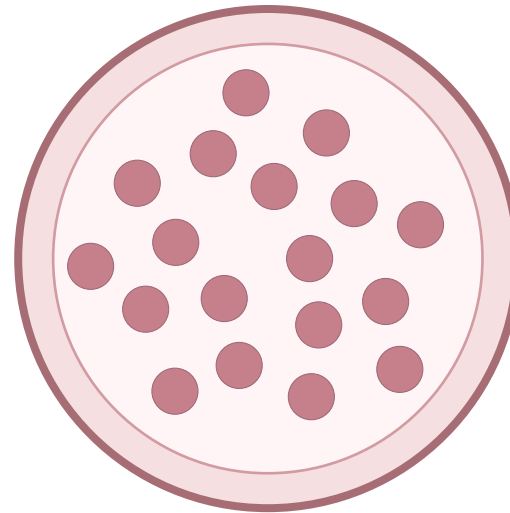
- A spherule diameter of 20–60 μm .
- Size is assessed together with wall thickness and internal endospores.
- Do not infer organism identity from a round shape alone.



20–60 μm

The diagnostic role of the thick wall

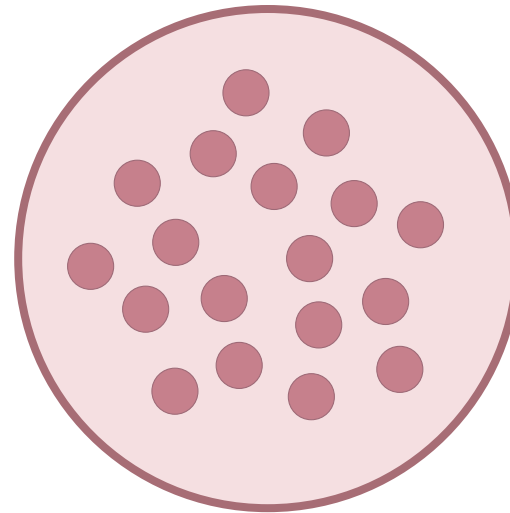
- A prominent boundary defines the mature tissue spherule.
- The wall encloses multiple endospores when the spherule is mature.
- This internal organization differentiates it from a single budding yeast cell.



Schematic: Prominent enclosing wall

Endospores develop within the spherule

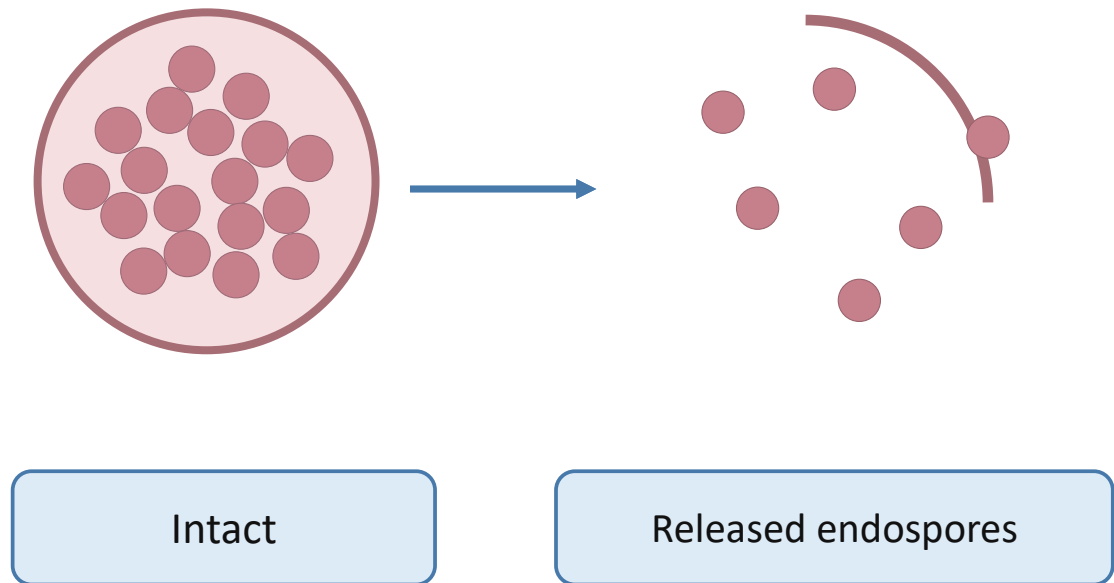
- A mature spherule contains numerous smaller endospores.
- Endospores are a defining internal feature' morphology description.
- The parent spherule and its contained elements should be interpreted together.



Schematic: Endospore-containing spherule

Rupture releases endospores

- A spherule can rupture and discharge endospores.
- This may place multiple small fungal elements into adjacent tissue.
- Robbins explicitly associates rupture with an additional pyogenic reaction.



Why neutrophils enter the lesion

- The source links pyogenic inflammation to spherule rupture.
- Released endospores are therefore associated with an acute inflammatory component.
- This explains why granulomatous and neutrophil-rich foci can coexist.



Simplified conceptual sequence

Three inflammatory patterns are possible

- Pure granulomatous inflammation.
- Pure pyogenic inflammation.
- A mixed granulomatous–pyogenic lesion.

Granulomatous

Pyogenic

Mixed

Macrophage
aggregates

Neutrophil-rich
response

Both components

One infection, variable tissue reactions

- The lesion's cellular composition is not fixed across all sites.
- Granulomatous, pyogenic and mixed responses can each occur.
- The defining fungal structure remains the most direct morphologic clue.

Variable

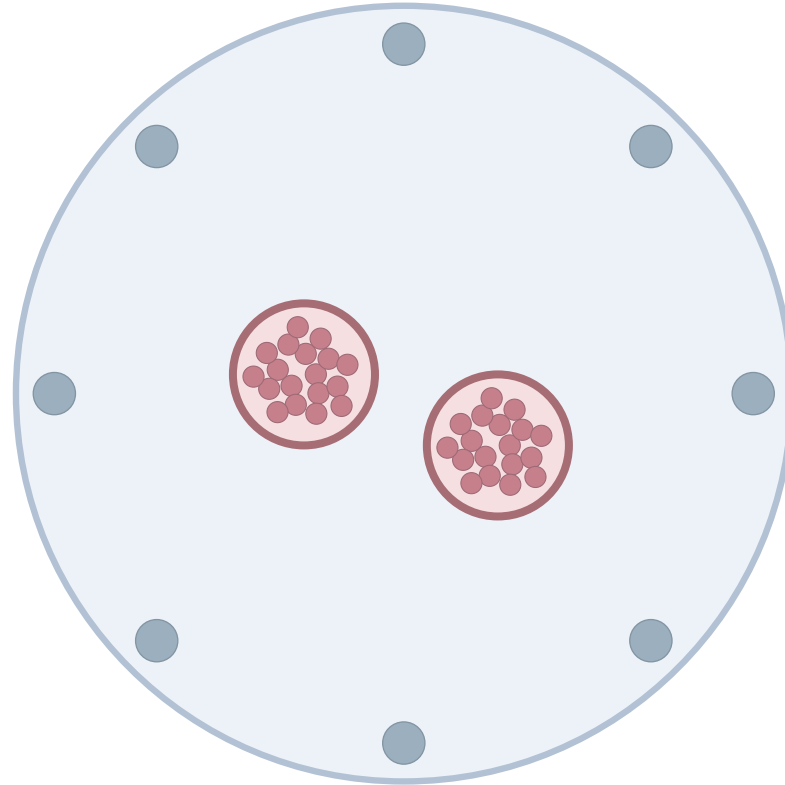
Host inflammatory
pattern

Characteristic

Coccidioides tissue
spherule

The source figure: What to look for

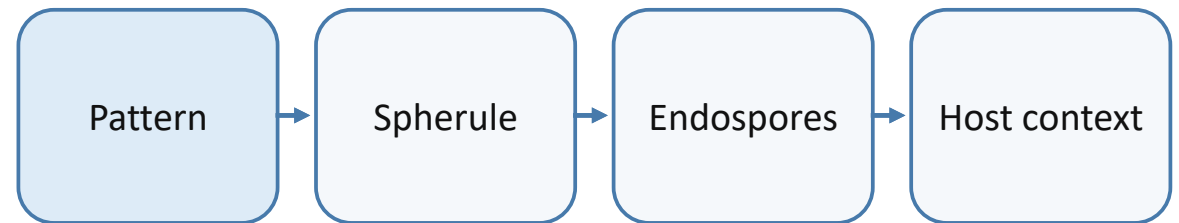
- Robbins Fig. 8.50 describes a well-defined granuloma.
- A large multinucleated giant cell contains two small spherules.
- Higher magnification demonstrates intact and ruptured endospore-bearing forms.



Multinucleated giant cell (schematic)

A stepwise tissue-recognition checklist

- First: Identify the inflammatory pattern.
- Second: Search for thick-walled nonbudding spherules.
- Third: Determine whether internal endospores or rupture are present.
- Fourth: Connect morphology with the relevant exposure and immune setting.



Morphology: What is specific and what is not

- Granulomatous inflammation alone is not species-specific.
- A pyogenic reaction alone is likewise not etiologically specific.
- Thick-walled spherules containing endospores provide the distinctive tissue clue.

Nonspecific

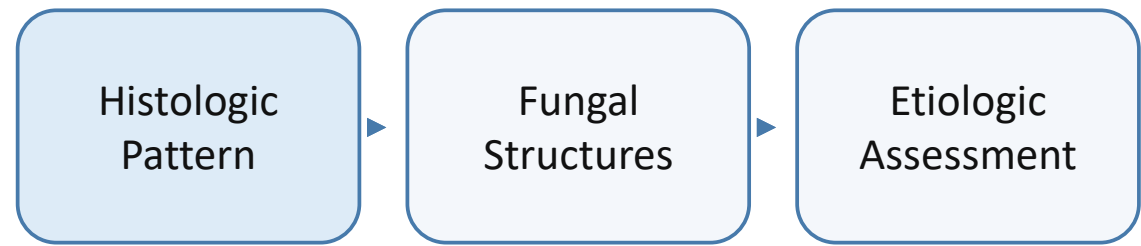
Granulomas /
neutrophils

Characteristic

Nonbudding endospore-
filled spherules

The diagnosis belongs to the lesion

- Fungi can be detected by histologic examination.
- Definitive fungal identification sometimes requires culture.
- In a granulomatous lesion, organism detection is stronger evidence than morphology of inflammation alone.



Simplified conceptual sequence

Granulomatous differential diagnosis

- Tuberculosis and sarcoidosis can also produce granulomatous lesions.
- Several dimorphic fungi produce granulomatous pulmonary inflammation.
- Identification of the causative agent is the key safeguard against pattern-only diagnosis.

Inflammation

Common pathway

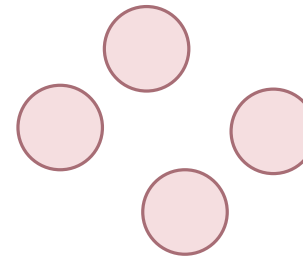
Organism

Differential
discriminator

Histoplasma: A contrasting fungal form

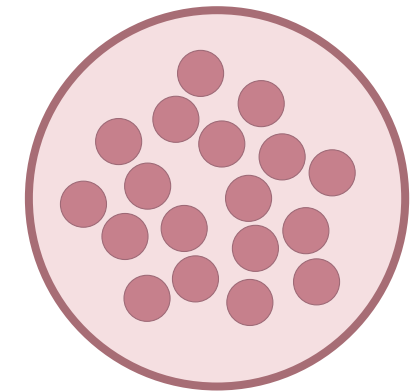
- Small thin-walled tissue yeasts measuring approximately 3–5 μm .
- The yeasts may remain within phagocytes and persist in tissue.
- Their size and yeast morphology contrast with the larger *Coccidioides* spherule.

Histoplasma



Small tissue yeasts

Coccidioides

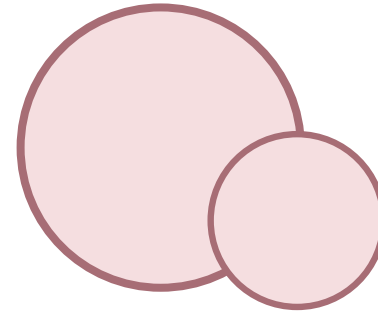


Spherule with endospores

Blastomyces: A second contrasting form

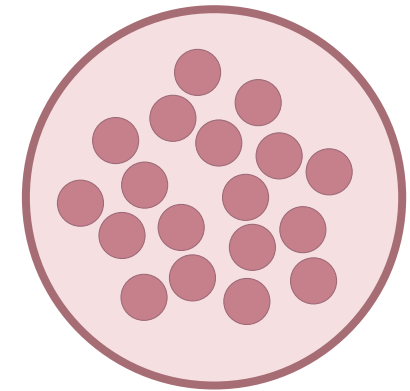
- A round thick-walled yeast measuring approximately 5–15 μm .
- Broad-based budding is a characteristic structural clue.
- Coccidioides spherules do not show broad-based budding.

Blastomyces



Broad-based bud

Coccidioides



Spherule with endospores

Dimorphic fungi: Tissue-morphology table

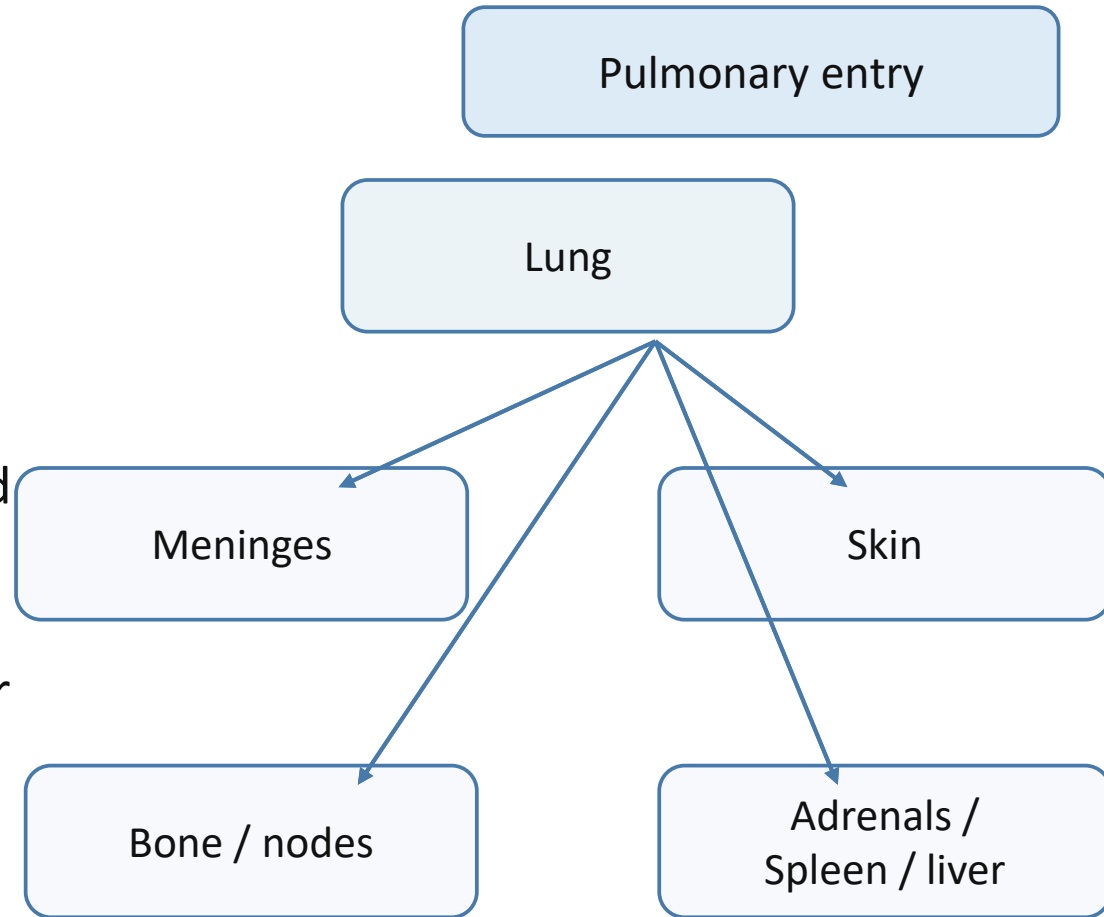
Organism	Key tissue form	Approximate diameter
Coccidioides	Thick-walled nonbudding spherule with endospores	20–60 μm
Histoplasma	Small thin-walled yeasts	3–5 μm
Blastomyces	Thick-walled broad-based budding yeast	5–15 μm

Comparing the inflammatory patterns

Infection	Robbins-described pulmonary response
Coccidioidomycosis	Granulomatous / pyogenic / mixed
Blastomycosis	Suppurative granulomas
Histoplasmosis	Often necrotizing granulomas

Dissemination extends beyond the lung

- Disseminated infection is uncommon description.
- Skin and meninges are frequently involved when spread occurs.
- Rare progressive disease can involve other organs and lymphoid tissues.



Skin involvement

- The skin is a frequently named site of disseminated *Coccidioides* infection.
- Skin lesions belong in the differential diagnosis in a patient with relevant exposure.
- The same spectrum of granulomatous, pyogenic, or mixed inflammation may be seen.

Site

Skin

Expected pathology

Variable inflammatory
pattern

Meningeal involvement

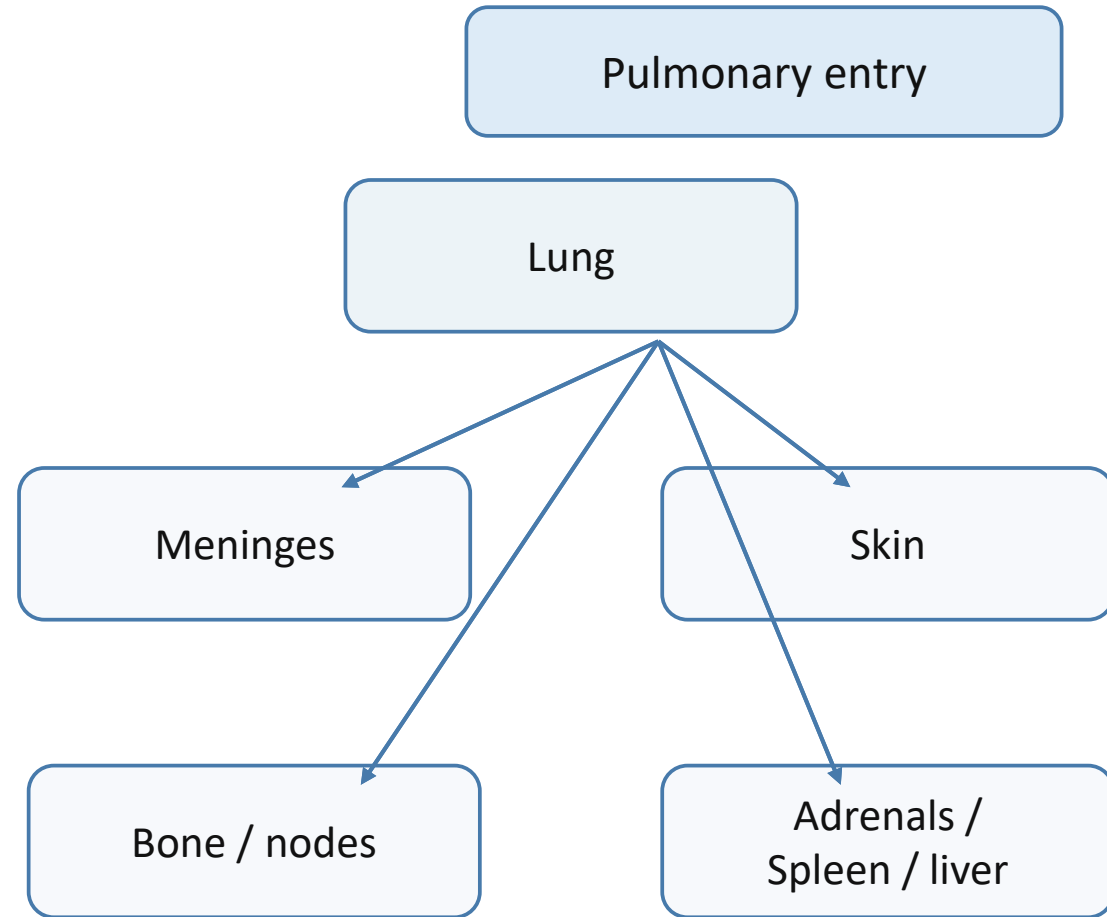
- The meninges are a frequently affected site in dissemination.
- *Coccidioides* among endemic fungi that can involve the CNS.
- CNS fungal involvement often follows widespread dissemination, especially with impaired immunity.



Simplified conceptual sequence

Other sites of progressive disease

- Bones and lymph nodes as possible sites.
- Adrenals, spleen, and liver may also be involved.
- Organ distribution demonstrates that the disease can become systemic rather than remain pulmonary.



Anatomic site does not fix histologic pattern

- Across listed sites, inflammation may be granulomatous.
- A pyogenic response may dominate in other areas.
- Mixed lesions require deliberate search for the *Coccidioides* spherule.

Lung

Variable

Skin / meninges

Variable

Other organs

Variable

From lung to multiorgan disease: Synthesis

- Entry begins with inhaled arthroconidia.
- Macrophage evasion is an early pathogen advantage.
- Suppressed T-cell immunity favors spread beyond the pulmonary focus.



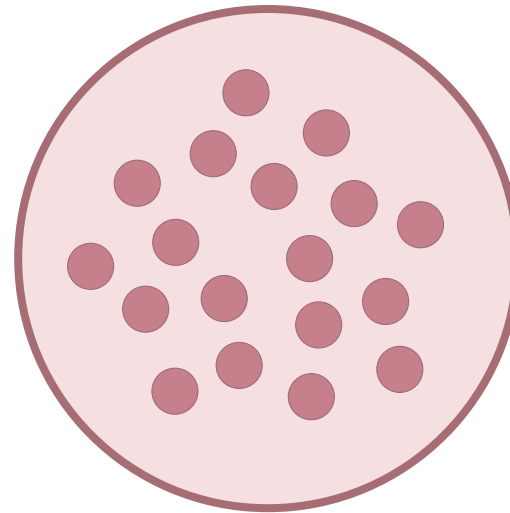
Simplified conceptual sequence

Case 1 — pulmonary granuloma

- Teaching vignette (hypothetical): A patient has lived in an endemic part of the southwestern United States.
- A lung biopsy shows granulomatous inflammation with a large nonbudding spherule.
- Question: Which additional morphologic feature best supports *Coccidioides*?

Case 1 — interpretation

- Numerous internal endospores favor *Coccidioides*.
- Spherule rupture may explain a superimposed neutrophil-rich reaction.
- Geography supports the setting, but the tissue structure is the decisive pathologic clue.



Schematic: Endospore-containing spherule

Case 2 — concern for dissemination

- Teaching vignette (hypothetical): A patient receiving immune-suppressing transplant treatment develops a pulmonary lesion.
- Additional assessment identifies meningeal involvement.
- Question: Which host mechanism helps explain the broader distribution?

Case 2 — interpretation

- Transplantation-associated suppression of T-cell immunity as a risk factor.
- Meningeal involvement is consistent with disseminated disease.
- A regional pulmonary process has become a systemic clinicopathologic problem.



Simplified conceptual sequence

Case 3 — a misleading granuloma

- Teaching vignette (hypothetical): A biopsy is initially reported as “granulomatous inflammation.”
- A large thick-walled round organism with internal bodies is subsequently recognized.
- Question: Why does the organism matter more than the generic granuloma label?

Case 3 — interpretation

- Granulomatous inflammation is shared by multiple infections and inflammatory diseases.
- The nonbudding endospore-containing spherule supplies etiologic specificity.
- The pathologic report should distinguish response pattern from identified organism.

Pattern

Granulomatous
inflammation

Etiology

Coccidioides spherule

Five concepts that integrate the disease

- Inhaled arthroconidia initiate infection.
- Interference with phagosome–lysosome fusion promotes intracellular persistence.
- T-cell immunity and DTH shape the host response.
- Endospore-containing nonbudding spherules define tissue morphology.
- Rare dissemination favors skin, meninges, and other organs in susceptible hosts.

Reference and figure provenance

- Primary text: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th edition (2026).
- Supporting Robbins material: granulomatous inflammation, delayed-type hypersensitivity, chronic pneumonia, and CNS fungal infections.
- All displayed organism and immunopathology diagrams are original, editable, simplified schematics—not photomicrographs.