Review on Histoplasmosis

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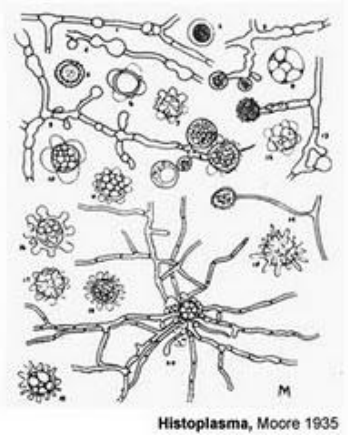
Disclosures

- No conflict of interest related to this presentation

Histoplasma Discovery

- Discovered *Histoplasma capsulatum* in 1905 by Samuel Darling, a pathologist in Panama
- Isolated from a young man diagnosed as miliary tuberculosis

Samuel Darling (1872-1925)



Histoplasma, Moore 1935

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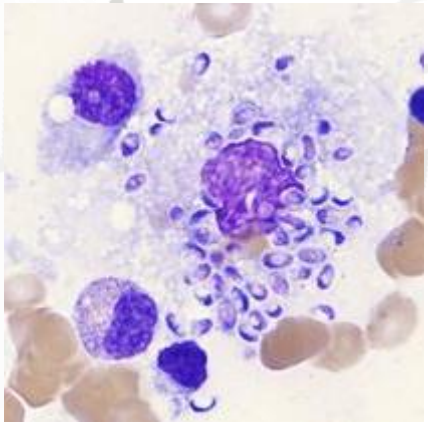
Histoplasma cansulatum

Histo = cell (intracellular)

Plasma = though to be a parasite (*Plasmodium*)

Capsulatum = clear zone surrounding the cell (actually NOT capsule)



Acquisition of *Histoplasma*

- Bat/bird droppings, guano-rich soil
- Mold in environment, yeast in human body
- Inhalation of spores, convert to yeast, survive in macrophages
- Spread via lymphatic/blood to other organs
- Cell-mediated immunity is key for control
- Infect both immunocompromised and immunocompetent hosts

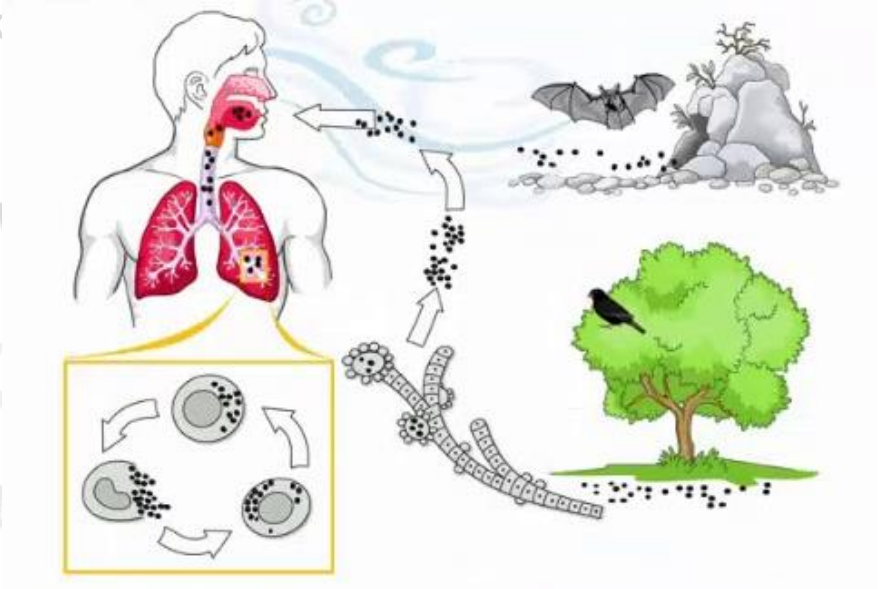


Image courtesy from Mayo Clinic

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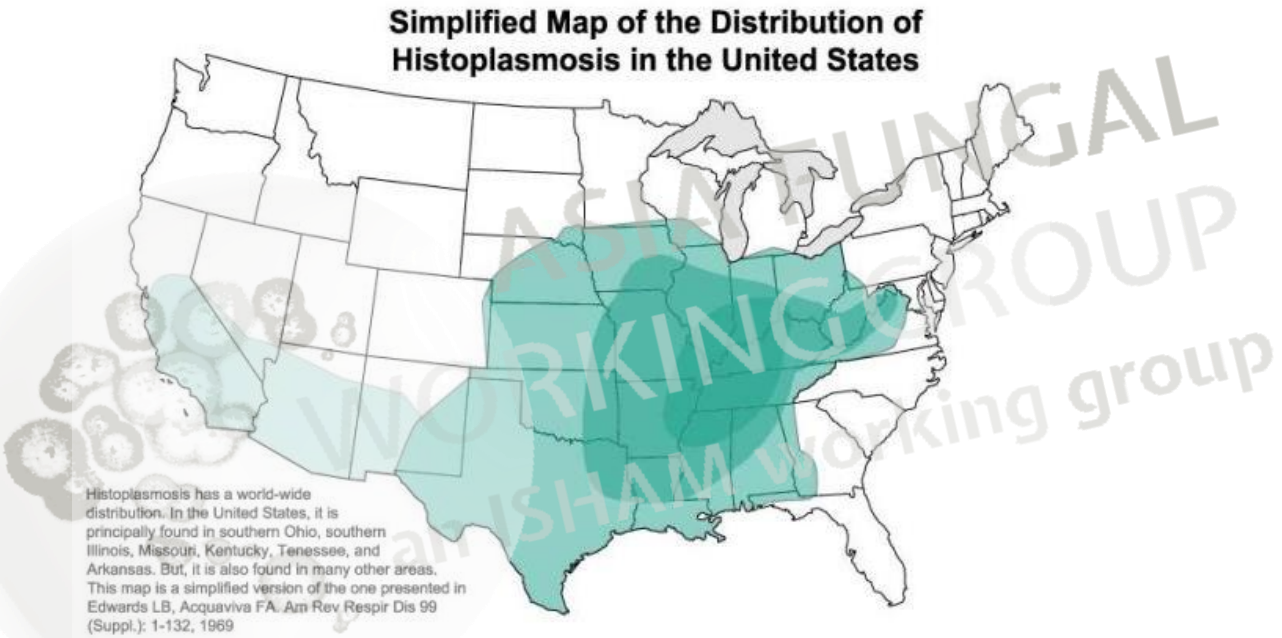
Histoplasmosis

- Immune responses to form granuloma containing the conidia after it is inhaled
- Cytokines production : TNF-α, IFN-γ, and IL-17
- Calcification of the primary and residual lesions
- In immunocompromised individuals, the granulomas may be poorly organized, leading to progressive fungal dissemination throughout the body

Eichenberger EM, et al. Infect Dis Clin North Am 2025;39(1):145-61

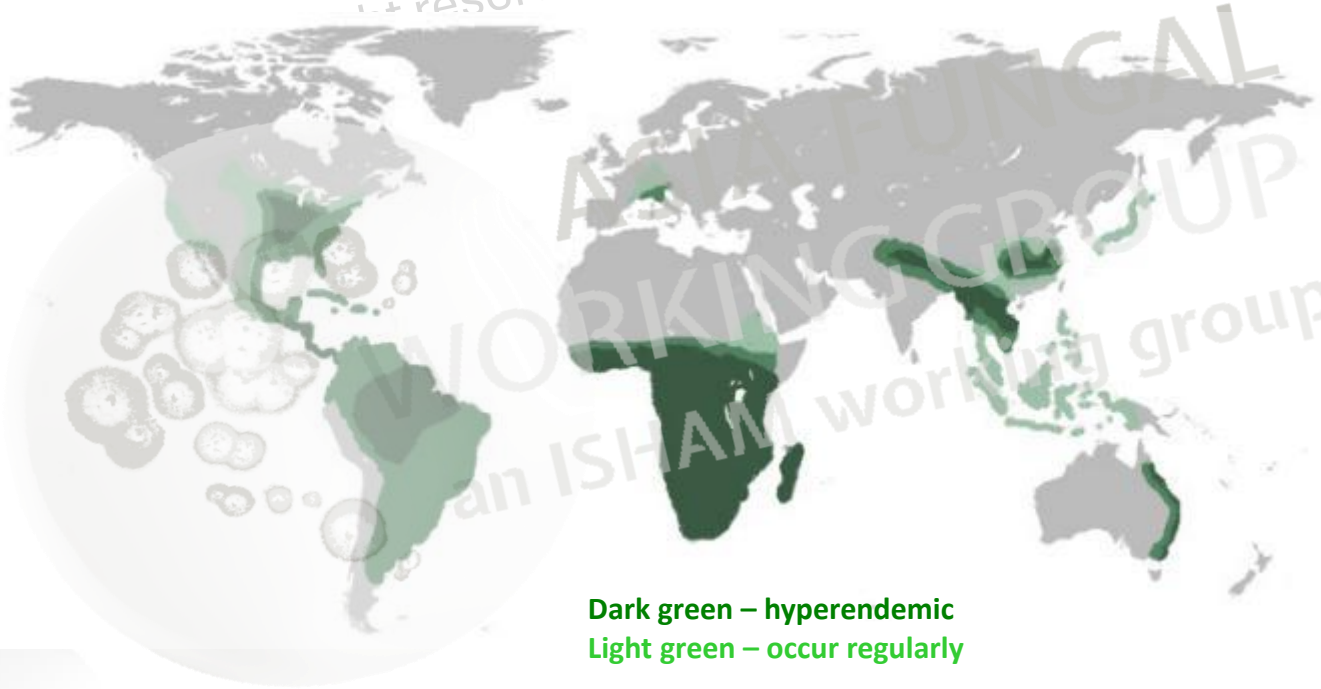
Distribution of Histoplasmosis



Also found in 55 countries around the world

World Distribution of Histoplasmosis

H. capsulatum var. *capsulatum* has been identified on all continents except for Antarctica

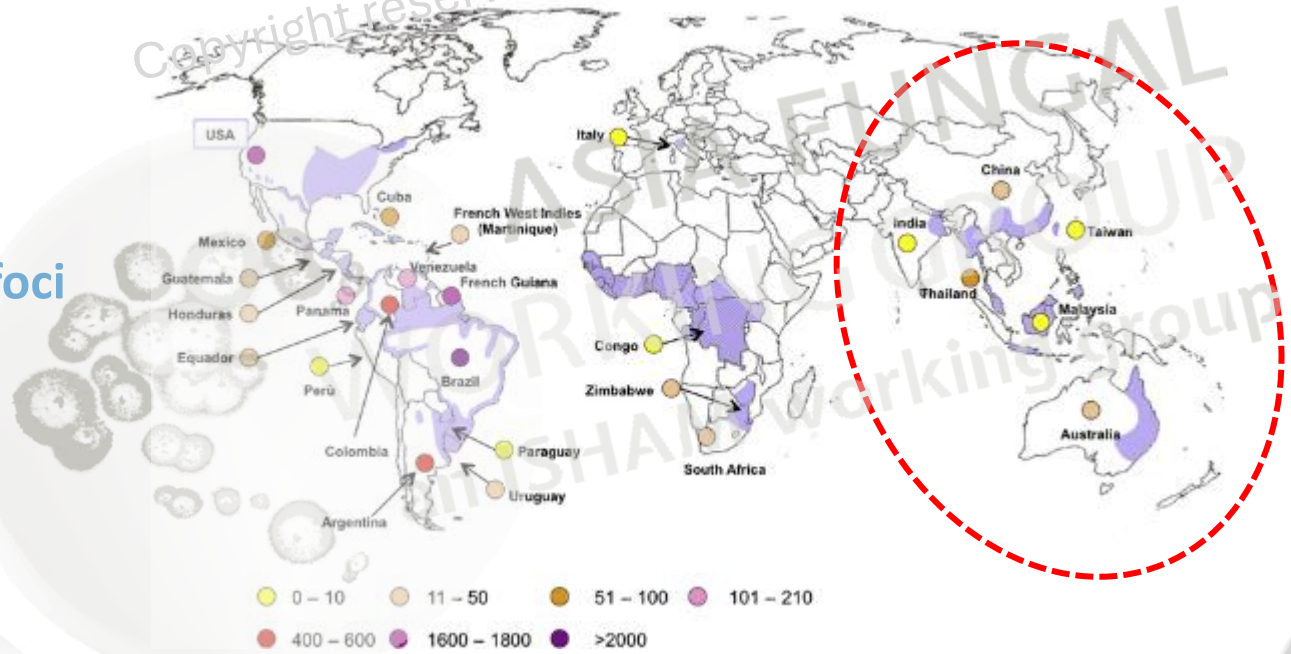


Dark green – hyperendemic
Light green – occur regularly

Barros N, et al J Fungi 2023;9(2):236.

World Distribution of Histoplasmosis

Microfoci



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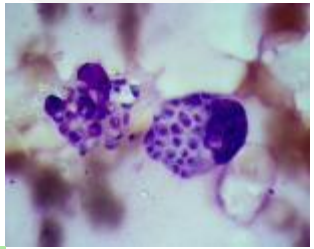
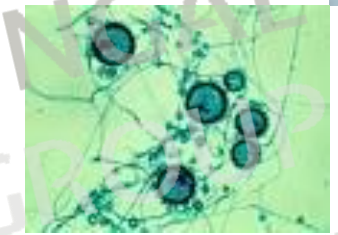
Wheat LJ, et al. Infect Dis Clin North Am 2016;30(1):207-27

Histoplasma capsulatum





- Used to be classified into 3 varieties:
  - *H. capsulatum* var. *capsulatum*
  - *H. capsulatum* var. *duboisii*
  - *H. capsulatum* var. *farciminosum* (animal pathogen)
- **Recently**, 5 genetically distinct clades,
  - NAm 1 (also referred to as the *H. mississippiense*)
  - NAm 2 (also referred to as the *H. ohiense*)
  - LAm A (also referred to as the *H. suramericanum*),
  - Panama lineage H81 (also referred to as the *H. capsulatum* sensu stricto)
  - African *H. capsulatum* var. *duboisii*
- In 2022, a new Indian lineage was reported but not yet been accepted as valid species

Sepúlveda, et al. mBio. 2017;8(6):e01339-17

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Clinical Manifestations

- Acute and subacute pulmonary histoplasmosis
- Chronic pulmonary histoplasmosis (CPH)
  - Chronic cavitary pulmonary histoplasmosis
  - Histoplasma nodule
- Mediastinal histoplasmosis
  - Mediastinal adenitis
  - Mediastinal granuloma
  - Fibrosing mediastinitis
- Progressive disseminated histoplasmosis
- Other forms
  - CNS histoplasmosis
  - Ocular histoplasmosis
  - African histoplasmosis

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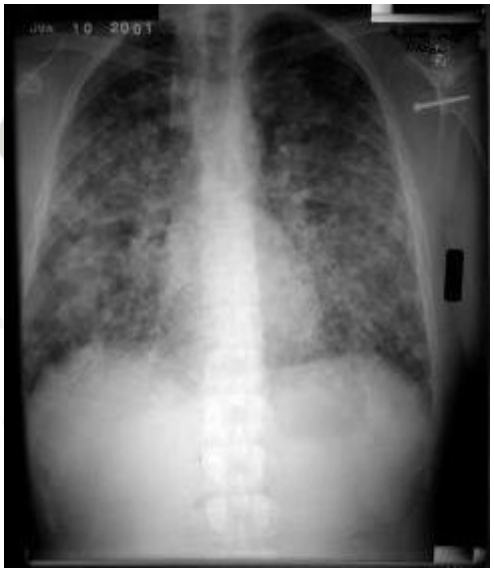
Acute Pulmonary Histoplasmosis

- In highly endemic areas, 80–90% of the population will be exposed to histoplasmosis during their lifetime
- > 90% of exposed individuals will have an unrecognized disease
- < 5% of those exposed to low-level inoculum develop symptoms
- 75% of people develop symptoms following high-inoculum exposure
- Incubation period - 14 days (7-21 days) in symptomatic patients

Barros N, et al J Fungi 2023;9(2):236.

Acute Pulmonary Histoplasmosis

- **Asymptomatic** or flu-like illness
  - Fever, malaise, headache, weakness, non-productive cough, chest pain
  - Extrapulmonary S&S: arthralgia, erythema nodosum, erythema multiforme (5%), pericarditis
- Delayed diagnosis – common (average 39.5 days)
- Resolve within 30 days (> 90% unrecognized) or longer (subacute pulmonary histoplasmosis)
- Chest radiograph
  - Mediastinal or nodes enlargement
  - Patchy infiltrates
  - Calcifications



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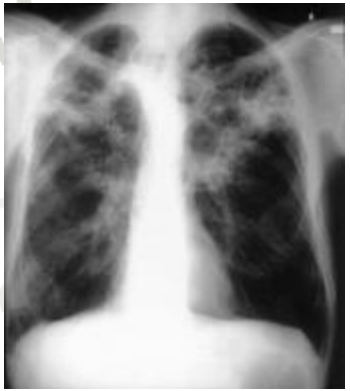
Barros N, et al J Fungi 2023;9(2):236

Chronic Pulmonary Histoplasmosis

- **Cavitary**
  - 2% - 8% of histoplasmosis
  - Low-grade fever, weight loss, productive cough, dyspnea, chest pain, hemoptysis
  - Mimic TB: upper lobe cavitation (98%), right apex (84%)
  - Thick-walled cavities with pleural thickening
  - Hilar or mediastinal lymphadenopathy is rare
- **Nodules**
  - 57% in endemic area
  - occasionally contain no live organisms
  - Asymptomatic



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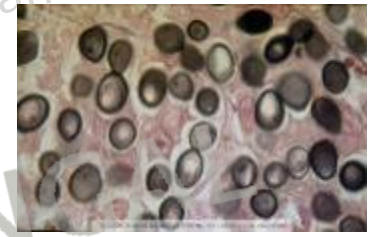
Pulmonary Histoplasmosis

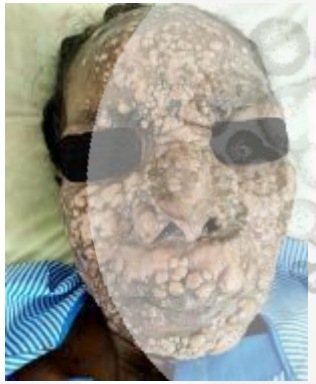
Clinical Form				
Characteristic	**Acute**	**Subacute**	**Nodular**	**Chronic Cavitary**
Age	Any	Any	Any	**> 50-year-old with structural lung disease**
Clinical manifestation	Fever, headache, dry cough, chills, chest pain, malaise, myalgias and arthritis	Same as acute but symptoms are milder	**Usually asymptomatic**	Fever, productive cough, dyspnea, weight loss, hemoptysis, night sweats, chest pain
Symptom duration	1–2 weeks	Weeks to months	-	Months to years
Mimicked disease	Community acquired pneumonia	Community acquired pneumonia	Neoplasm	Tuberculosis, Sarcoidosis
Pathology	Granuloma with acute lung injury	Well-formed granulomas	Well-formed granulomas	Cavities with granulomas, tissue destruction
Radiologic findings	Diffuse bilateral patchy opacities	Focal or patchy opacities	Nodules	Cavitation, fibrosis, volume loss, pleural thickening. Right upper lobe is common
Hilar/Mediastinal LN	Enlarged	Enlarged	**Not enlarged**	**Not enlarged. Occasionally calcified**
Calcifications	None	None	**Present**	**Present**
Indications for treatment	Severe disease	Symptoms over 1 month	**None**	Yes

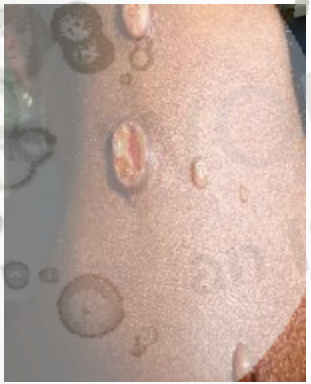
Barros N, et al J Fungi 2023;9(2):236

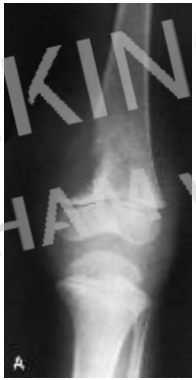
African Histoplasmosis

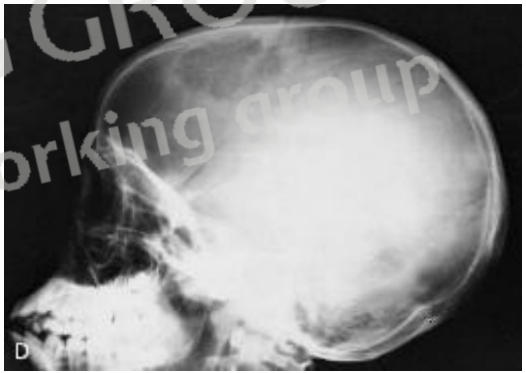
- Caused by *H. capsulatum var. duboisii* (larger yeast-15 µ, with thicker wall)
- Disseminated disease
- **Skin and bone** are the most frequent organ involved











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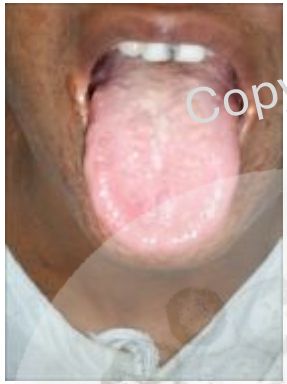
Ocansey BK, et al. PLoS Negl Trop Dis. 2022;16(2):e0010111

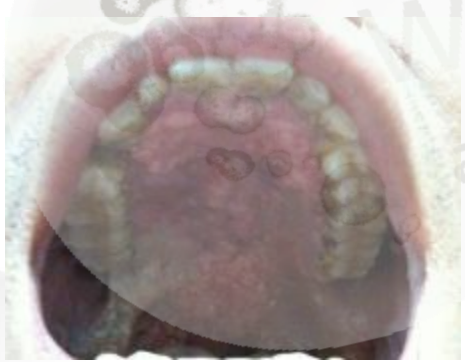
Progressive Disseminated Histoplasmosis

- Immunocompromised hosts: HIV, hematologic malignancies,
- Immunocompetent hosts
- Multiple organ involvement
  - **Lungs:** cough, patchy pneumonitis, hilar/mediastinal lymphadenopathy
  - **GI:** uropharyngeal lesions (50%), diarrhea, hepatosplenomegaly (30%)
  - **Skin lesion:** mollluskum-like (10-30%)
  - **Blood:** cytopenia
  - **CNS:** meningitis, cerebritis, mass lesions
  - **Endovascular:** endocarditis
  - **Adrenal glands**

Eichenberger EM, et al. Infect Dis Clin North Am 2025;39(1):145-61

Progressive Disseminated Histoplasmosis





Oral Lesions

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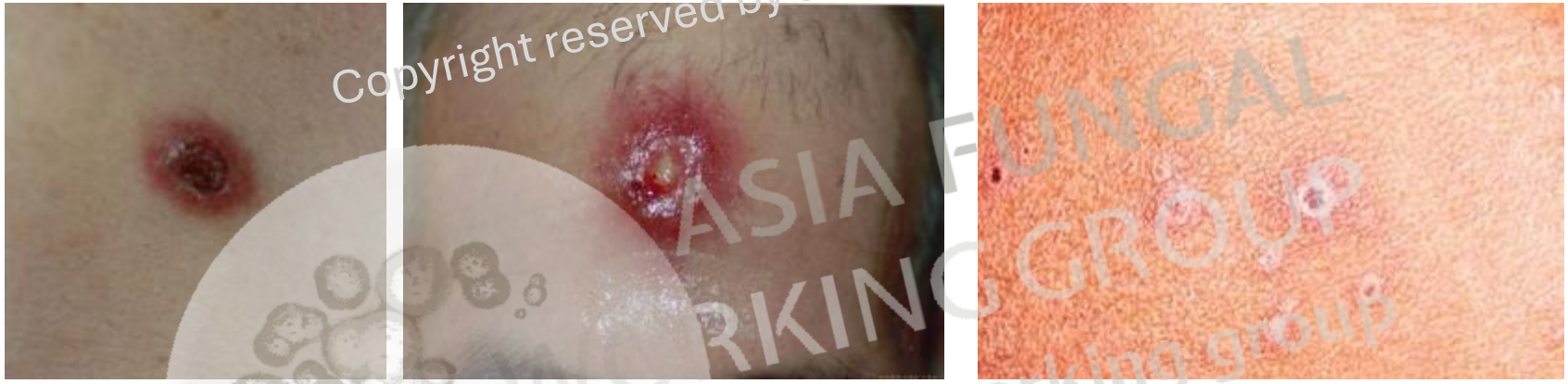
One Month After Itraconazole Treatment

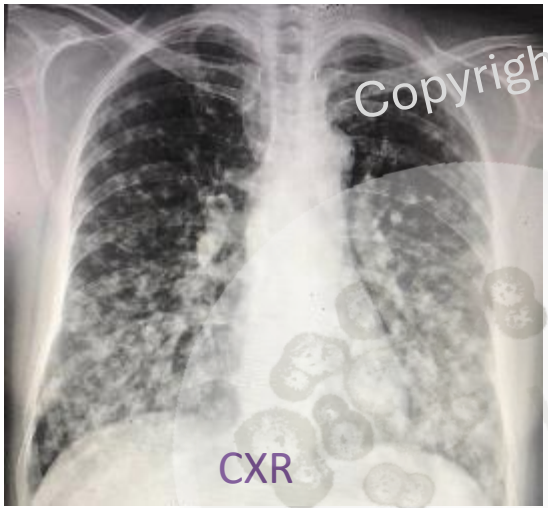
Cutaneous Lesions in Histoplasmosis

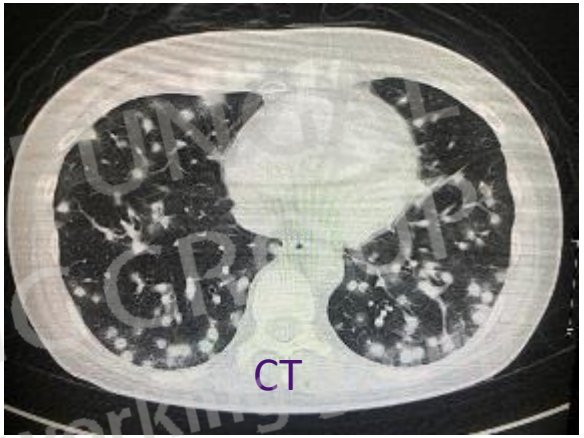


Discrete skin-colored papules on erythematous base with central umbilication (molluscum-like)

Phanuphak N ADR 2006;19:69-72

Chest X-rays and Chest CT





Left adrenal gland 0.5 x1.1 cm
Mild splenomegaly

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Travel history: 2 weeks before symptoms

Lesser false vampire bat
(*Megaderma spasma*)

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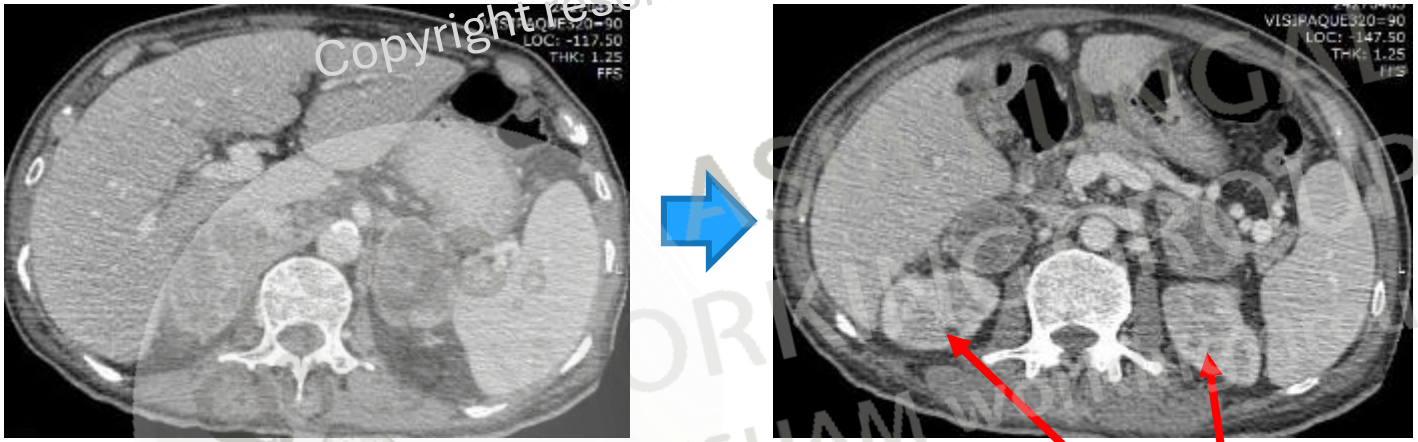
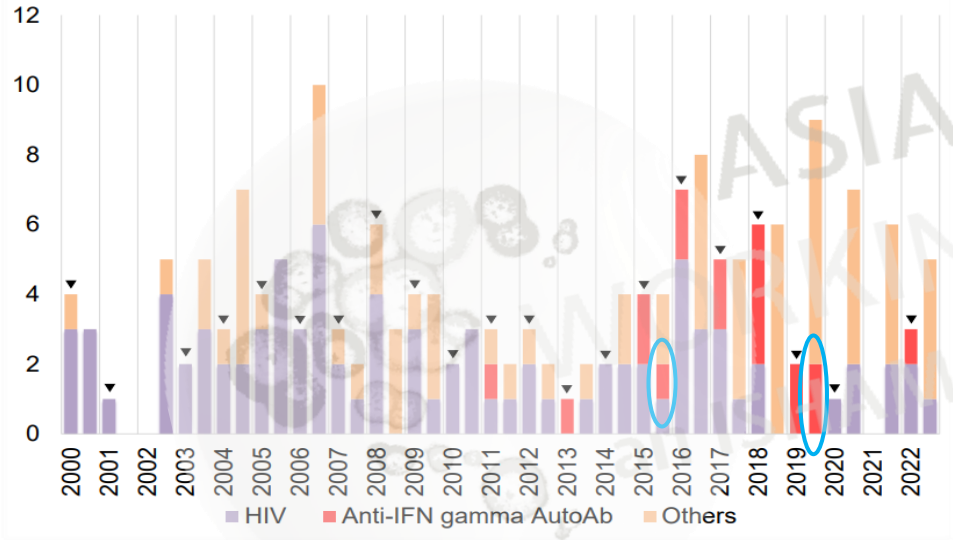
Abdominal CT Scan



Adrenal histoplasmosis

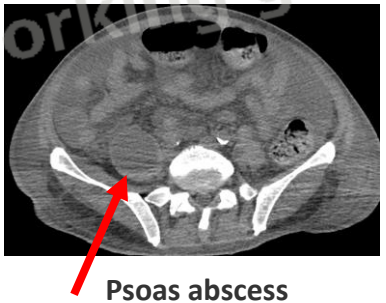
Kidney

Histoplasmosis and Interferon Gamma Autoantibodies



Talaromycosis: Labeled as arrow head (▾), Histoplasmosis: Unlabeled

- **Non-HIV with interferon gamma autoantibodies**
  - Histoplasmosis 3/62 (4.8%)
  - Talaromycosis 15/24 (62.5%)
- **We found 1 case with anti-GM CSF autoantibodies**



Psoas abscess

Taechasansiri Y and Chayakulkeeree M, ECCMID 2024

A Case Scenario

A 58-year-old woman

- History of mitral valve regurgitation, post mitral valve replacement
- Presented with fever and weight loss for 2 months, dyspnea

Echocardiography

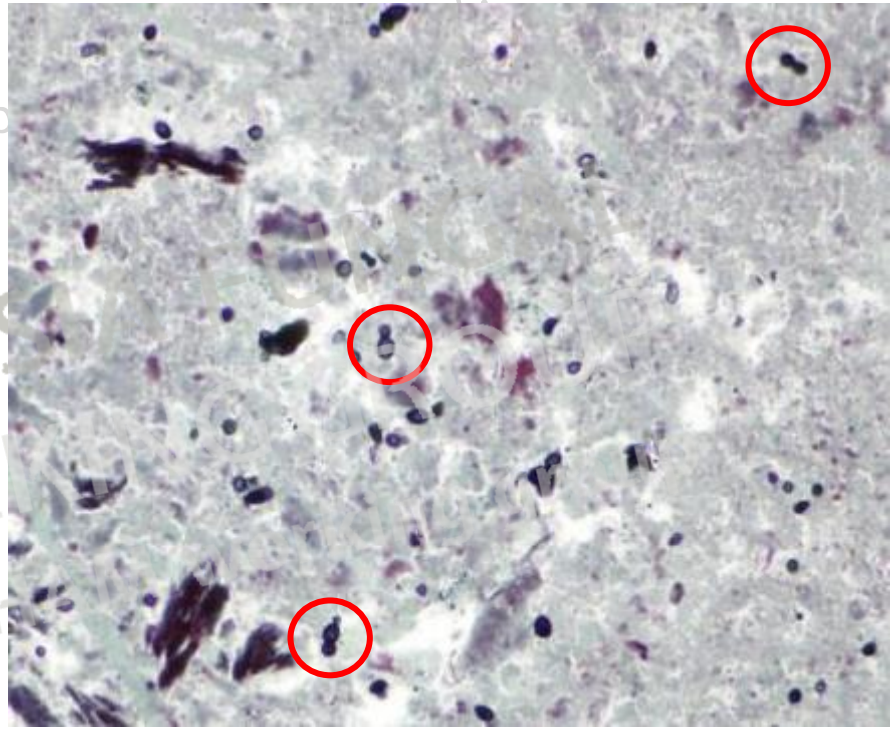
- Mitral prosthetic valve endocarditis: vegetation size 1.5x 1 cm and 0.5 cm in diameter attach to mitral prosthetic valve
- Mild mitral prosthetic regurgitation

Diagnosis

- Infective endocarditis

Pathology

- Mitral valve replacement
- Vegetation was sent for histopathology
- Budding yeasts were demonstrated



Courtesy Department of Pathology, Siriraj Hospital

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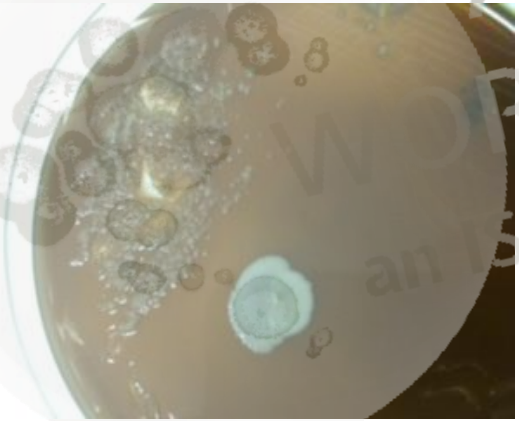
Vegetation Culture

From bacterial lab (37°C)



From fungal lab (25°C)

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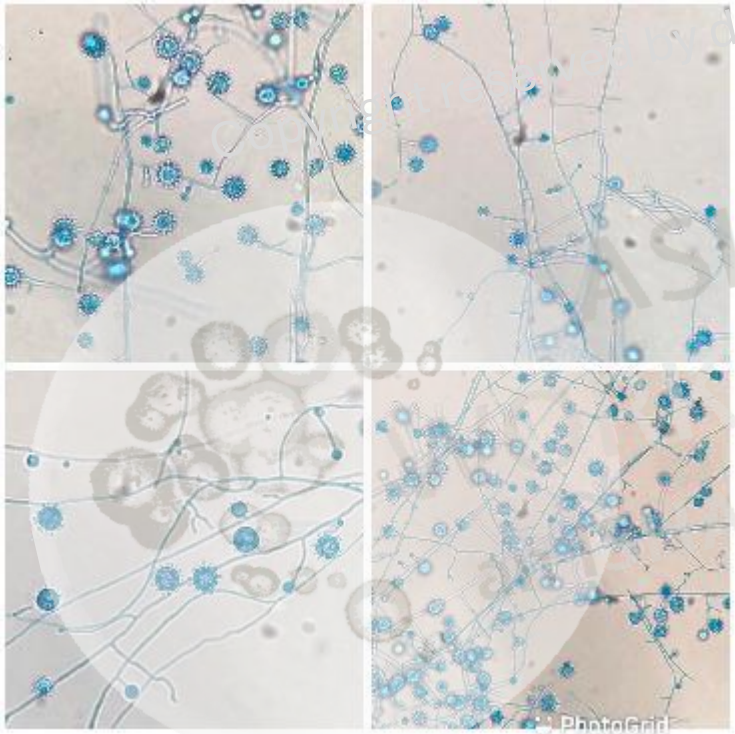
Fungal Culture



Hisoplasma capsulatum
prosthetic valve endocarditis

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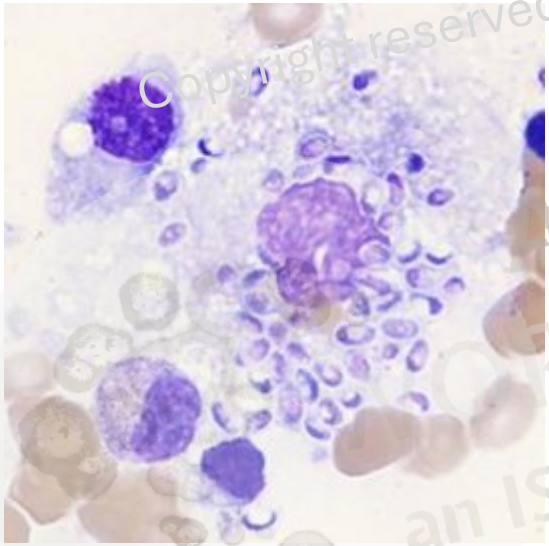
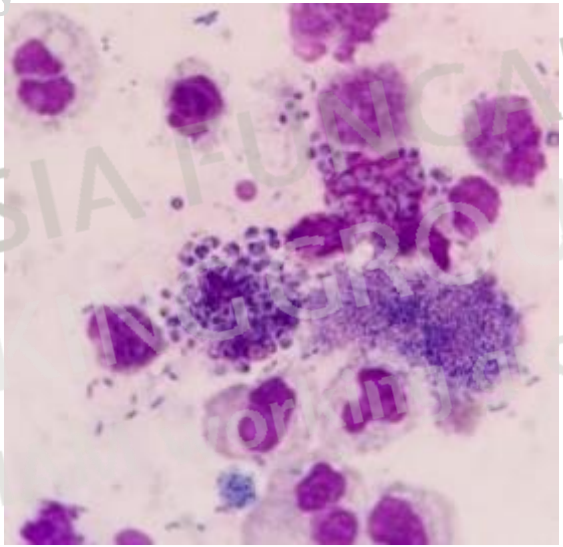
Diagnosis of Histoplasmosis

- Clinical suspicion and exposure history
- Imaging : chest X-ray, thoracic CT
- Microbiology tests:
  - Culture (grow slowly)
  - Histopathology (yeast forms)
  - Antigen detection (urine/serum)
    - EIA
    - Lateral flow assay (LFA)
  - Antibody test
  - PCR (emerging method)

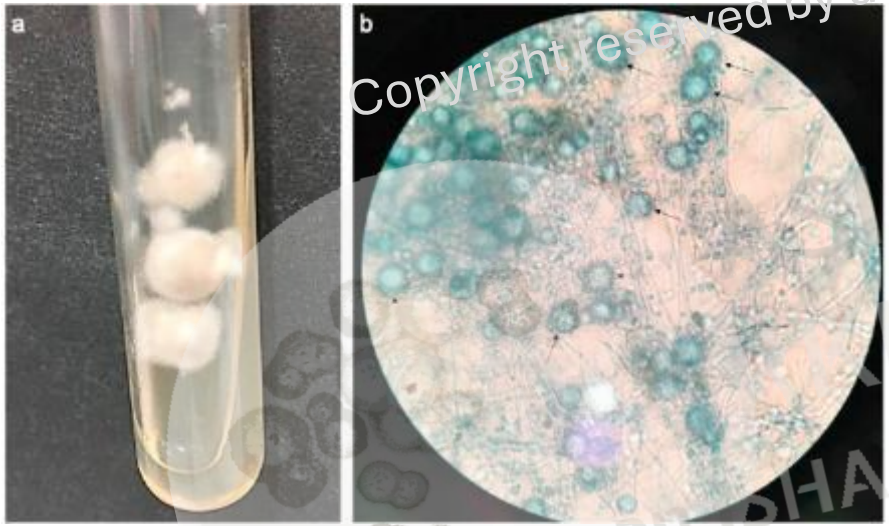
Diagnosis - Microscopy





Histoplasma capsulatum

Diagnosis – Fungal culture



- Colony and microconidia resemble *Blastomyces dermatitidis*
- Macroconidia may be similar to *Sepedonium* species
- Tuberculated macroconidia

Murata Y, et al. Med Mycol. 2007;45(3):233-47

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Urine *Histoplasma* Antigen Test

Positive

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Diagnostic Tests for Histoplasmosis

	Pulmonary			Mediastinal			Progressive Disseminated
Method	**Acute**	**Subacute**	**Chronic Cavitary**	**Adenitis**	**Granuloma**	**Fibrosis**	
Antigen	83%	30%	88%	May be positive	Usually negative	Negative	92%
Antibody	64%	95%	83%	Usually positive	Usually positive	Usually positive	75%
Pathology	20%	42%	75%	May be positive	May be positive	Uncommonly positive	76%
Culture	42%	54%	67%	May be positive	Uncommonly positive	Negative	74%

Barros N, et al J Fungi 2023;9(2):236

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Treatment of Disseminated Histoplasmosis

- Induction therapy : L-AmB at 3 mg/kg daily for 1-2 weeks
  - Superior to AmB-deoxycholate in patients with advanced HIV and disseminated histoplasmosis
- Consolidation therapy : itraconazole (200 mg trice daily for 3 days, followed by twice daily) for at least 1 year

- For less severe disease, itraconazole can be initiated
  - Fluconazole has a lower success rate than itraconazole
  - Voriconazole is not routinely recommended

Thompson GR 3rd, et al. Lancet Infect Dis. 2021 ;21(12):e364-e374.

Treatment of Disseminated Histoplasmosis

- Histoplasmosis secondary to TNF-α inhibitor therapy requires discontinuation of the TNF-α blocker during antifungal therapy
- Duration is around 12 months and the test results are negative for *Histoplasma* spp. Antigen

- Pulmonary histoplasmosis
  - Mild-to-moderate cases, treatment is usually unnecessary
  - Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) in patients with symptoms over 1 month

Thompson GR 3rd, et al. Lancet Infect Dis. 2021 ;21(12):e364-e374.

Take home messages

- Histoplasmosis is prevalent in Asia and chronic disseminated form is the most common manifestation
- Acute pulmonary histoplasmosis can be self-limited, treatment required only severe and refractory cases
- Chronic pulmonary histoplasmosis may mimic pulmonary tuberculosis
- The fungus is slow growing and can be missed if a fungal culture is not requested
- Treatment with amphotericin B followed by itraconazole is recommended

Thank you

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