Fungal Infection
Clinical Case Studies
[Fungal Morphology Recognition]

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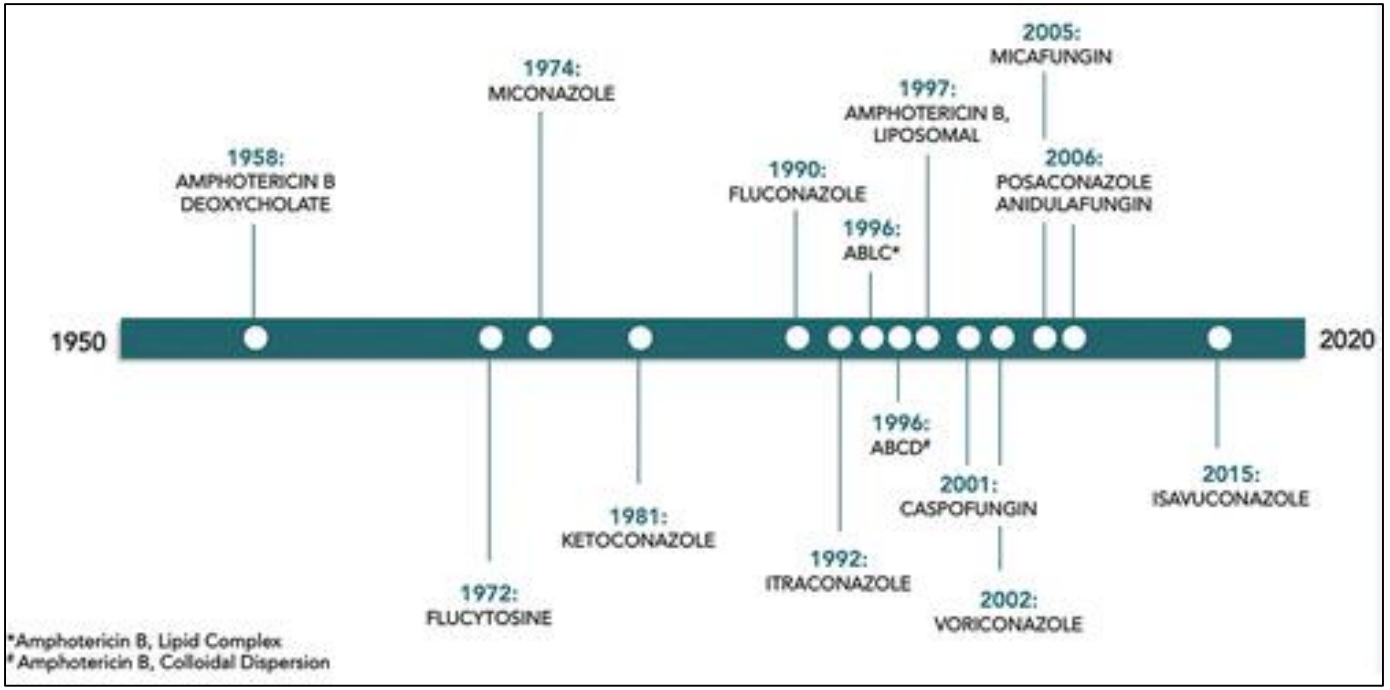
Fungal Fantasy World

- They all look the same!
- I'll give them those questions on:
  - Step 2
  - Step 3
  - Internal Medicine ITE
  - ABIM Exam
- Treatment (Ampho B) is toxic so I will leave that to those crazy ID people!

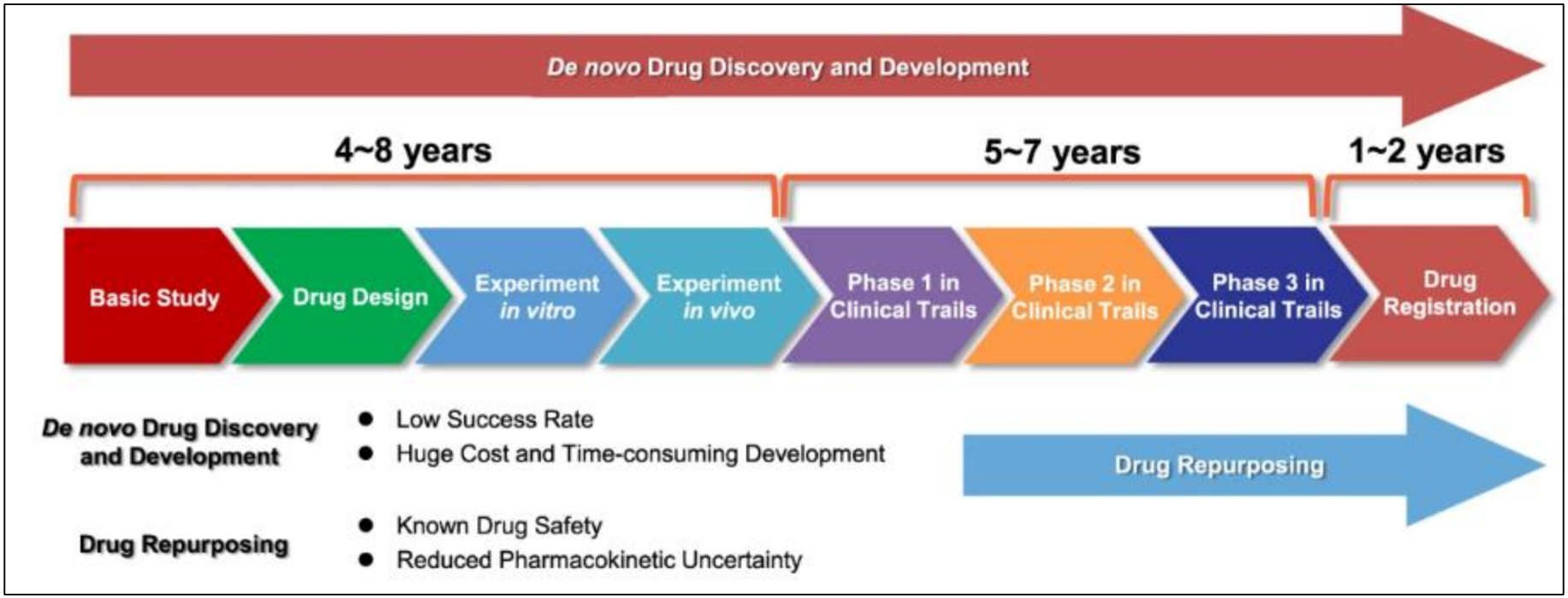
FDA-Approval of Sysemic Antifungal Agents

Drug Class	Discovery date	Approval date
	1949	1957 (Amphotericin B)
		1989 (Amphotericin B lipid formulations)
Azoles	1944	1981-2013 (Ketoconazole)
		1990 (Fluconazole)
		1992 (Itraconazole)
		2002 (Voriconazole)
		2006 (Posaconazole)
		2015 (Isavuconazole)
Echinocandins	1970	2001 (Caspofungin)
		2005 (Micafungin)
		2006 (Anidulafungin)
5-Fluorocytosine	1957	1971 (Flucytosine)

*Approval date for invasive fungal infections



New Drug Development Timeline



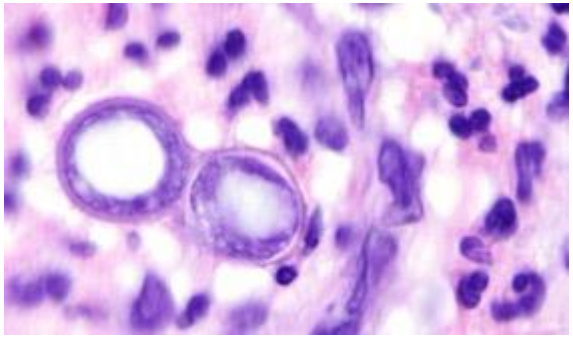
Fungal Real World

- There are only 11-12 to learn
- They do NOT look the same
- We now have many non-toxic treatment alternatives as shown for many of these infections

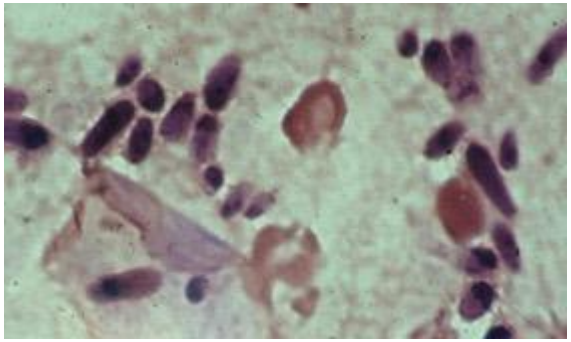
The Real Fungal Facts

- What you need to know:
  - Shape
  - Size
  - Patient History/Epidemiology

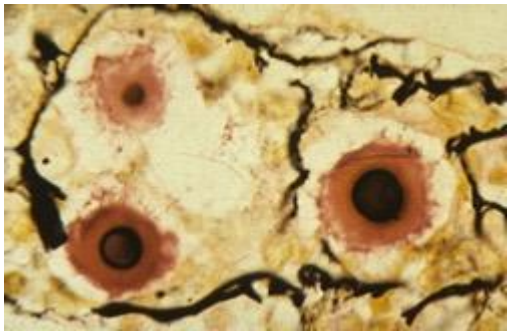
Yeast in Tissue



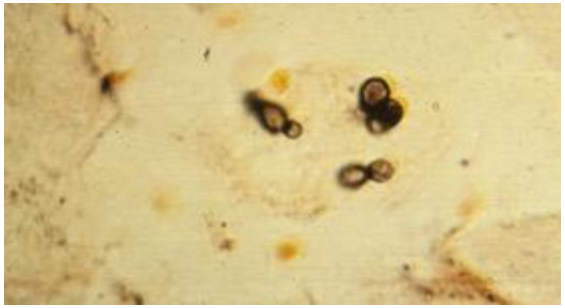
Blastomycosis: 10-12 µm



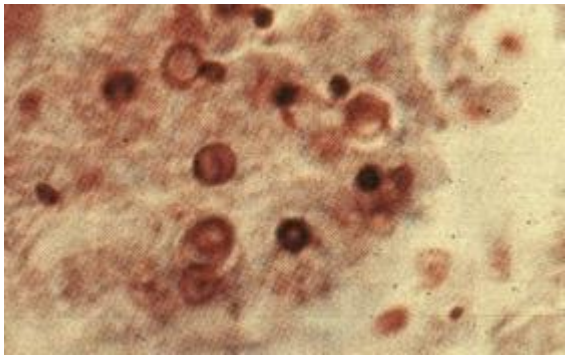
Candidiasis: 6-8 µm



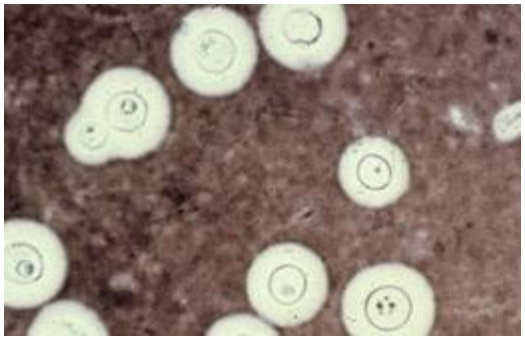
Cryptococcosis: 6-8 µm
Mucicarmine Stain



Histoplasmosis: 2-5 µm

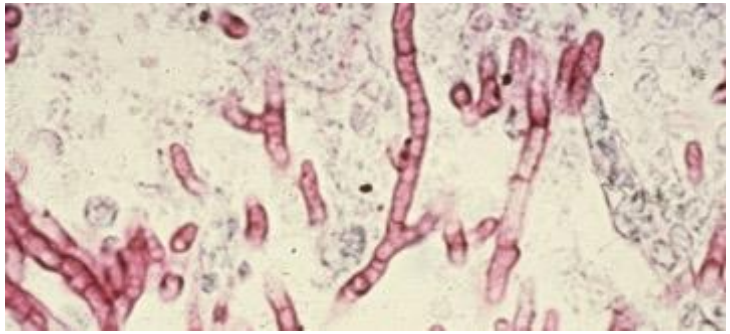


Sporotrichosis: 6-8 µm

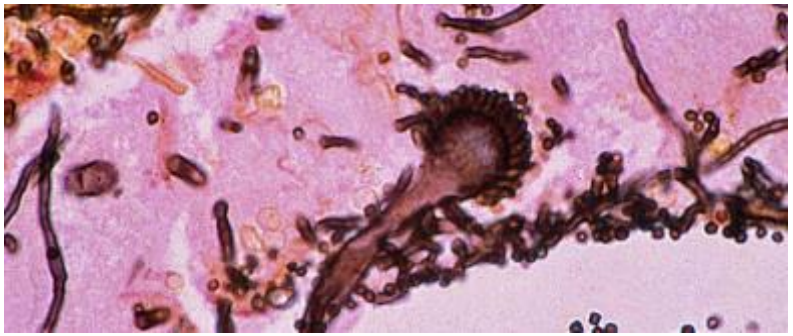


Cryptococcosis: 6-8 µm
India Ink Prep (CSF)m

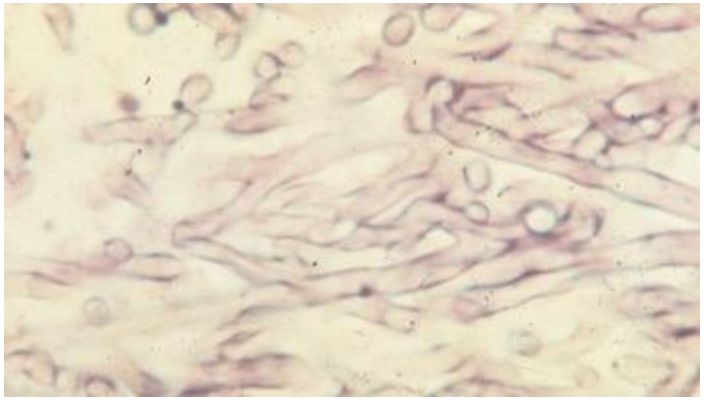
Hyphal Forms in Tissue and Vasculo-Invasive *Aspergillosis* and *Mucormycosis*



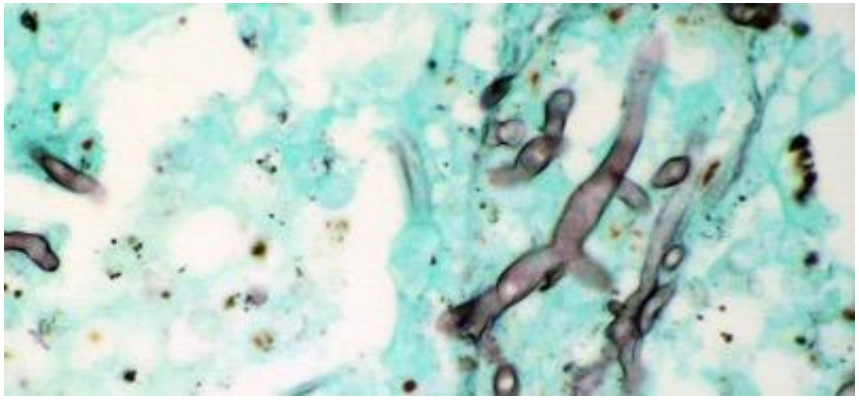
Aspergillosis: Septate Hyphae
H & E Stain of lung (5 µm)



Aspergillus in Methenamine Silver Stain of
Lung with "Fruiting Heads" (50 µm)

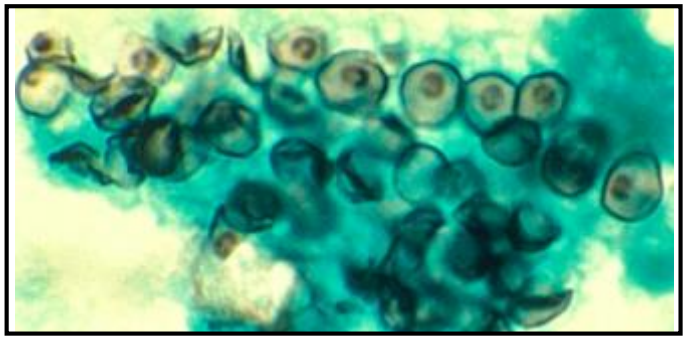


Mucormycosis: Non-Septate Hyphae
H & E Stain (7-30 µm)

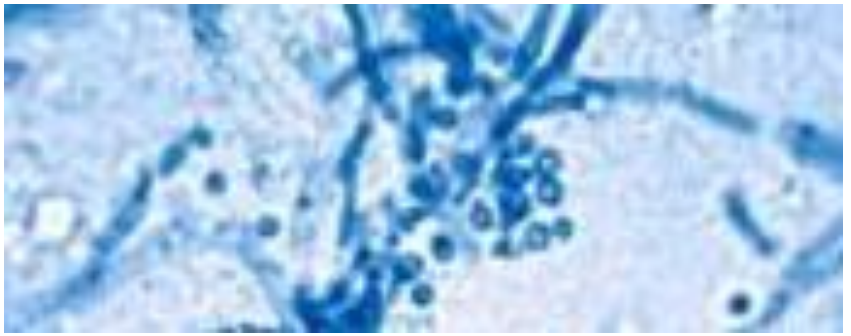


Mucormycosis: Non-Septate Hyphae
Silver Stain (7-30 µm)

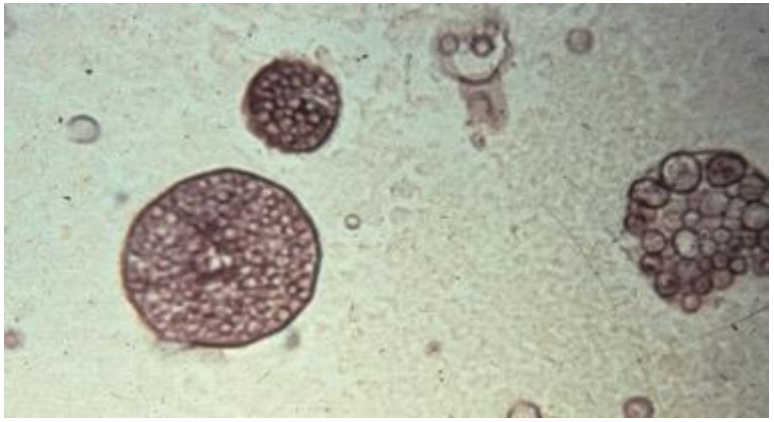
Easily Recognizable Morphology



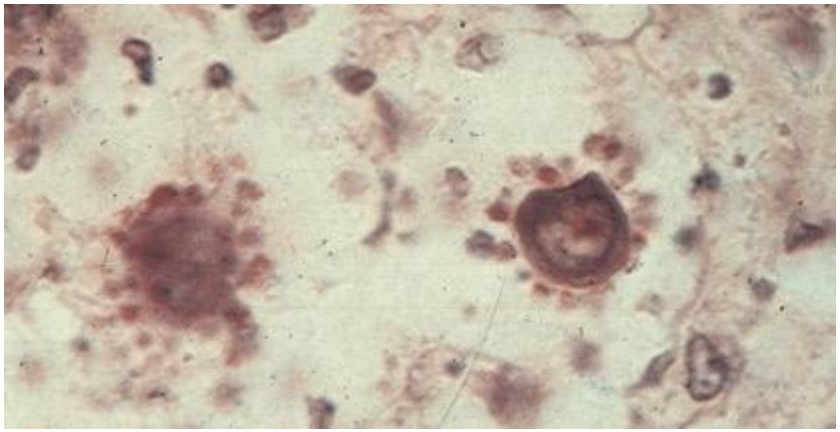
Pneumocystis: 5-8 µm



Malassezia furfur: 2,5-6 µm

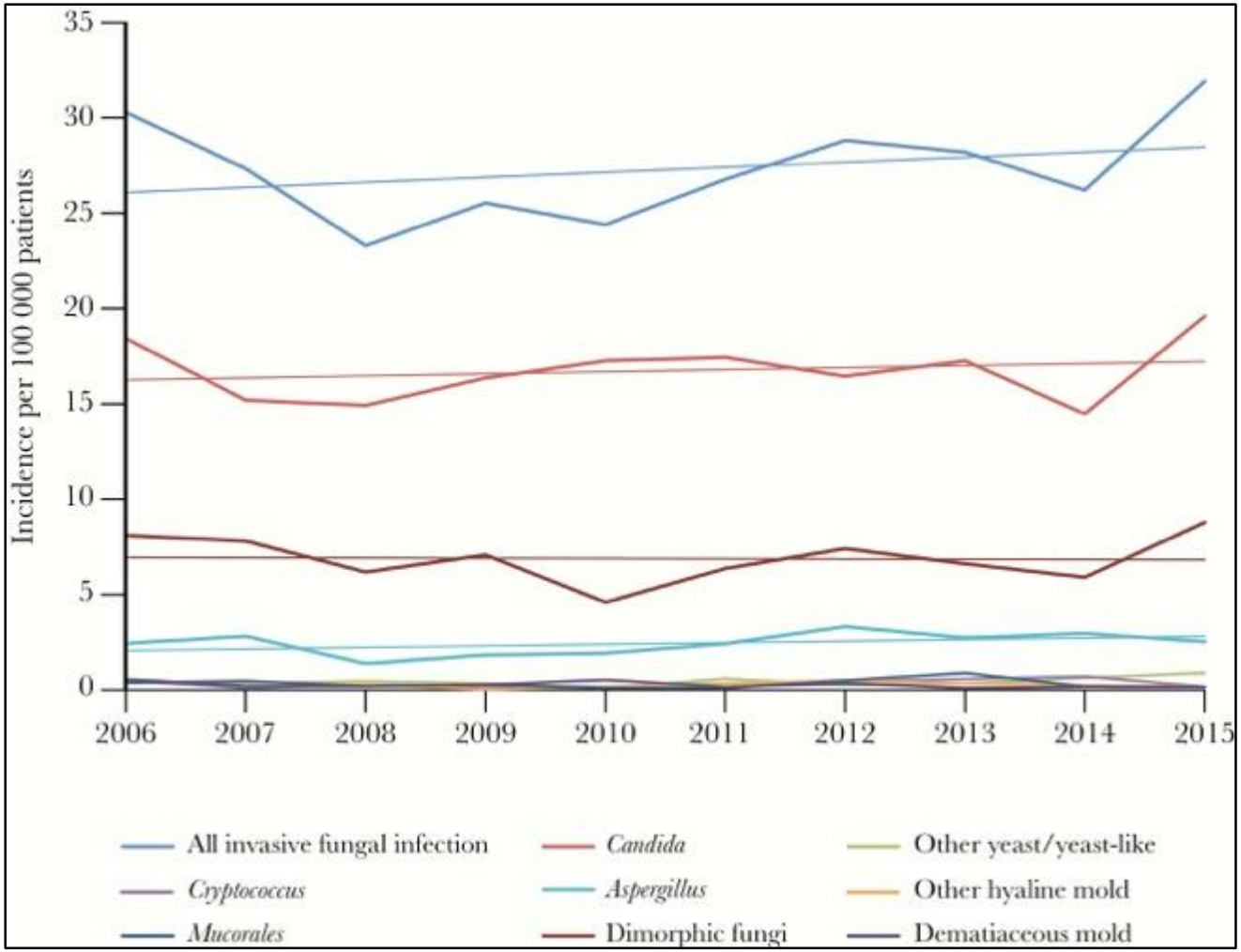


Coccidioides Spherule: 20-80 µm
Coccidioides Endospore: 2-5 µm



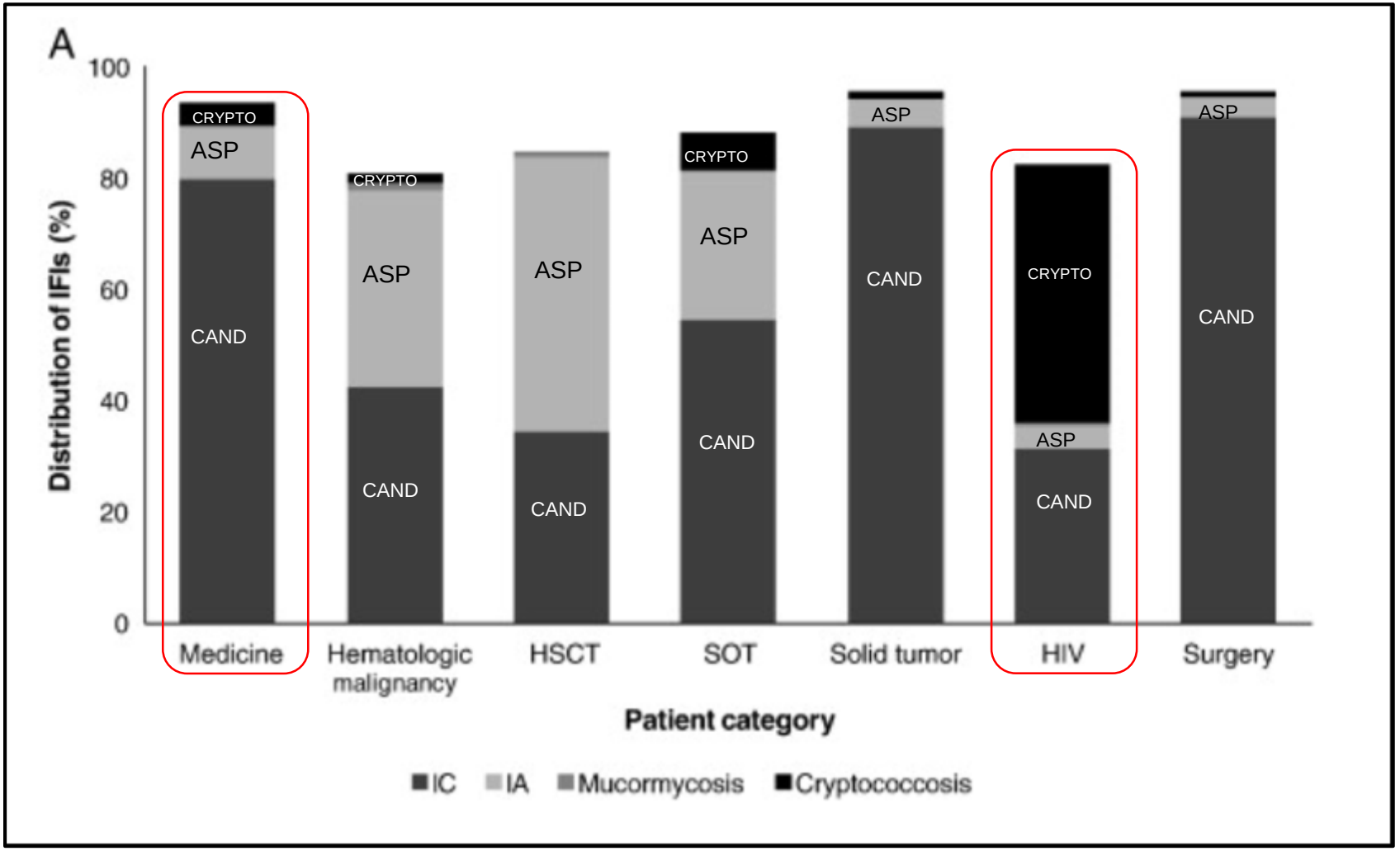
Paracoccioides: 4-60 µm

Figure 1. Incidence of invasive fungal infection (IFI) by category (per 100000 patients).



Open Forum Infectious Diseases, Volume 5, Issue 8, August 2018, ofy187, https://doi.org/10.1093/ofid/ofy187

Invasive Fungal Infection (IFI)



Reference. Azie N et al. Diagn Microbiol Infect Dis 2012; 73(4):293-300.

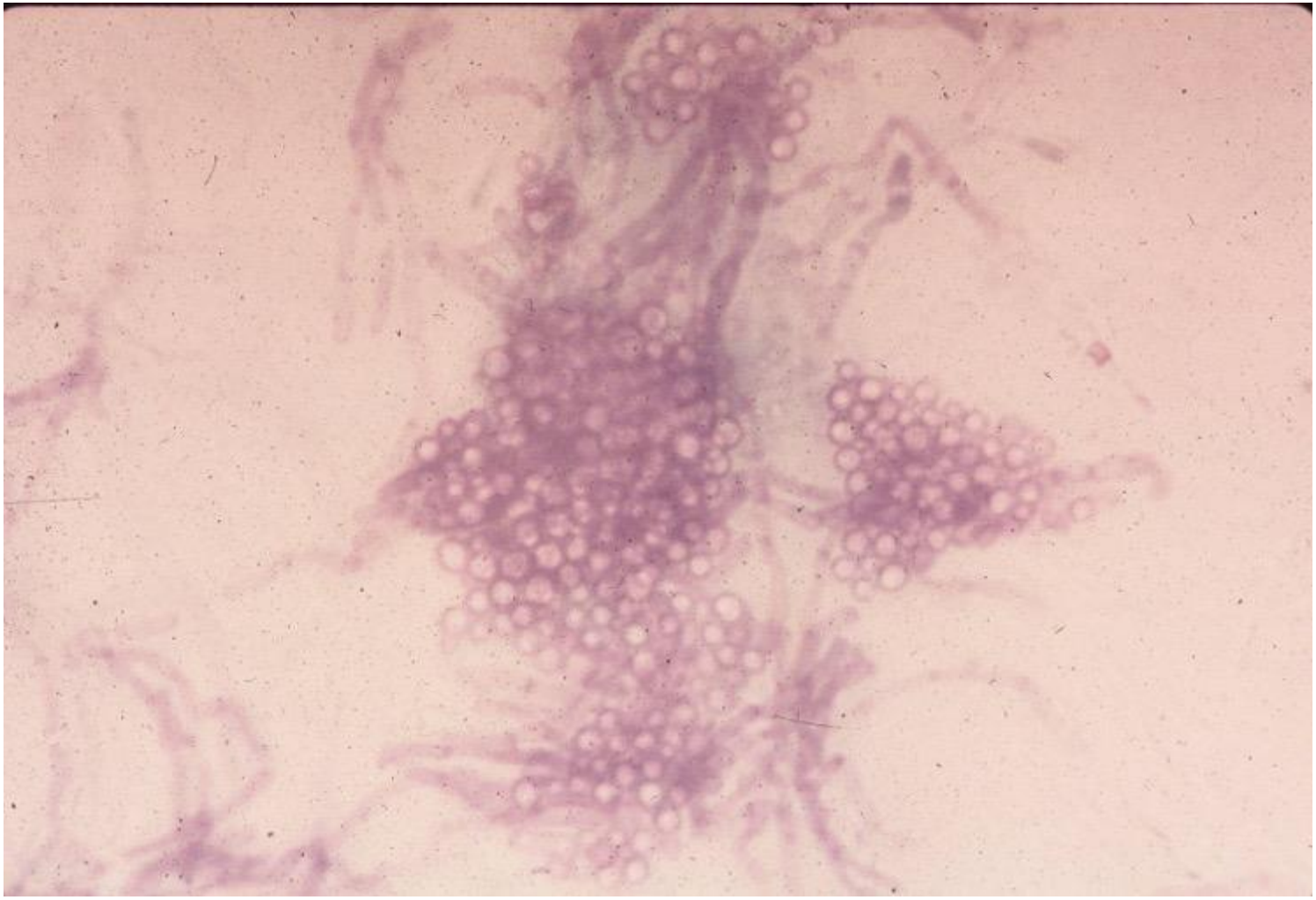
Case Study # 1

- 25 year old man with yearly recurrences of depigmented lesions and pruritis of the skin (see photo)
- Much worse in late Spring and early Summer of each year

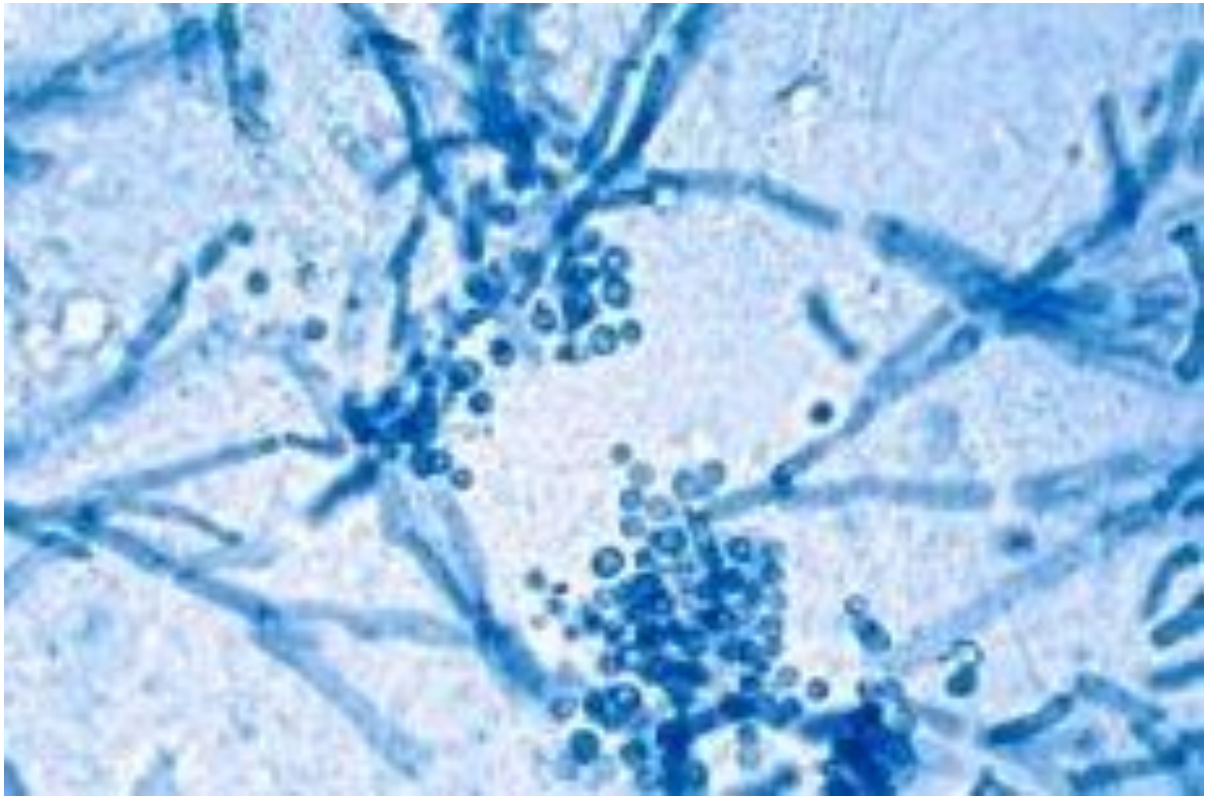
Case Study # 1

Alternative Inflammatory Presentation

Case Study # 1



Lactophenol Cotton Blue Stain



Case Study # 1 - Answer

- Tinea versicolor
- Caused by *Malassezia furfur*
- Fungemia may occur – TPN with lipid infusion-related central line infections (organism is lipophilic)
- Therapy: Topical therapy – see below.

Therapeutic regimens for tinea versicolor (pityriasis versicolor)

Drug	Dose	Duration
Topical therapies		
Various azole antifungal preparations (including creams, solutions, lotions, foams, and gels)*	Once- or twice-daily application	One to four weeks (typically two weeks)
Ketoconazole 2% shampoo	One five-minute application daily	Three consecutive days (a single application may be similarly effective)
Terbinafine 1% cream or gel	Twice-daily application	One week
Ciclopirox 0.77% cream	Twice-daily application	Two weeks
Selenium sulfide 2.5% shampoo	One ten-minute application daily	One week
Zinc pyrithione 1 or 2% shampoo	One five-minute application daily	Two weeks
Oral therapies¶		
Fluconazole	300 mg orally **once weekly**	Two weeks
Itraconazole	200 mg orally once daily	Five days

* Topical azole antifungals include: clotrimazole 1%, econazole 1%, efinaconazole 10%, ketoconazole 2%, luliconazole 1%, miconazole 2%, oxiconazole 1%, sertaconazole 2%, and sulconazole 1%. For additional detail on available formulations and frequency of application refer to the Lexicomp drug-specific monographs included with UpToDate.

¶ Oral therapy is reserved for patients with disease refractory to topical therapy or widespread disease that makes the application of topical therapy difficult. Oral terbinafine and griseofulvin are **not** effective; oral ketoconazole is not recommended (refer to topic discussion). Doses provided are for adults.

Case Study # 2

- 8 year old boy with skin and mucus membrane lesions as noted on the following slide
- He has had these (with gradual worsening) since age 2 or 3 as far as parents can remember
- No other known medical illnesses.

Case Study # 2

Case Study # 2

Figure 4. Candidal granuloma in an 11-year-old girl with chronic mucocutaneous candidiasis.

Reference. Edwards JE et al. Ann Intern Med 1978; 89: 91-106

Case Study # 2

Figure 2. Severe thrush in a 16-year-old girl with chronic mucocutaneous candidiasis.

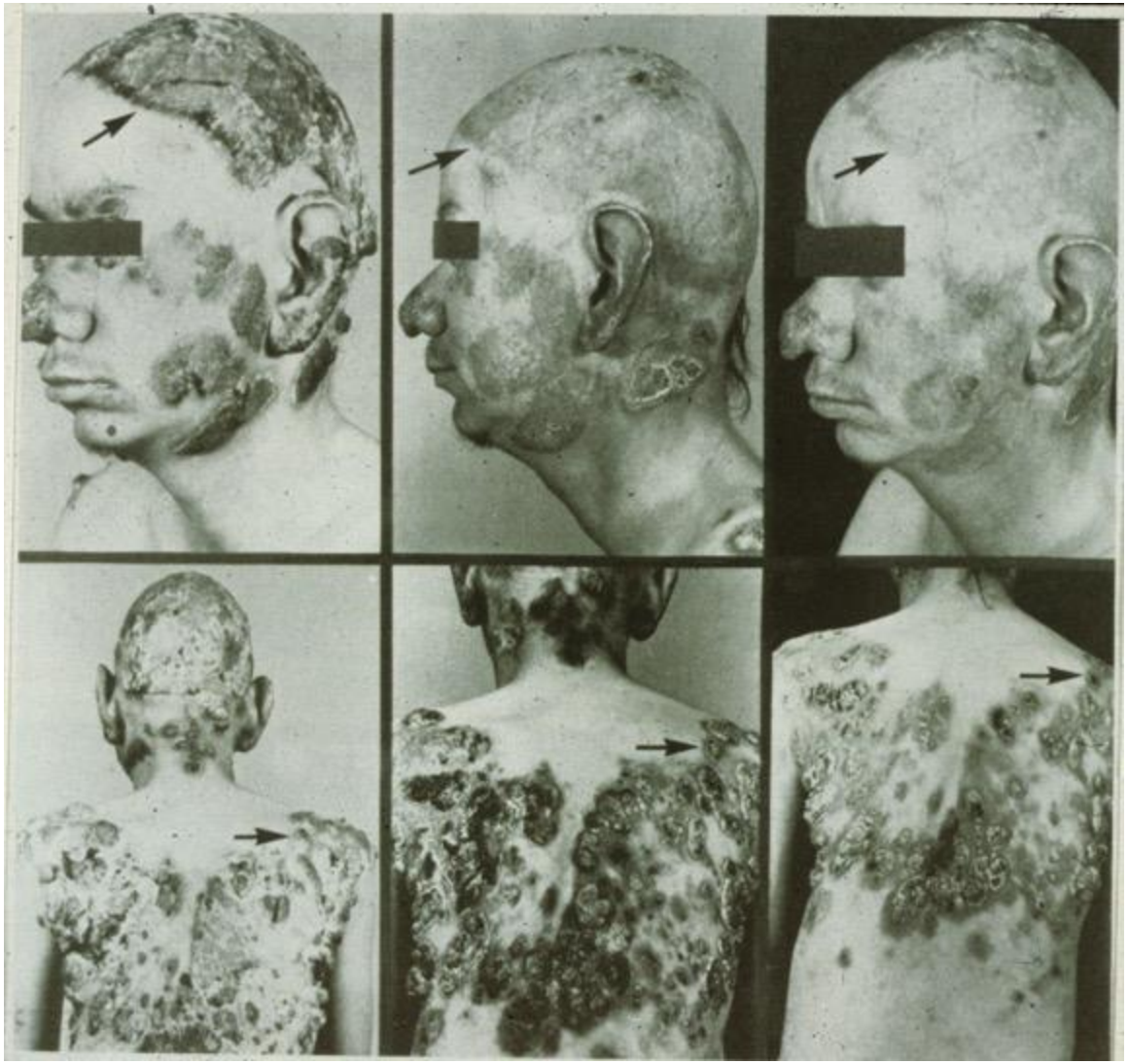
Edwards JE et al. Ann Intern Med 1978; 89: 91-106

Case Study # 2

Figure 3. Nails of a 9-year-old boy with chronic mucocutaneous candidiasis.

Reference. Edwards JE et al. Ann Intern Med 1978; 89: 91-106

Case Study # 2



Pre-treatment **2 mos. Rx** **5 mos. Rx**

Case Study # 2

Pre-Treatment

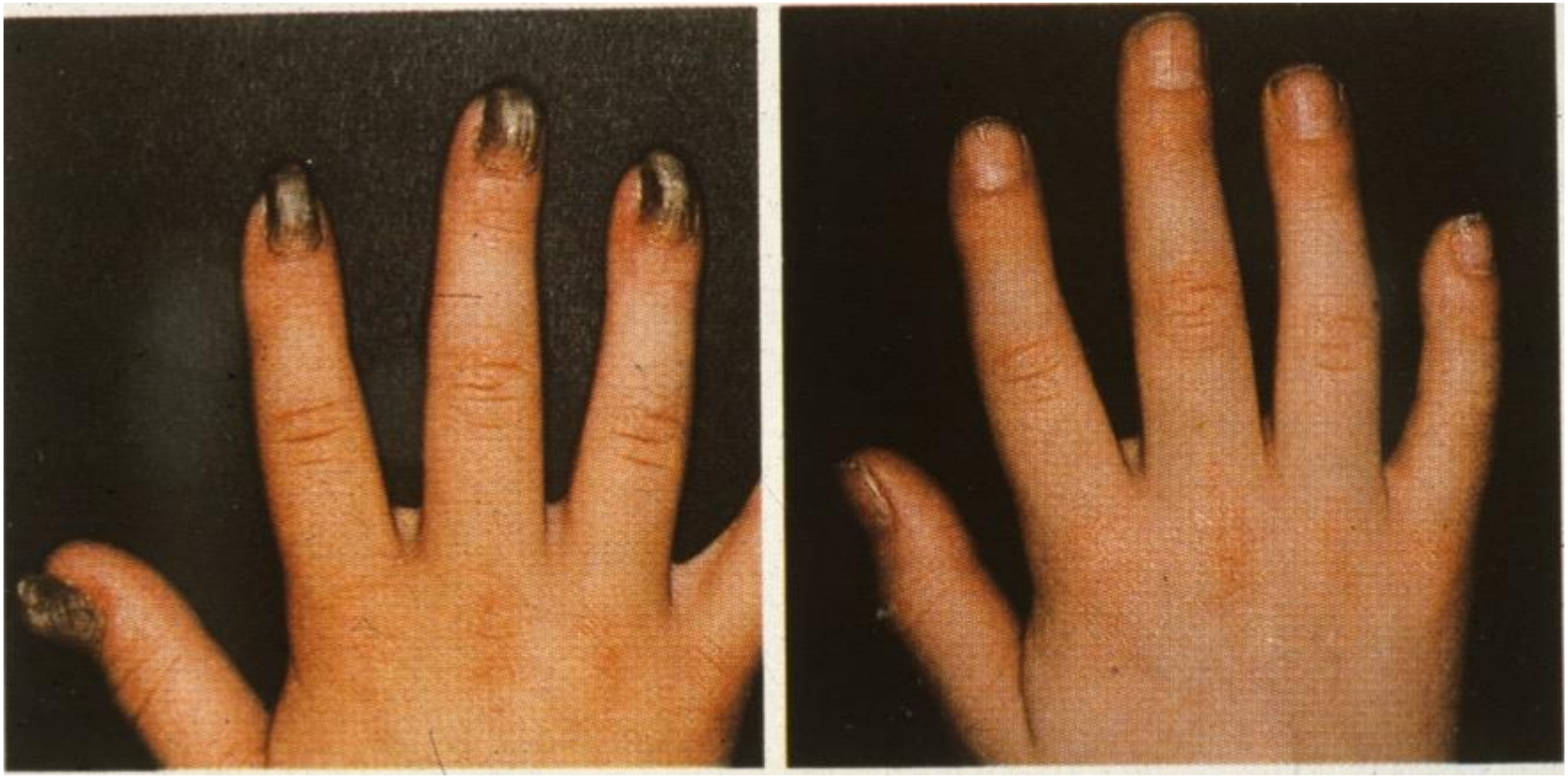
After 5 Months' Treatment

Case Study # 2

Pre-Treatment **After 5 months Treatment**

Reference. Peterson EA et al. Ann Intern Med 1980; 93(6):791-795.

Case Study # 2



Pre-Treatment **After 3 Months' Treatment**

Reference. Peterson EA et al. Ann Intern Med 1980; 93(6):791-795.

Case Study # 2 - Answer

- All of above are various manifestations of Chronic Mucocutaneous Candidiasis (“CMCC”)
- Pathophysiology: Inborn errors of IL-17 immunity (see next slide)

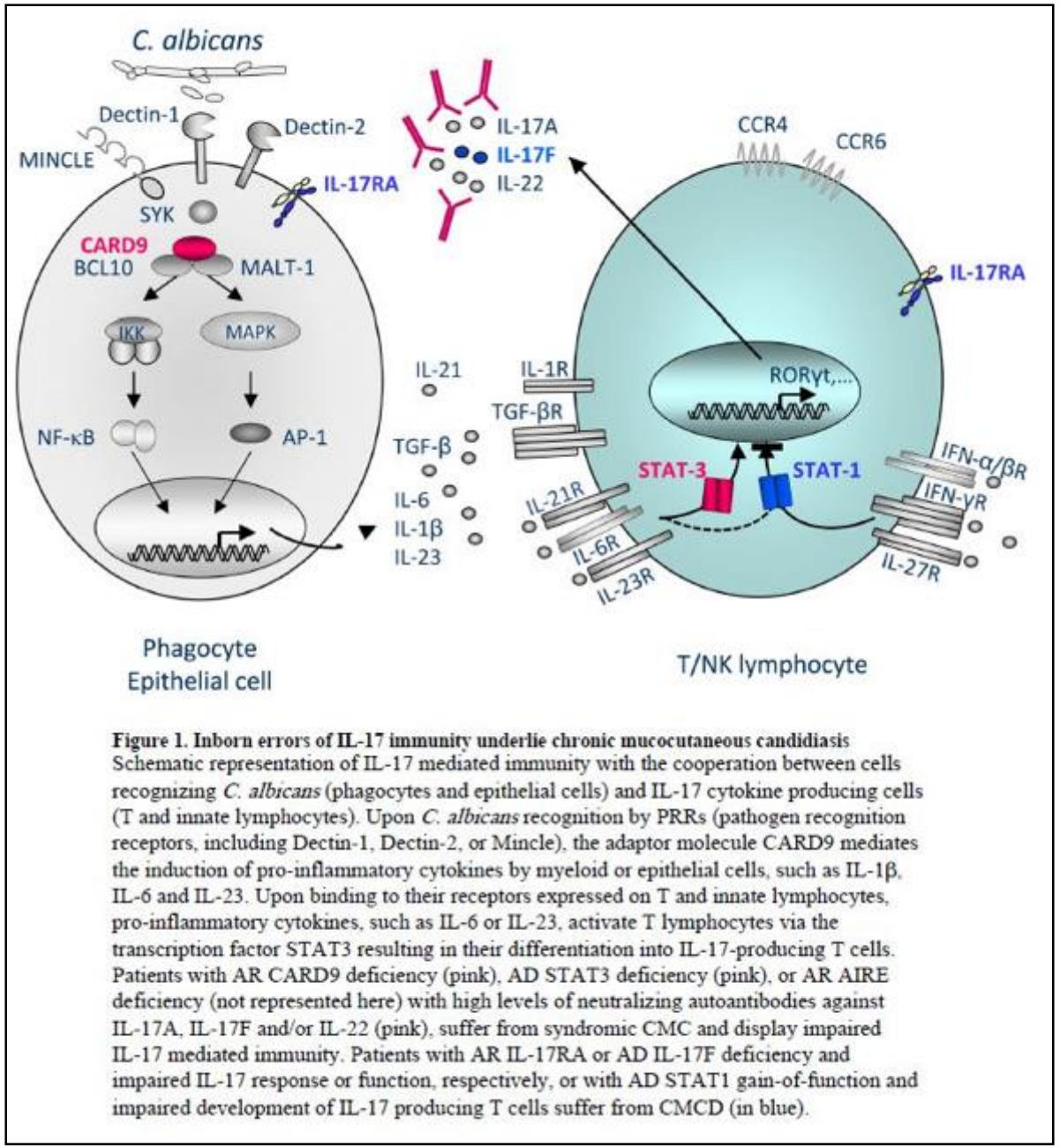


Figure 1. Inborn errors of IL-17 immunity underlie chronic mucocutaneous candidiasis
Schematic representation of IL-17 mediated immunity with the cooperation between cells recognizing *C. albicans* (phagocytes and epithelial cells) and IL-17 cytokine producing cells (T and innate lymphocytes). Upon *C. albicans* recognition by PRRs (pathogen recognition receptors, including Dectin-1, Dectin-2, or Mincle), the adaptor molecule CARD9 mediates the induction of pro-inflammatory cytokines by myeloid or epithelial cells, such as IL-1β, IL-6 and IL-23. Upon binding to their receptors expressed on T and innate lymphocytes, pro-inflammatory cytokines, such as IL-6 or IL-23, activate T lymphocytes via the transcription factor STAT3 resulting in their differentiation into IL-17-producing T cells. Patients with AR CARD9 deficiency (pink), AD STAT3 deficiency (pink), or AR AIRE deficiency (not represented here) with high levels of neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22 (pink), suffer from syndromic CMC and display impaired IL-17 mediated immunity. Patients with AR IL-17RA or AD IL-17F deficiency and impaired IL-17 response or function, respectively, or with AD STAT1 gain-of-function and impaired development of IL-17 producing T cells suffer from CMCD (in blue).

Reference. Curr Opin Allergy Clin Immunol 2012; 12(6): 616-622,

CMCC: Future Therapeutic Strateges

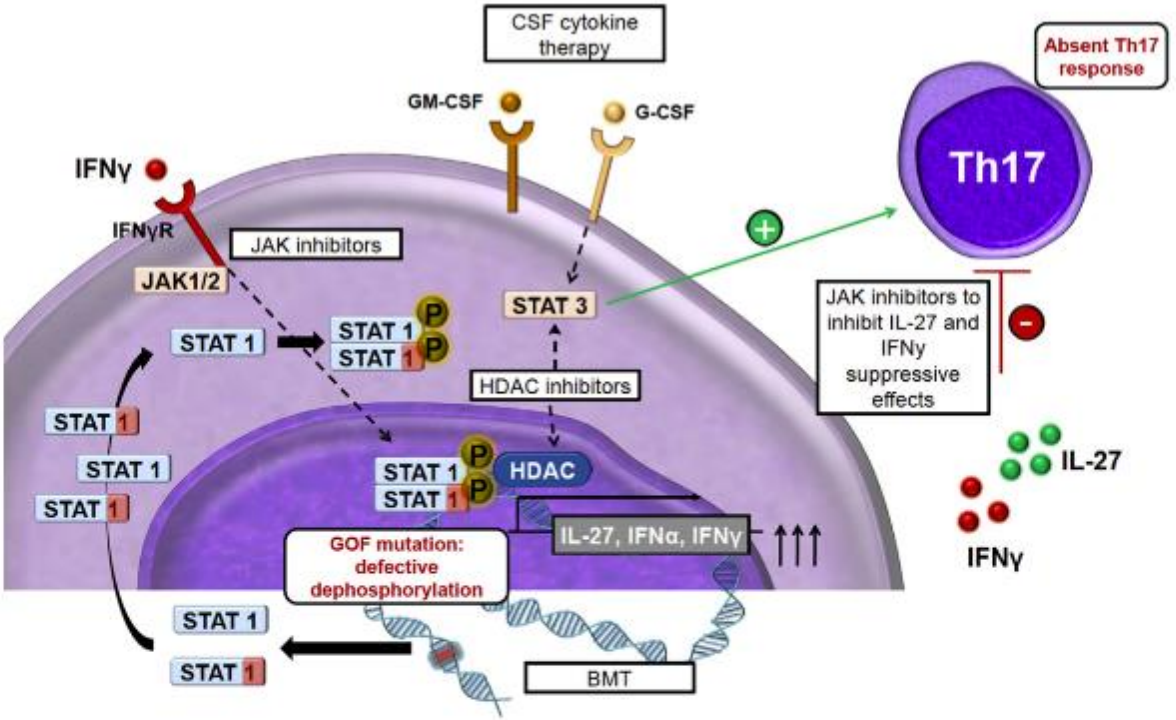


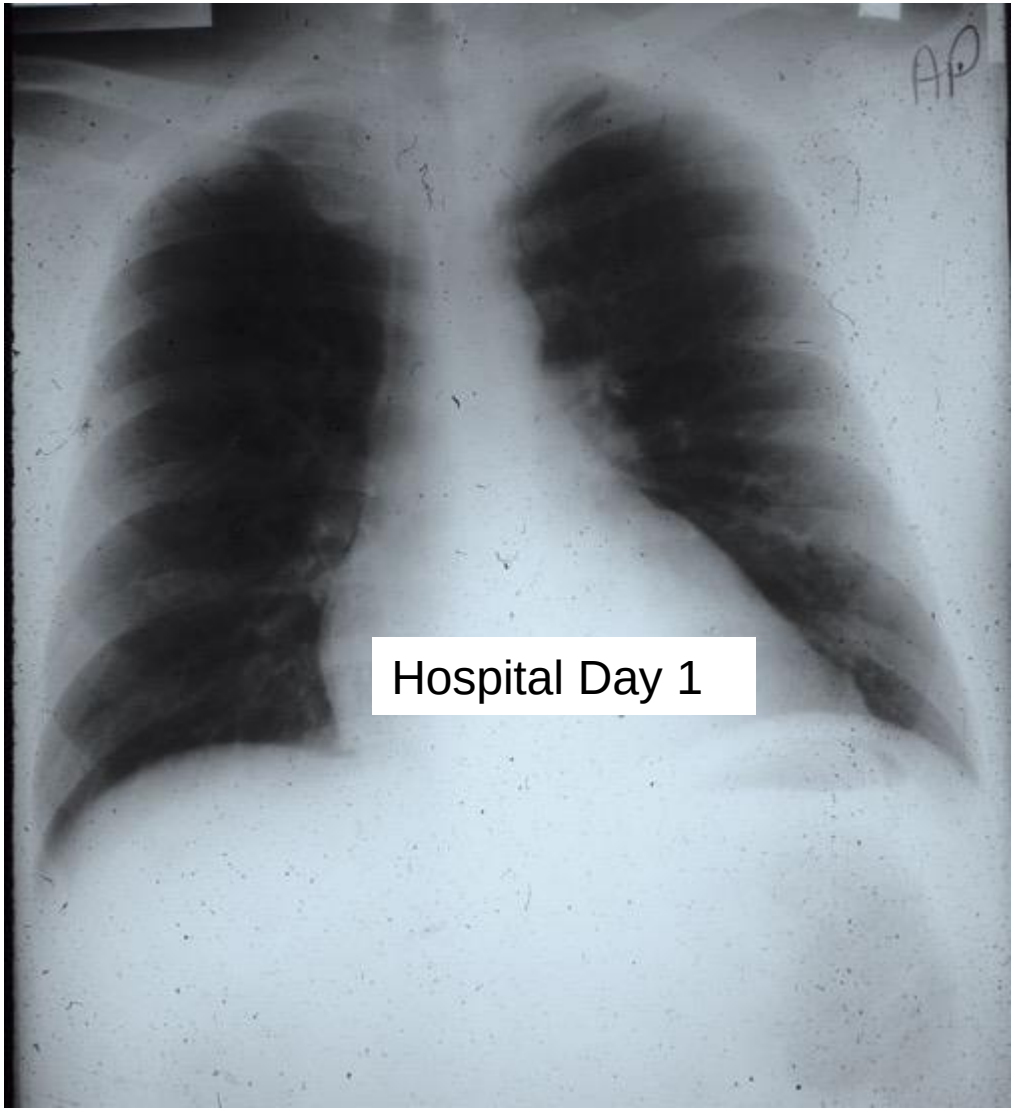
Figure 1 Therapeutic strategies that can be explored in *STAT1* GOF mutations. Mutations in *STAT1* are gain of function because of a defective dephosporylation in the nucleus, subsequently leading to an accumulation of phosphorylated STAT1 molecules in the nucleus. The immunological defect is characterized by an impaired IL-17-mediate immunity. Several approaches to restore defects in AD-CMC could be explored: **Inhibition of HDAC** to counteract the STAT1 hyperphosphorylation, enabling STAT1 molecules to exit the nucleus and to restore normal STAT1 function. Furthermore, it will activate the STAT3 pathway, thereby boosting the Th17 responses. Down-modulating STAT1 hyperactivity in AD-CMC patients cells by using **JAK1/2 inhibitors**; or to use these JAK inhibitors to suppress Th17 repressor cytokines, such as IL-27 to restore normal IL-17 immunity. The use of Colony Stimulating Factors (CSFs), such as **GM-CSF** and **G-CSF** might be used to restore the impaired Th17 response. G-CSF can also engage a STAT3 pathway. **Bone marrow transplantation (BMT)** as an option to correct the heterozygous *STAT1* GOF mutation.

Reference. Van de Veerdonk FL et al. Treatment options for chronic mucocutaneous candidiasis. J Infect 2016; 72:S56-S60

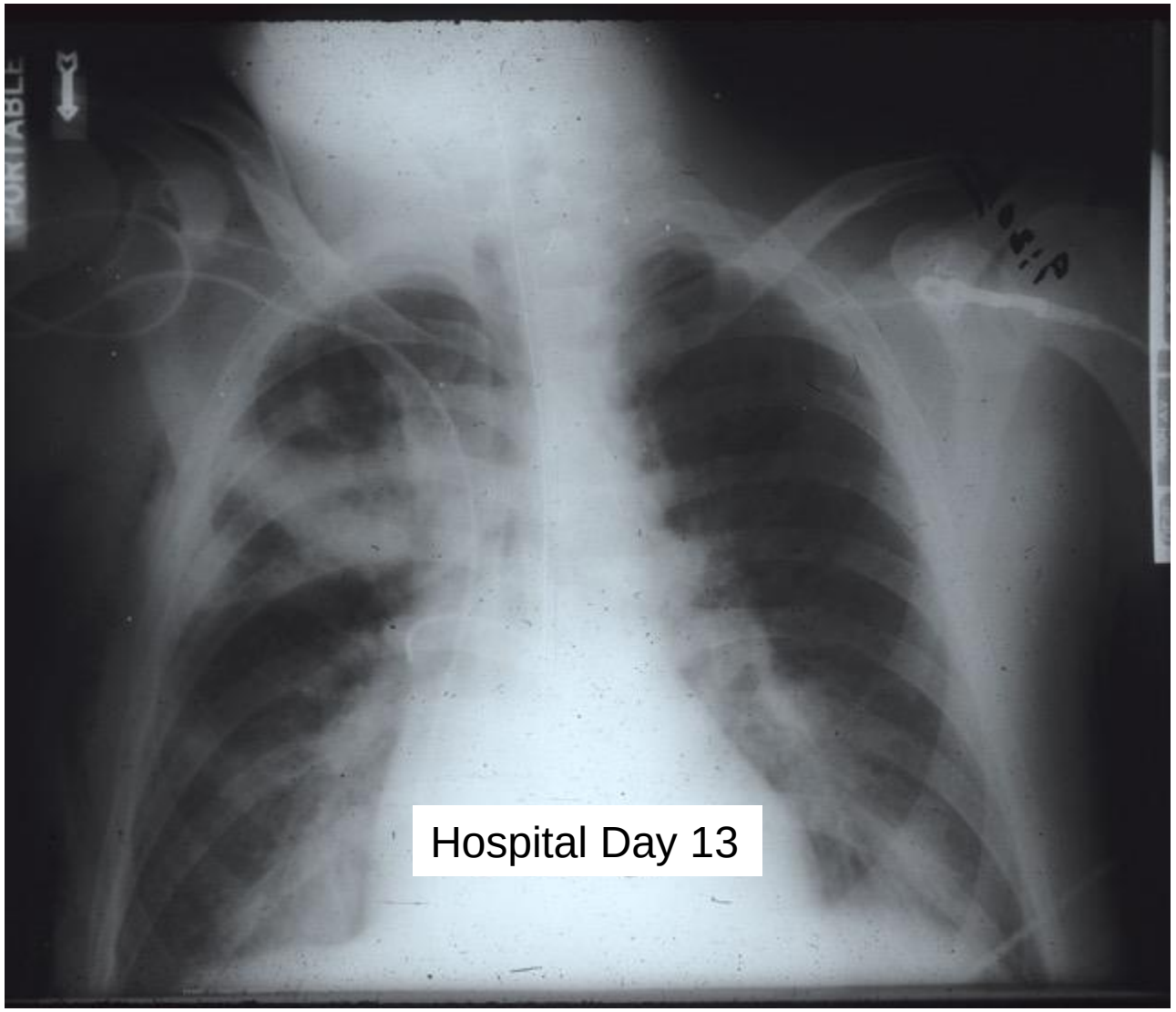
Case Study # 3

- 34 year old man with severe biopsy-proven small vessel vasculitis
- Treatment: High-dose (“Pulse-Dose”) methylprednisolone
- Subsequently developed pleuritic chest pain, tachypnea and hemoptysis
- Examination shows him to be acutely ill and gasping for air

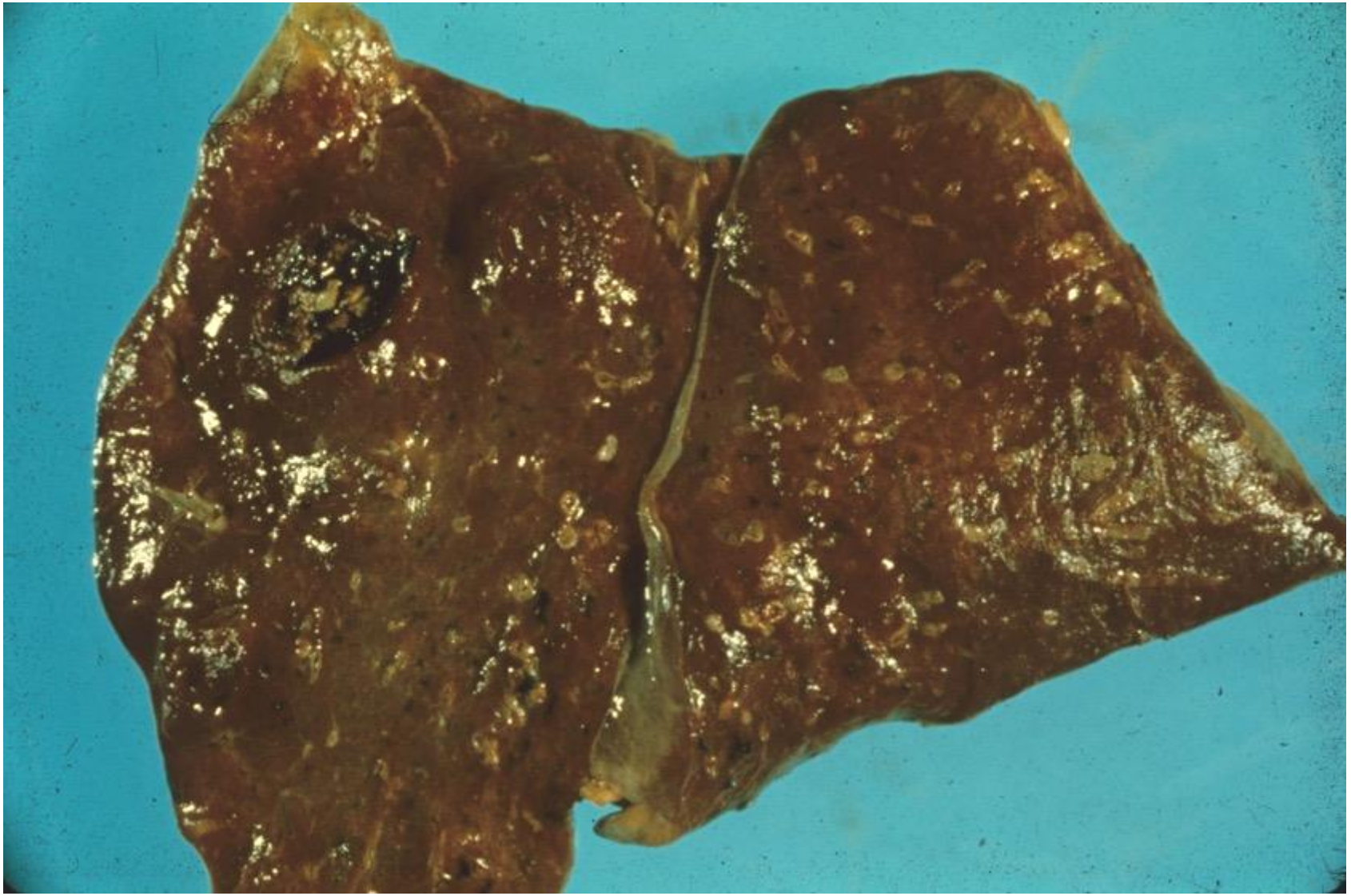
Case Study # 3



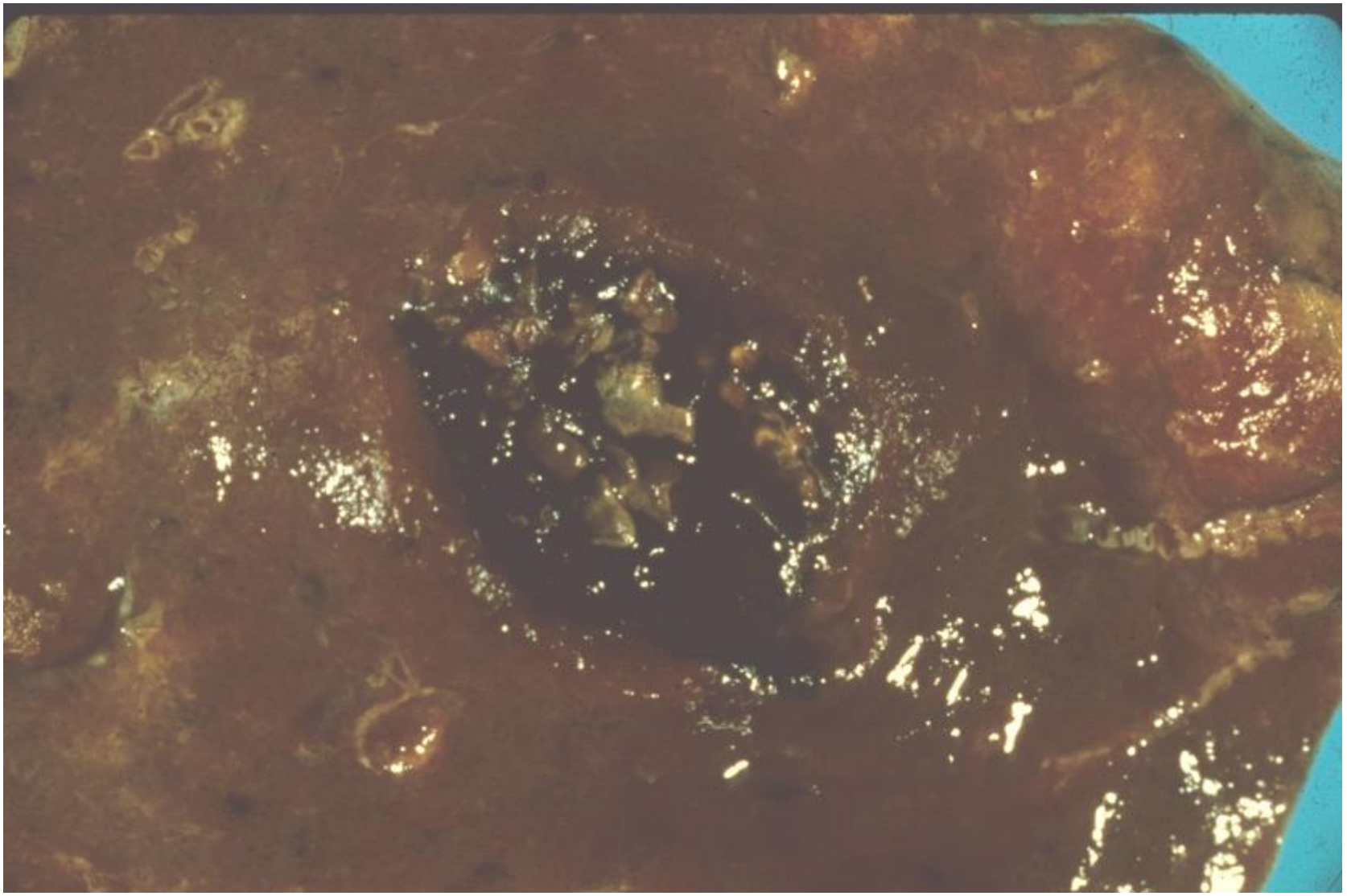
Case Study # 3



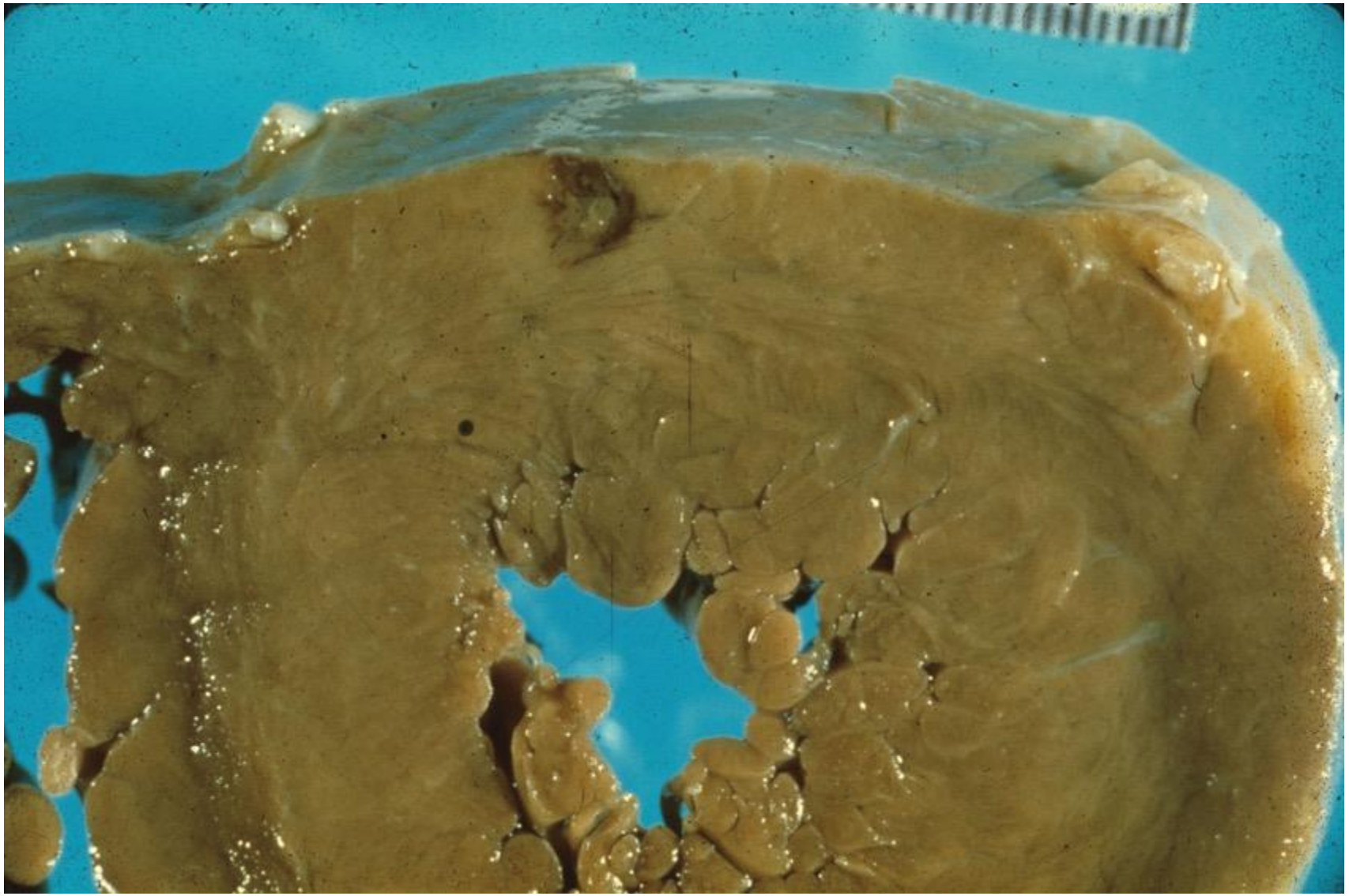
Gross Appearance of Right Lung at Autopsy



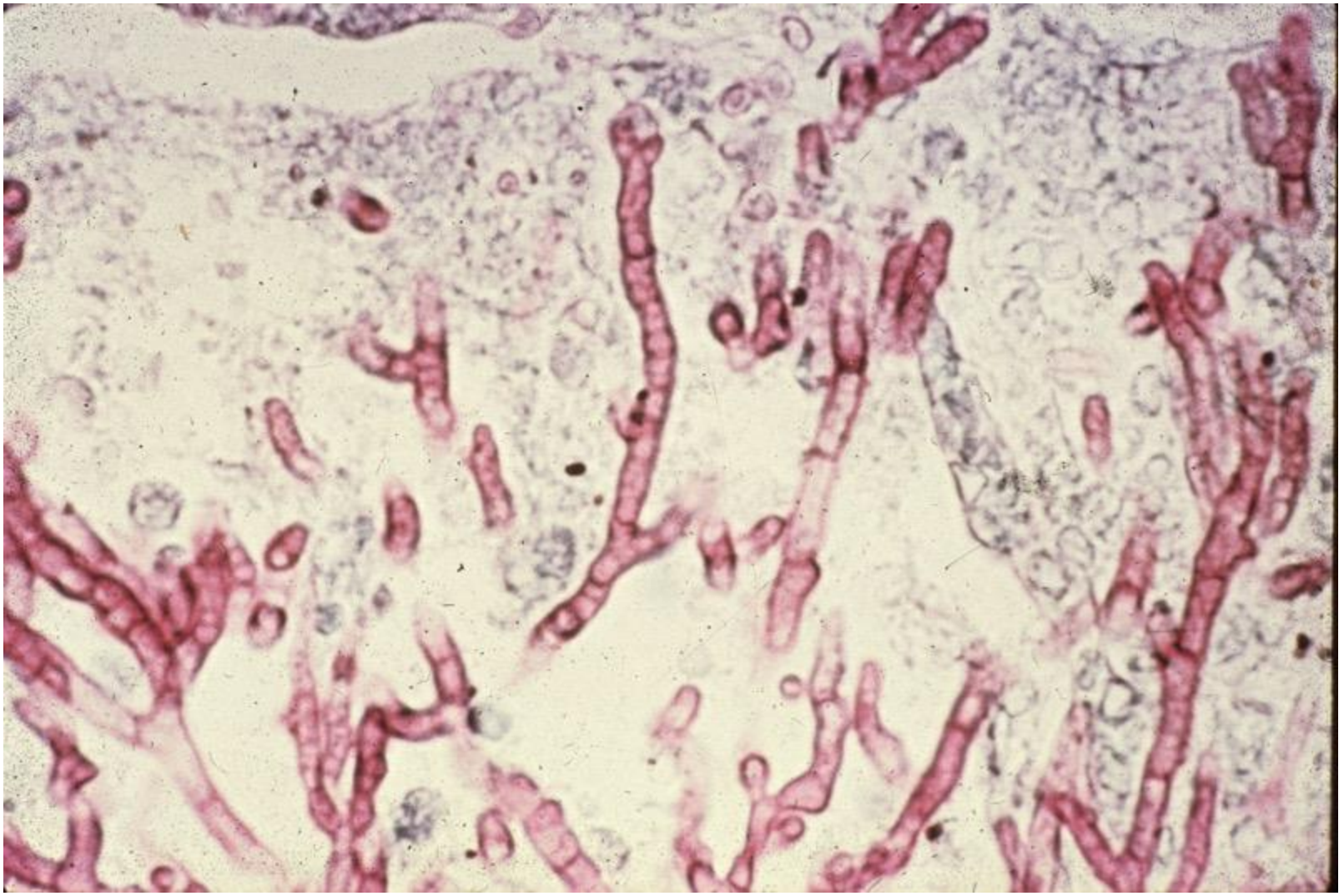
Lung Cavity At Autopsy



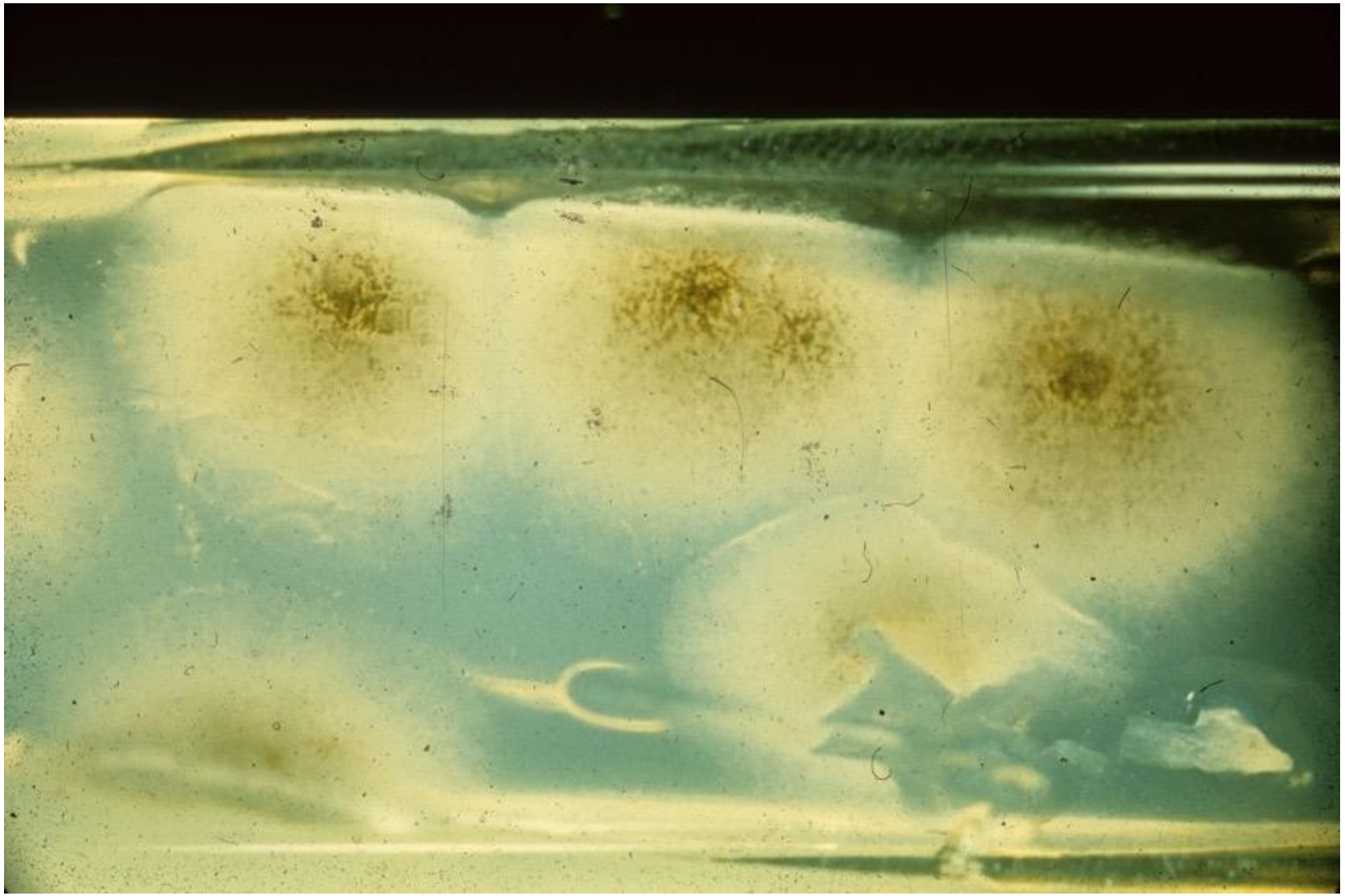
Myocardial Abscess at Autopsy



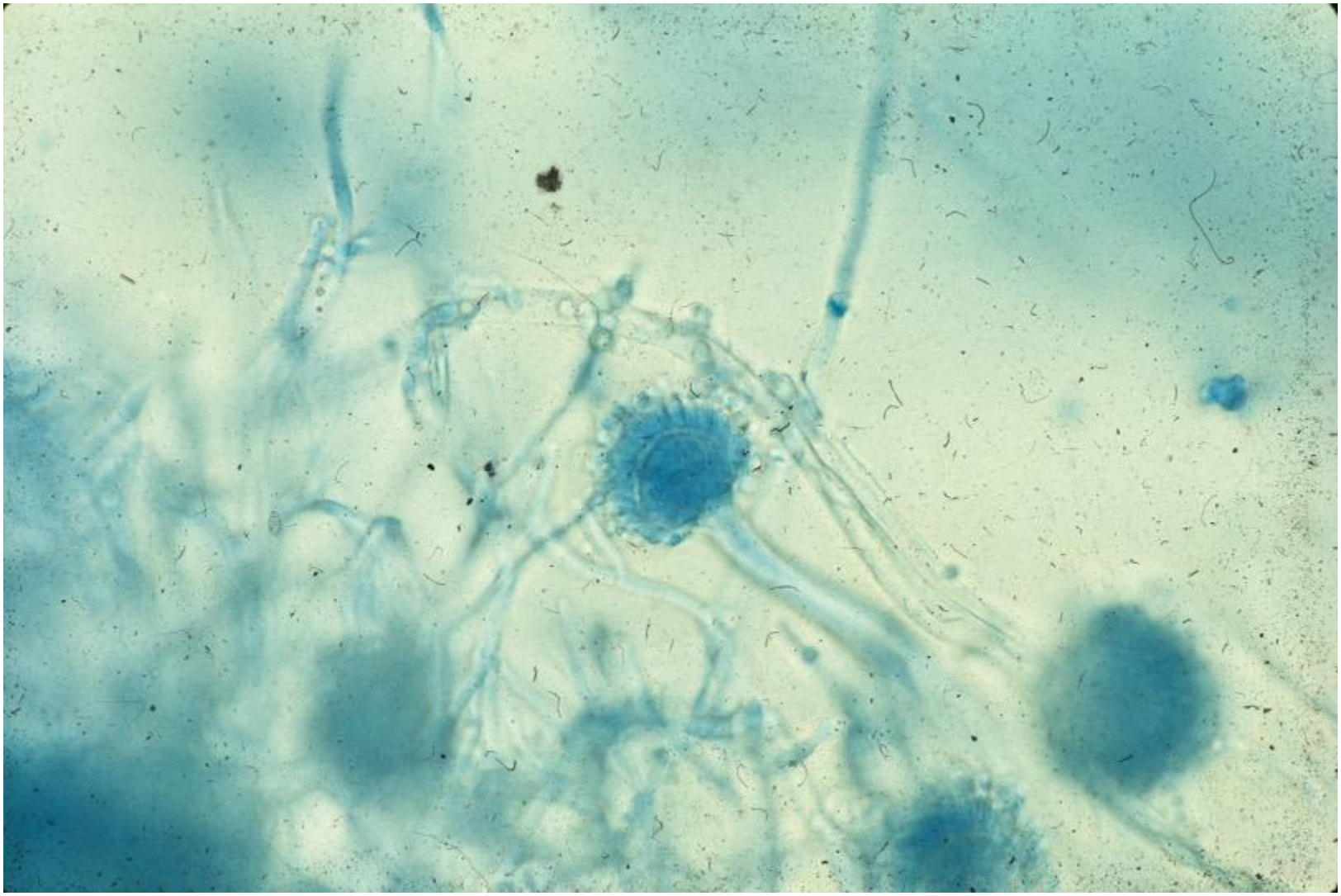
H&E of Lung Tissue
Septate Hyphae



Growth on Fungal Slant in Lab



Lactophenol Cotton Blue of Fungal Slant Growth Colony: Fruiting Heads



Methenamine Silver Stain: *Aspergillus* growing thru arterial wall

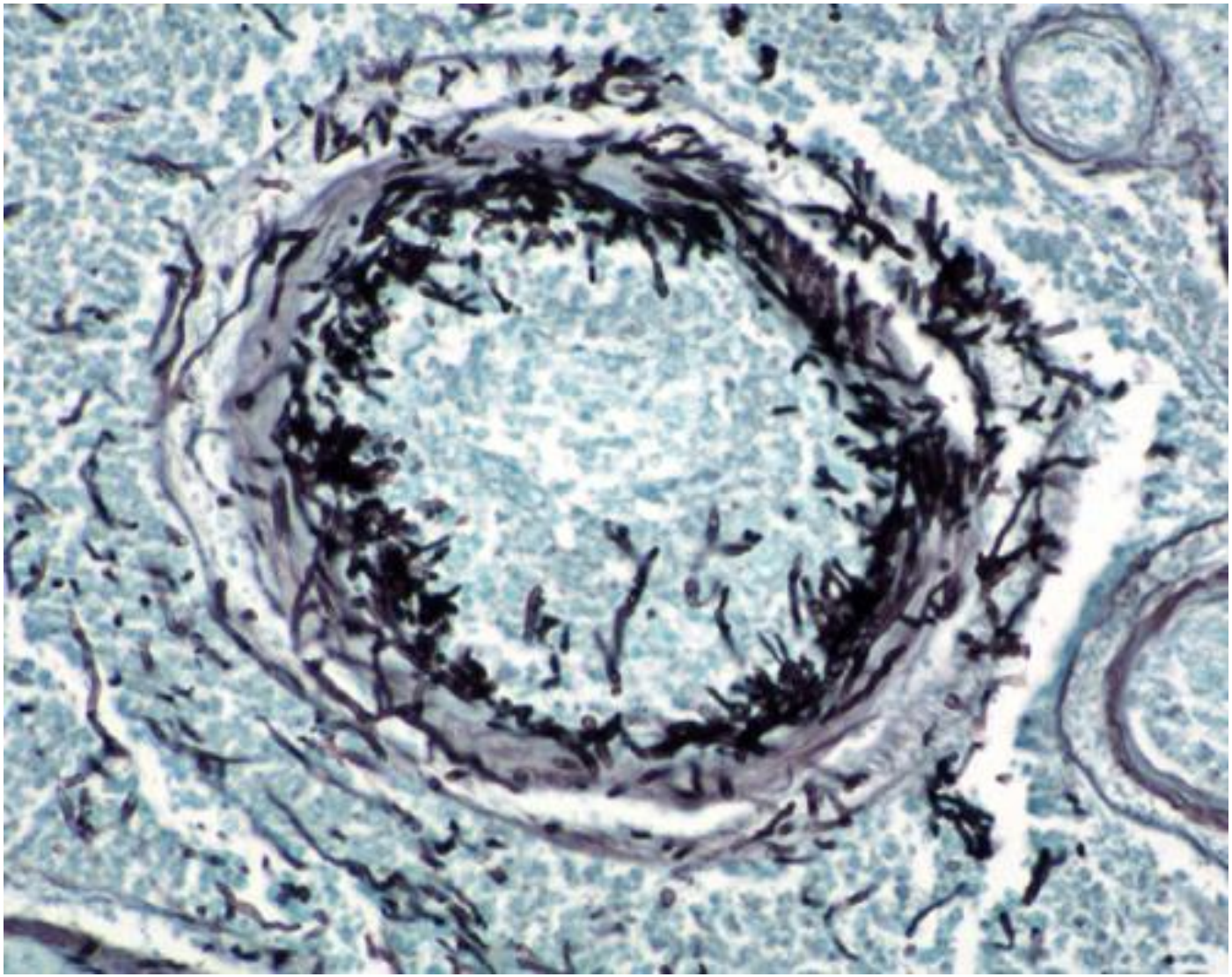
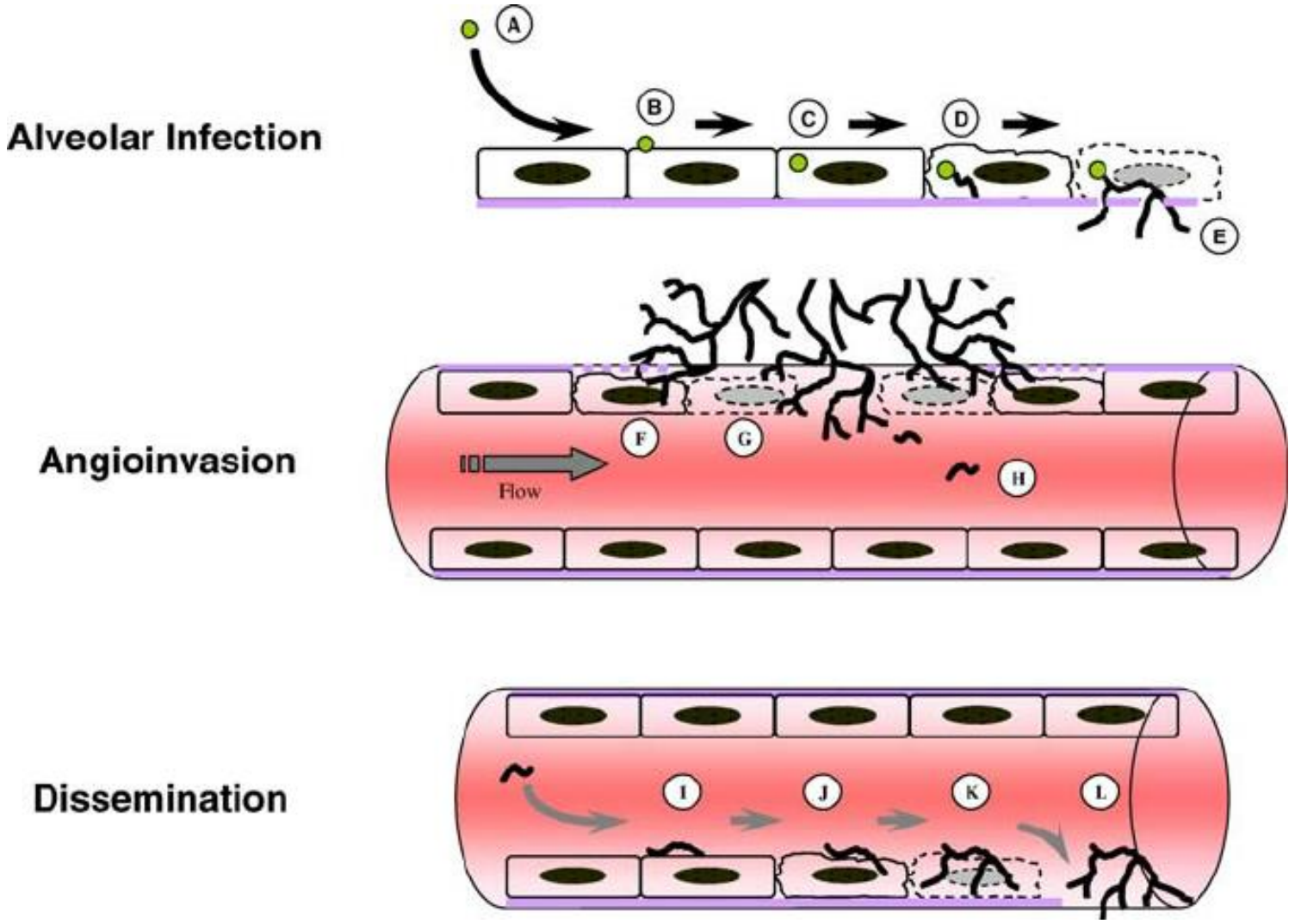


Illustration of Vascular Invasion by *Aspergillus* via Lung



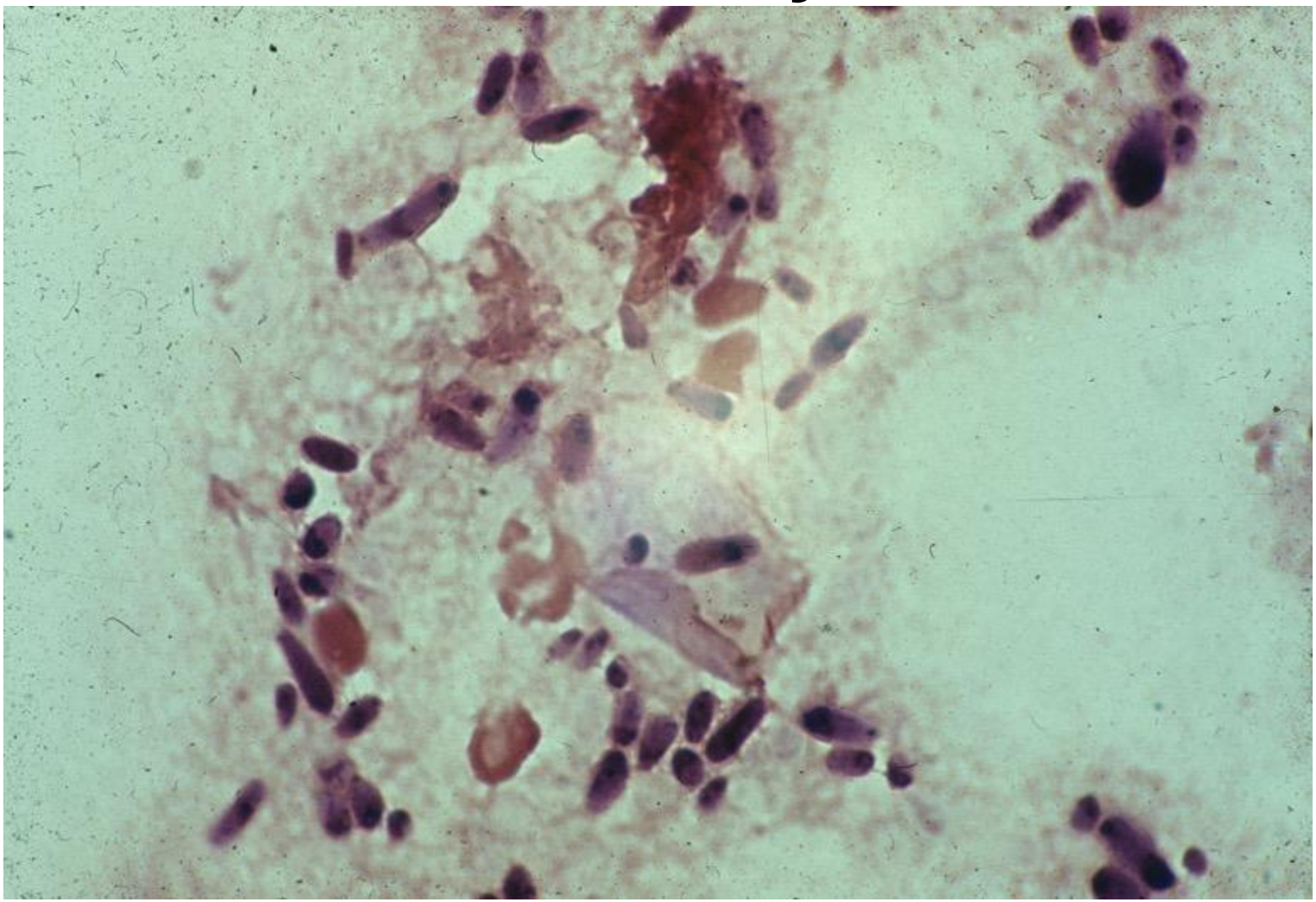
Case Study # 3 - Answer

- Acute invasive pulmonary and disseminated aspergillosis in compromised host (high-dose steroids for small-vessel vasculitis).
- Multi-System disease in this patient.
- Note the septate hyphae on H & E smear and the “fruiting heads” on the magnifications of the culture plate
- Treatment: Voriconazole OR Echinocandin + Voriconazole
- Alternate Treatment Regimens
  - Liposomal Amphotericin B
  - Isavuconazole

Case Study # 4

- 63 year old man with acute myelogenous leukemia who has undergone induction chemotherapy and develops severe neutropenia and fever (ANC = 0)
- Responds well to empiric vancomycin + piperacillin/tazobactam with defervescence but blood cultures negative
- 15 days into neutropenia, he develops new fever, confusion, and the noted palpable rash on chest and back

Case Study # 4

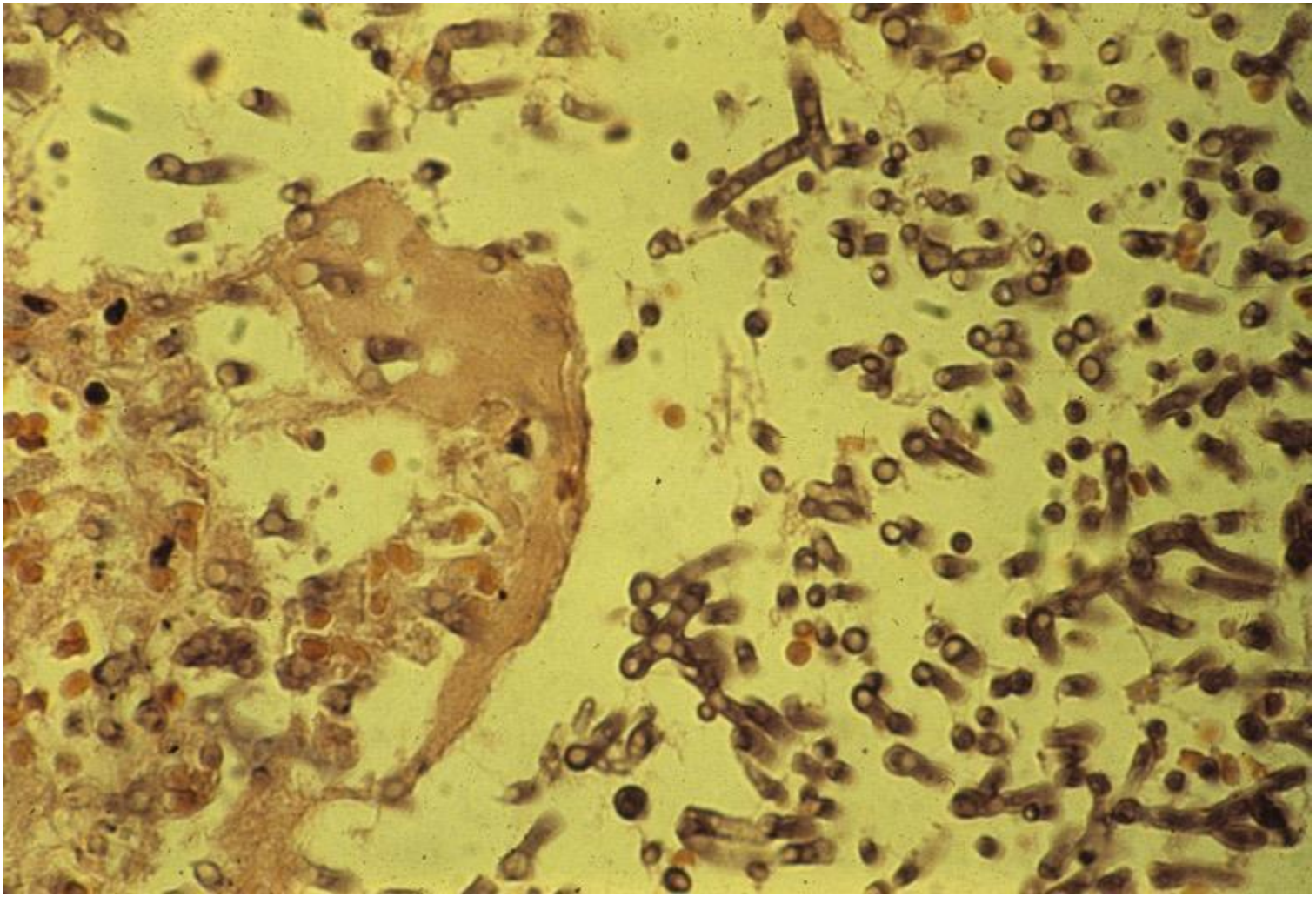


Gram-stained smear of scraping of one of the nodular skin lesions

Case # 5

- Started on amphotericin B deoxycholate, 1 mg/kg STAT and daily
- Despite this he continued to remain neutropenic and died 3 days later

Autopsy of Lung Tissue



Pathology of lung at autopsy – disseminated candidiasis evident throughout the tissue

Case Study # 4 - Answer

- Acute disseminated candidiasis in neutropenic febrile cancer patient
- Characterized by **non-tender nodular skin lesions** as seen in this patient
- Often caused by *Candida tropicalis*
- Treatment:
  - Voriconazole
  - Echinocandin
  - L-AMB, ABCD, ABLC (preps of amphotericin)

Case Study # 5

- 28 year old patient admitted to hospital with unilateral eye pain and recent loss of areas of vision
- Pertinent history is IV heroine use Ophthalmoscopic examination as shown

Case # 5

- Patient scheduled for ophthalmic surgery at 7AM
- Eloped overnight after first dose of liposomal amphotericin B
- Completely lost to follow-up

Case Study # 5 - Answer

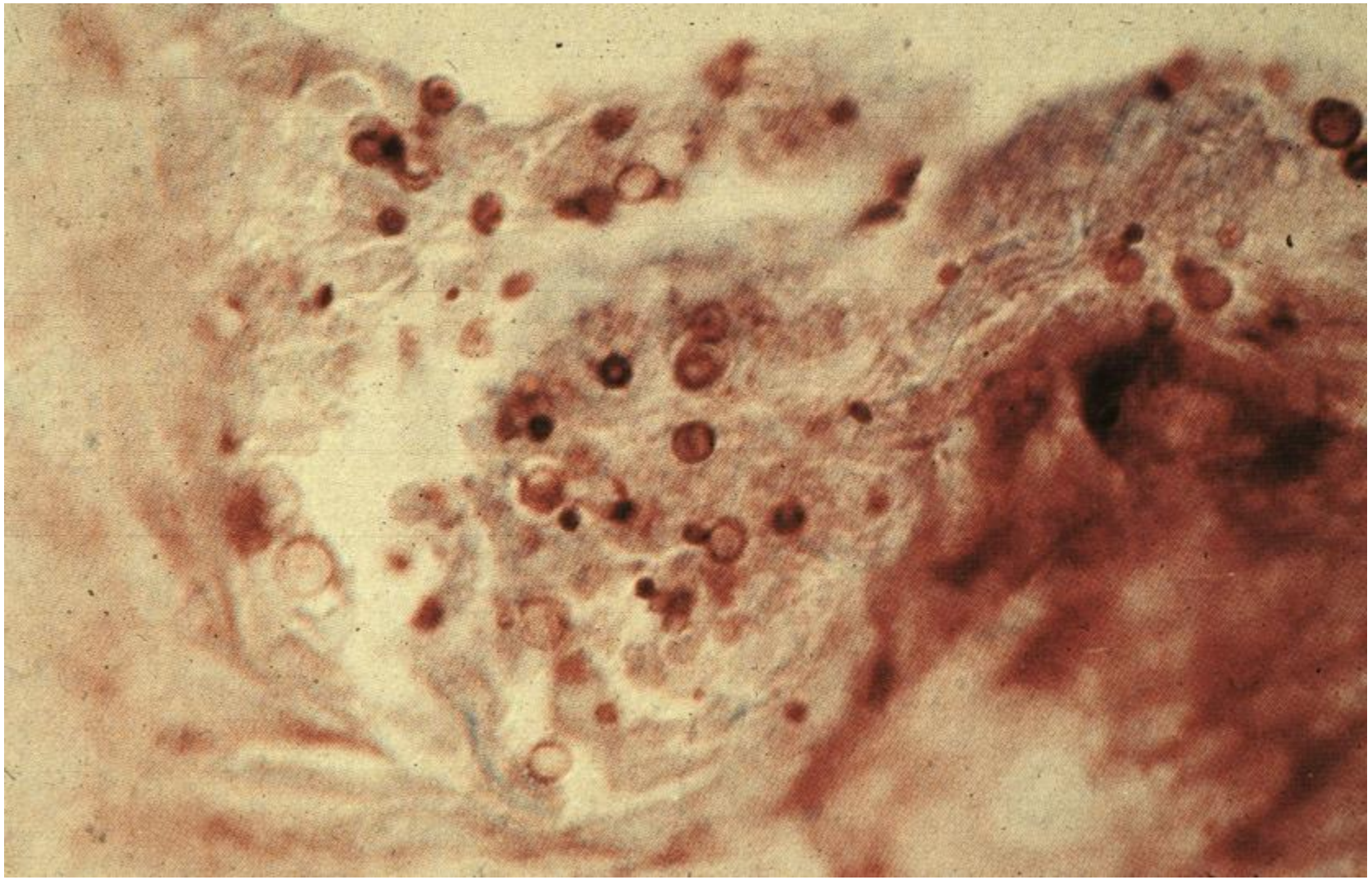
- Candida endophthalmitis
- From fungemic spread to eye
- Can occur anytime someone is fungemic
- Ophthalmic treatment:
  - Systemic antifungal agents (start with liposomal amphotericin B)
  - Intravitreal antifungal agent (ampho B 5 or 10 mcg OR voriconazole 100 mcg)
  - Vitrectomy (in “heavy vitritis”)

Case Study # 6

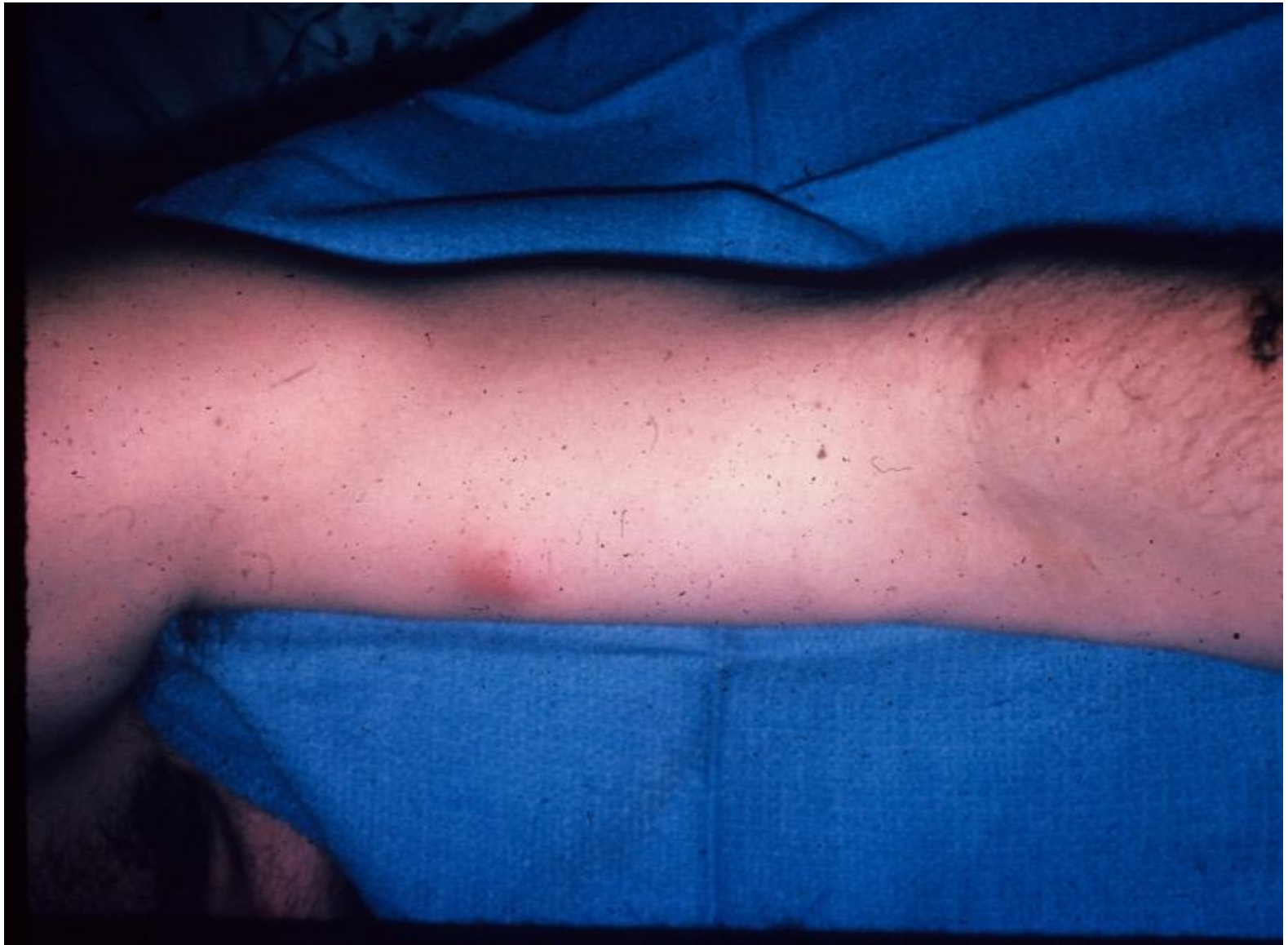
- 62 year old man presents with skin lesion on finger as noted in next slide
- Only pertinent history is that:
  - he is a rose gardener
  - frequently has puncture wounds of the hand from the thorns
  - Recently with the swelling noted proximally

Case Study # 6

Case Study # 6

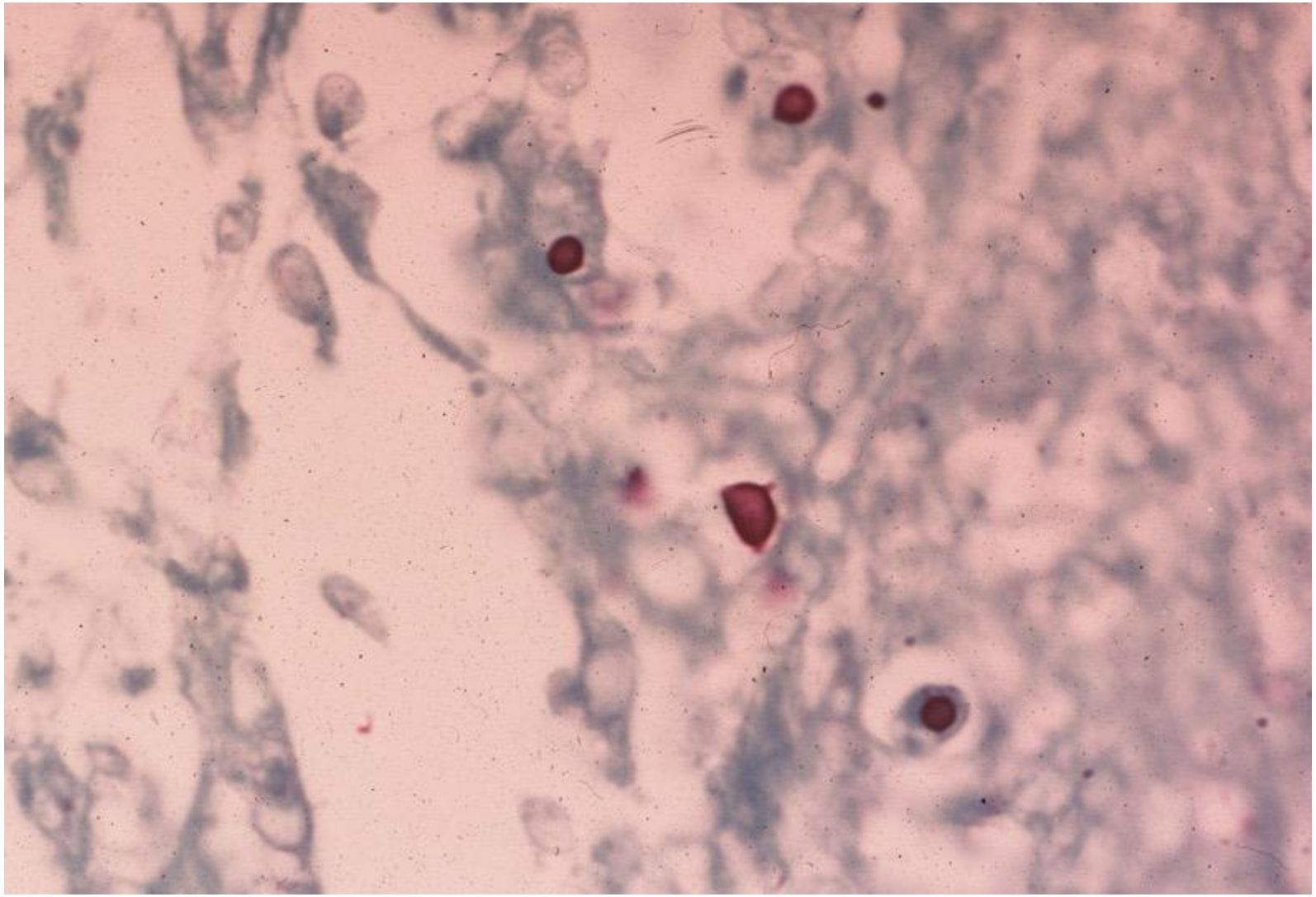


Case Study # 6



Case Study # **6**

Case Study # 6

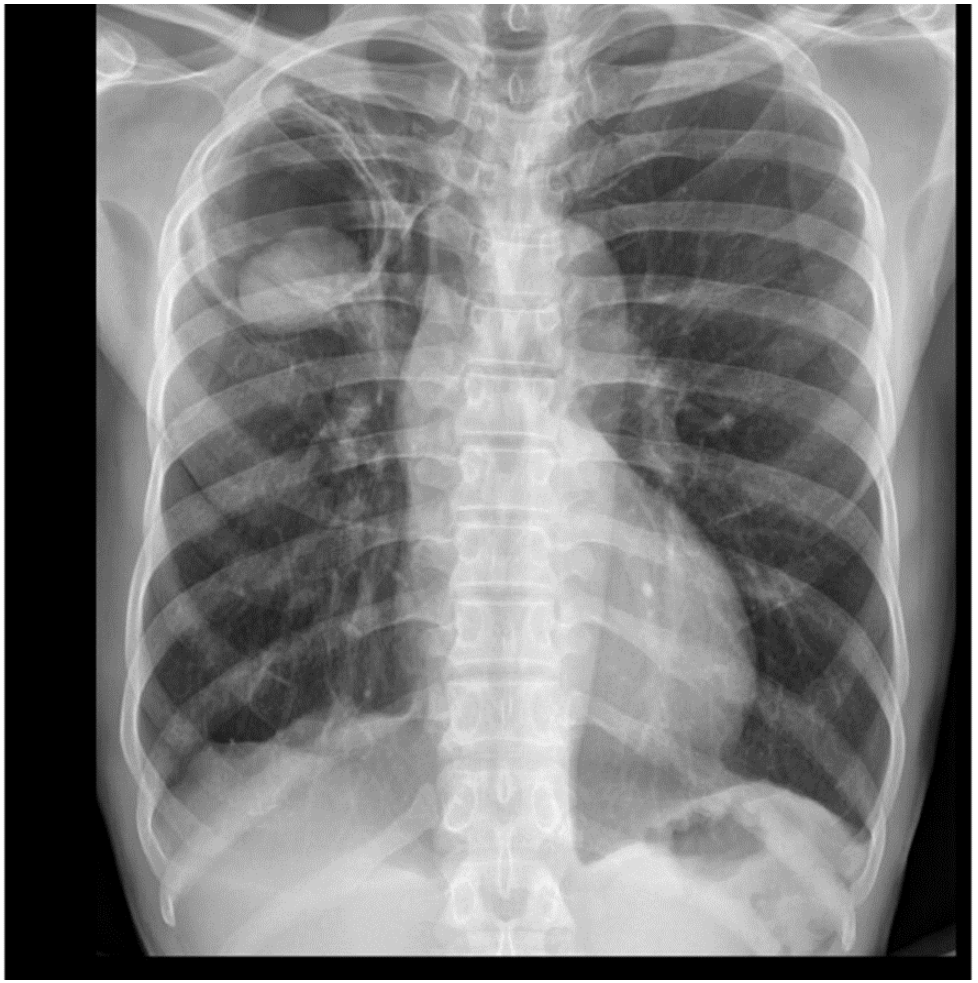


Case Study # 6 - Answer

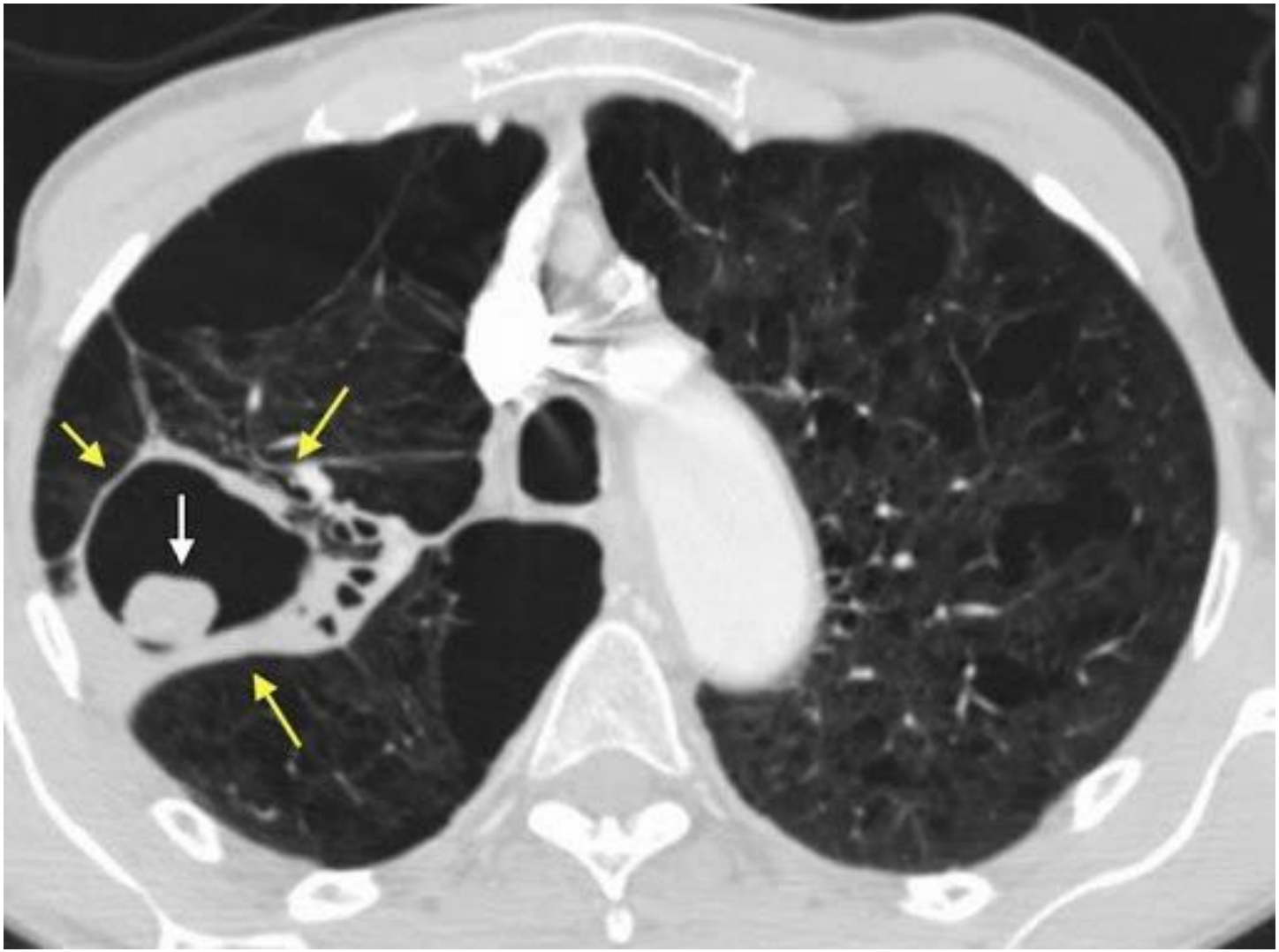
- Lymphocutaneous sporotrichosis
- *Sporothrix schenckii*
- Often grows in culture of biopsied area despite not always seeing the yeast on pathology
- Treatment:
  1. Itraconazole 200 mg bid (PO) [Sporanox®]
  2. Terbinafine 500 mg bid (PO) [Lamisil®]
  3. SSKI – no longer in vogue but is cheap AND effective

Case Study # 7

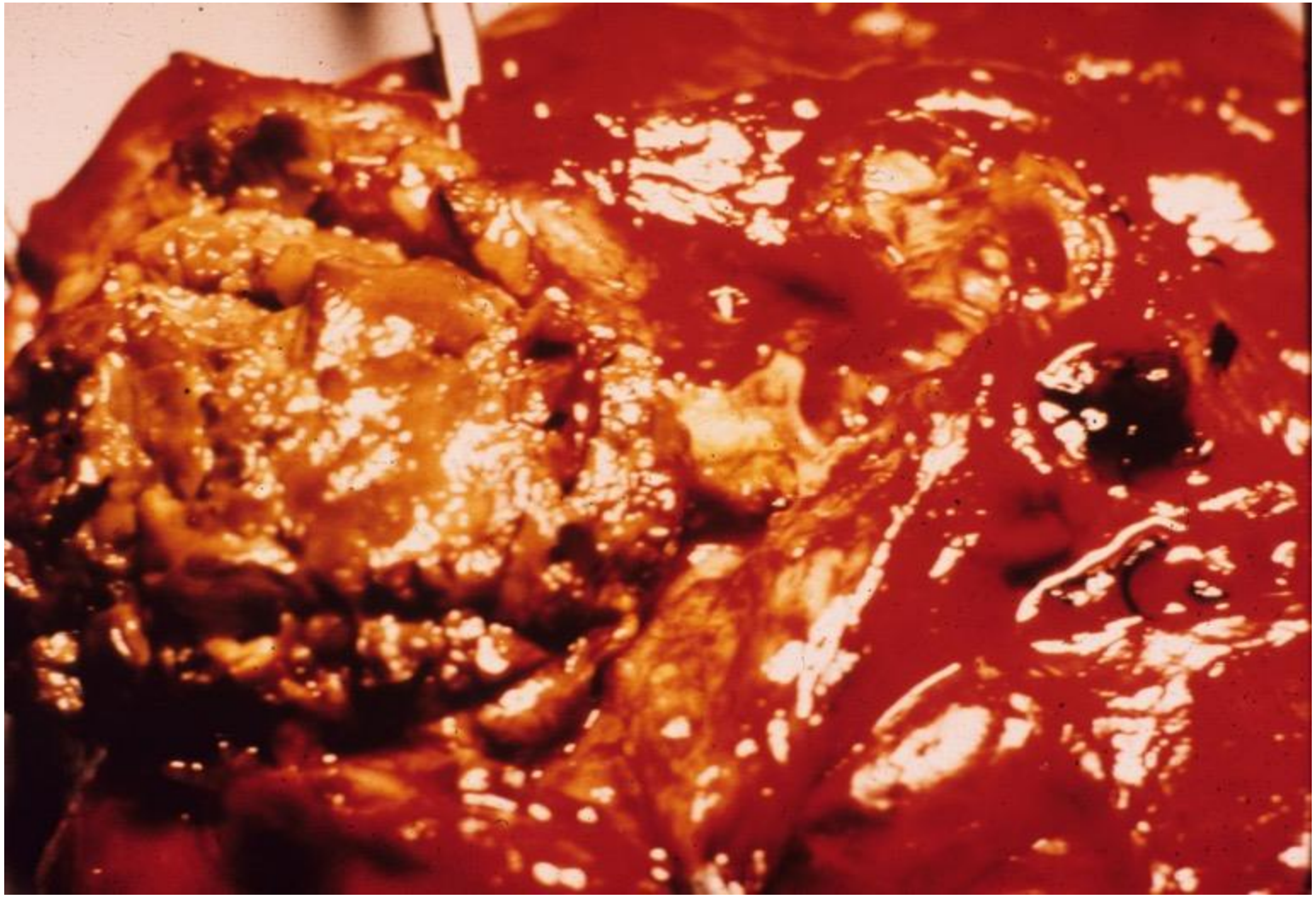
- 72 year old man presents to ED with shortness of breath and hemoptysis
- He has history of COPD but hasn't sought medical care for years and years
- Chest x-ray shown



CT of Chest



Surgical Extraction

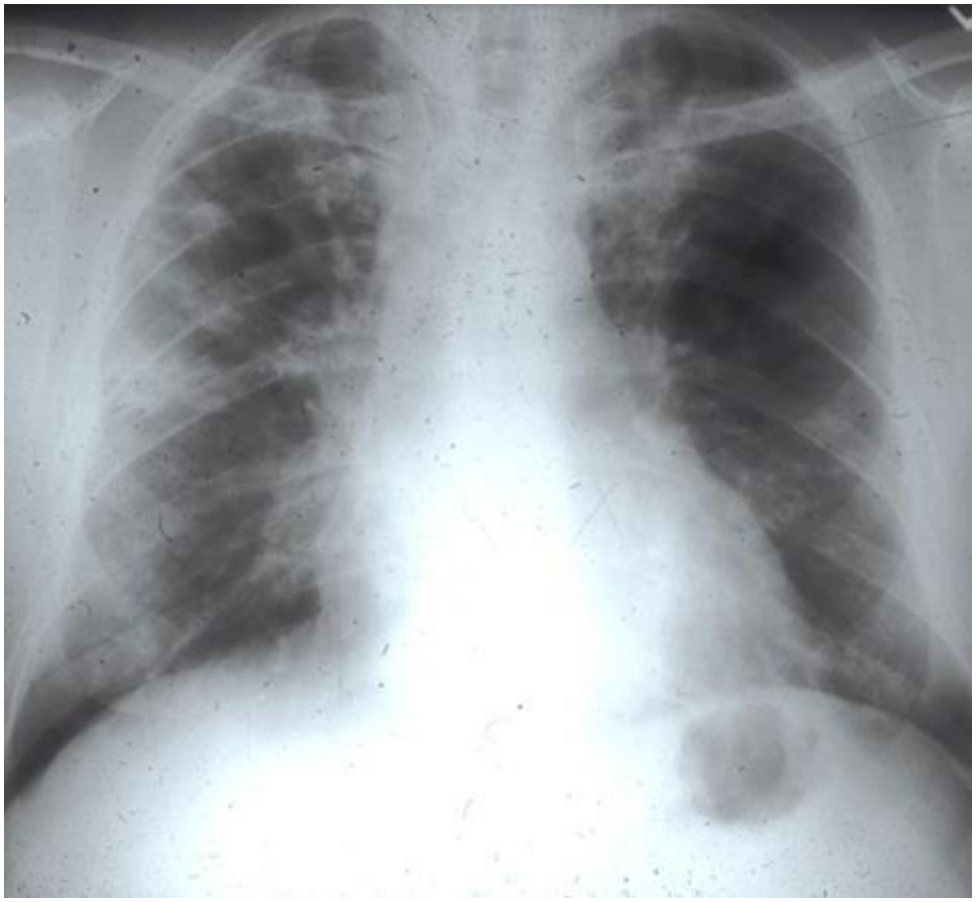


Case Study # 7 - Answer

- Mycetoma due to Aspergillus (“Aspergilloma”)
- Usually occur in pre-existing cavities in lung (e.g. sarcoid, old TB, etc.)
- Treatment: Interventional Radiology gel foam embolization; surgical resection (not without risks)
- Treatment: extended treatment course of voriconazole
- Surgical patient selection is critical as is experience with this disease (spread to pleura may occur post-op)

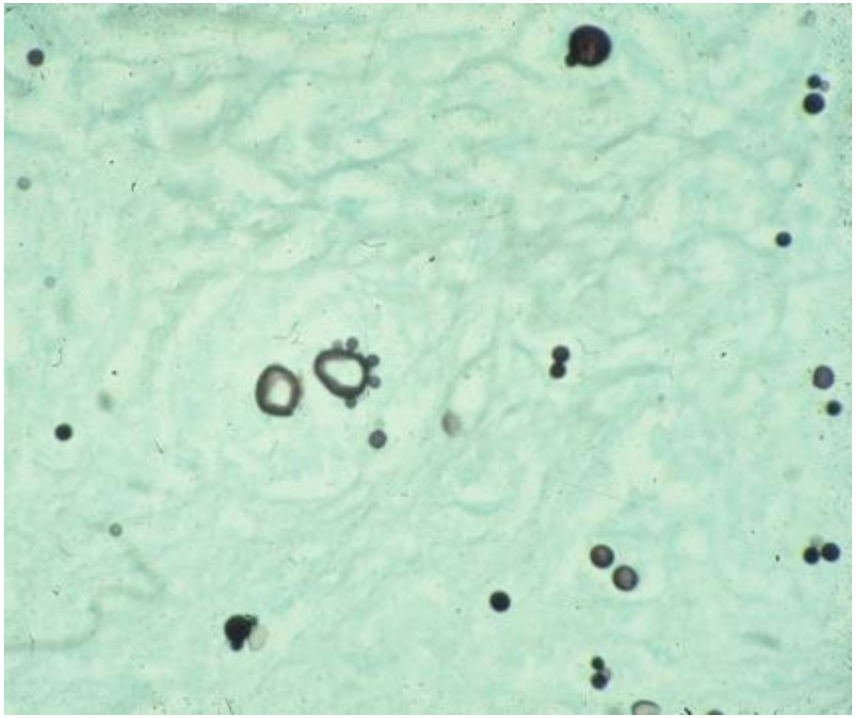
Case Study # 8

- Patient from **Central America** emigrates initially to **Southern California** for 5 years then to **NE Ohio** for job reasons.
- Patient presents with dry, non-productive cough and progressive shortness of breath
- No fever
- Exam shows few crackles
- Chest x-ray

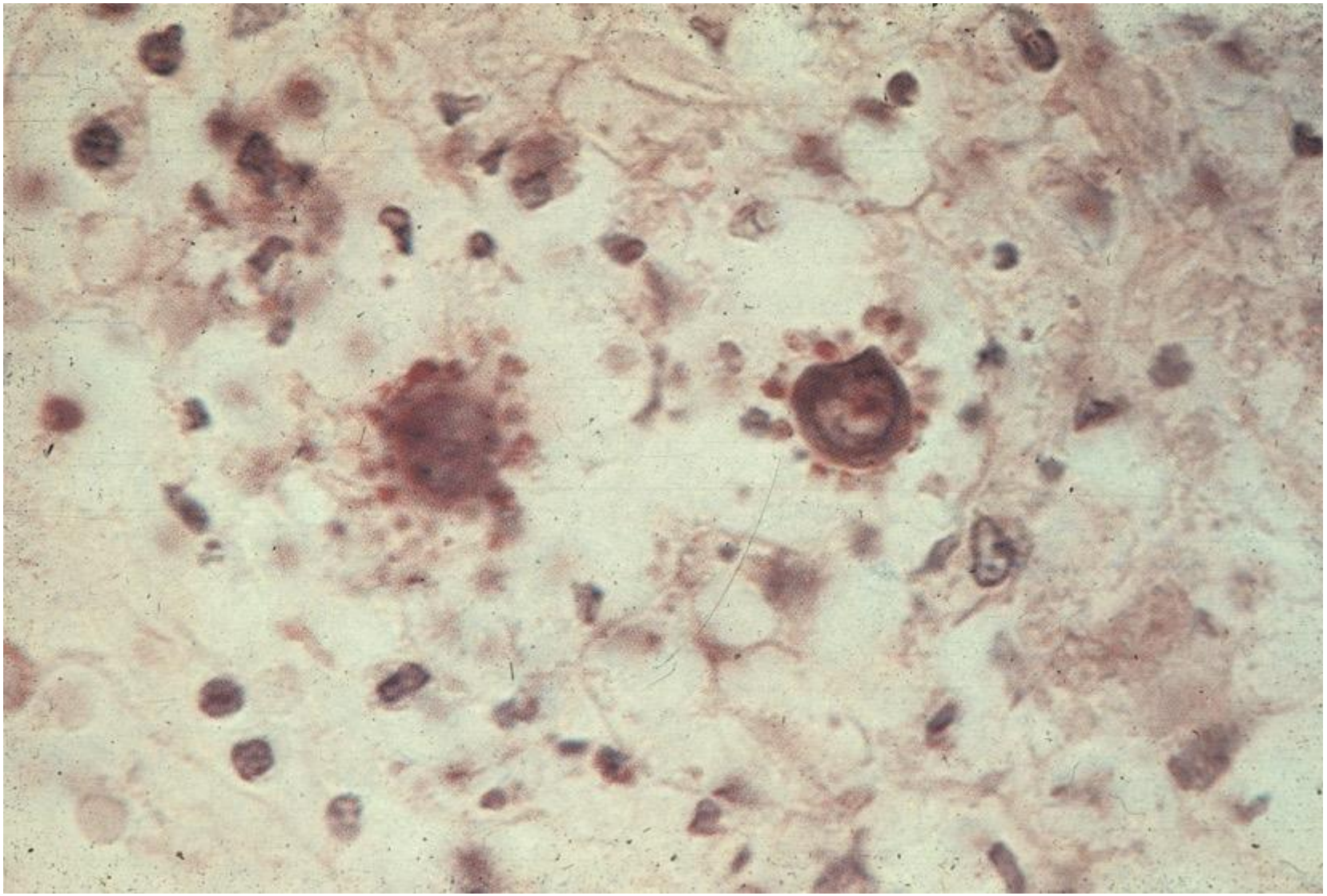


Case Study # 9

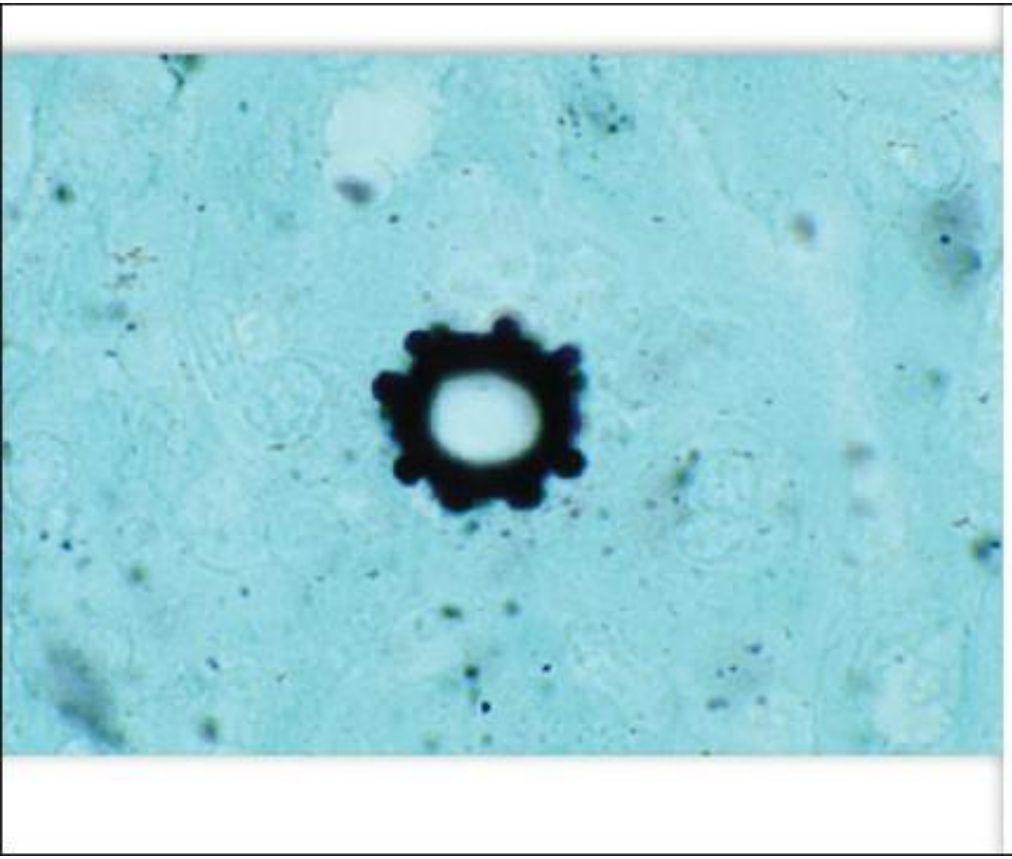
- Workup progesses rapidly to bronchoscopy because of oxygen desaturation
- Silver stain of bronchial washings reveals



H&E Stain of *Paracoccidioides*



P. Brasiliensis compared to Mariner's pilot wheel

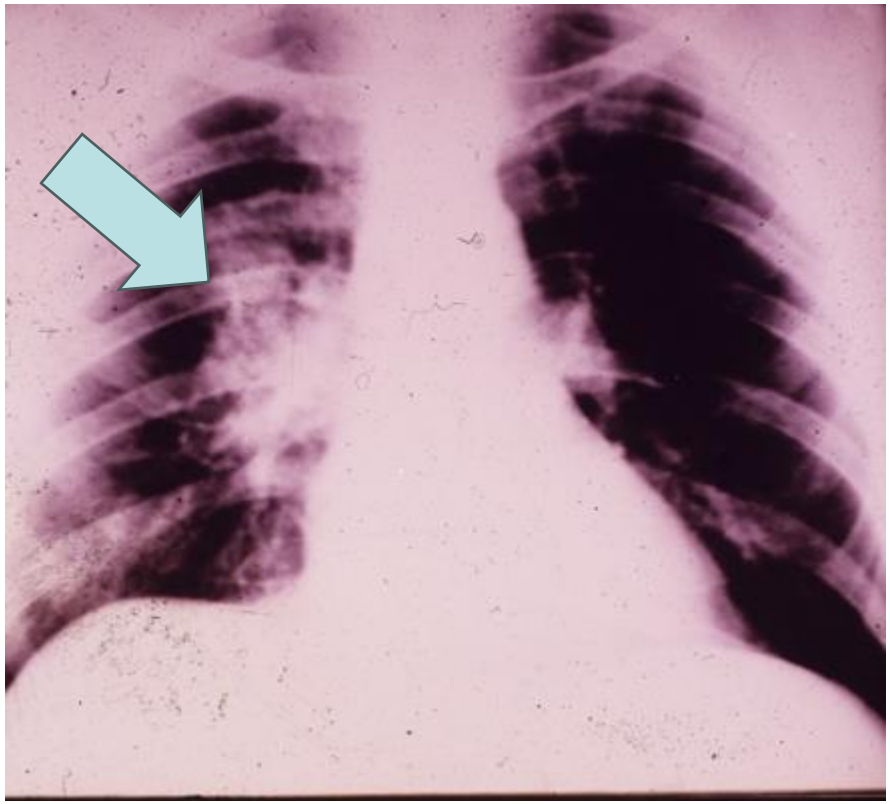


Case Study # 9 - Answer

- Paracoccidioidomycosis (“South American Blasto”)
- *Paracoccidioides braziliensis* or *P. lutzii*
- Treatment: Amphotericin B if severe, otherwise:
  1. Itraconazole x 6-18 months
  2. Voriconazole x 6-18 months
  3. TMP/SMX x 6-18 months

Case Study # 10

- 59 yo patient presents to hospital with gradual onset of progressive dry cough and shortness of breath
- Patient just moved from Seattle, WA to Athens, OH for new job as full Professor of Business Administration and Department Director at Ohio University
- Has O2 sat of 89% on room air
- Chest x-ray is obtained followed by bronchoscopy



Case # 10

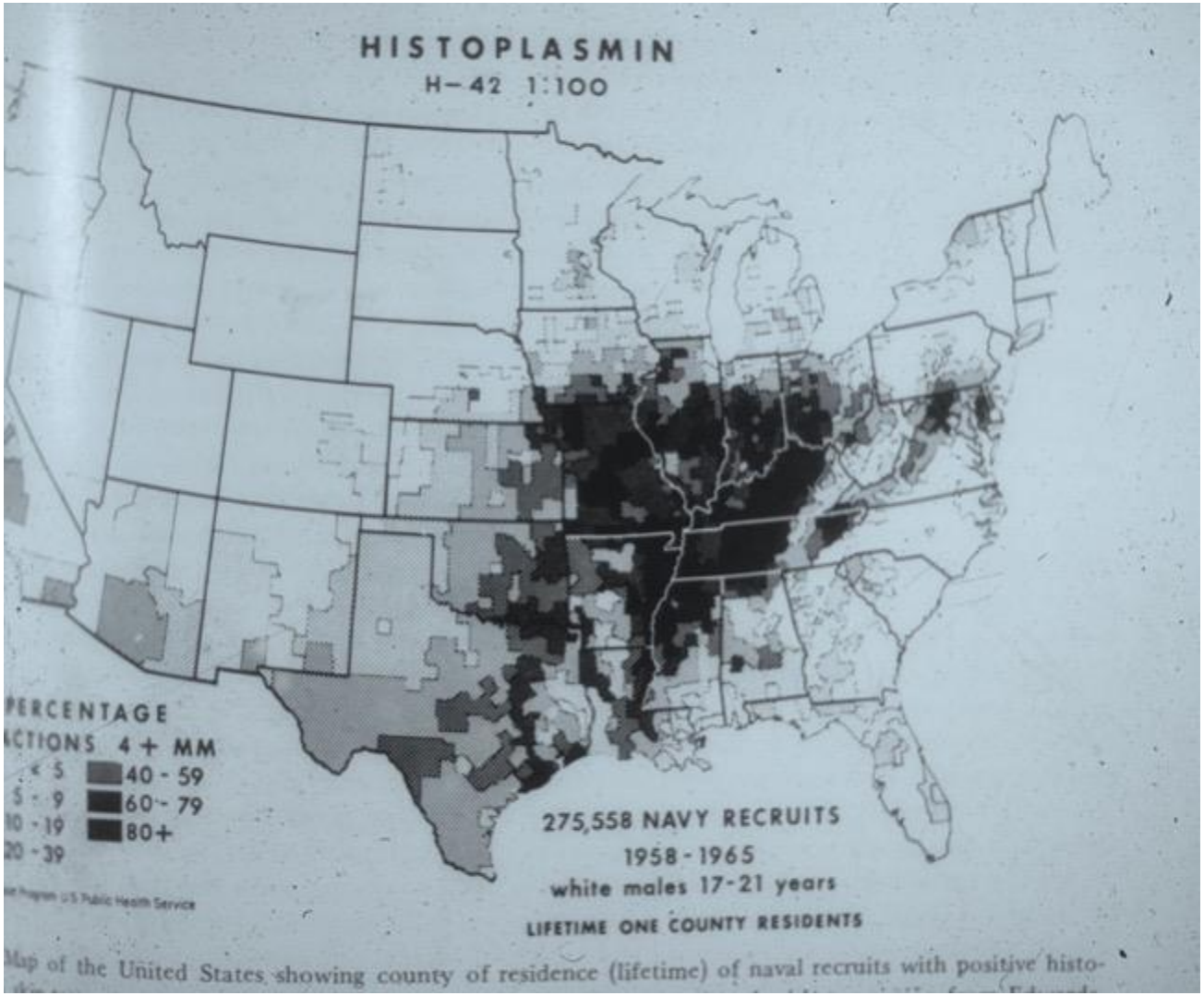
- Becoming more dyspneic
- Having greater oxygen desaturation
- Undergoes emergent bronchoscopy

Case Study # 10
Silver stain of bronch material

Case Study # 10 - Answer

- Dx: Acute primary pulmonary histoplasmosis
- *Histoplasma capsulatum*
- Very small yeast form and difficult to see unless on high power
- Treatment: dependent upon severity of illness:
  - lipid amphotericin B vs.
  - itraconazole vs.
  - voriconazole, isavuconazonium sulfate, posaconazole

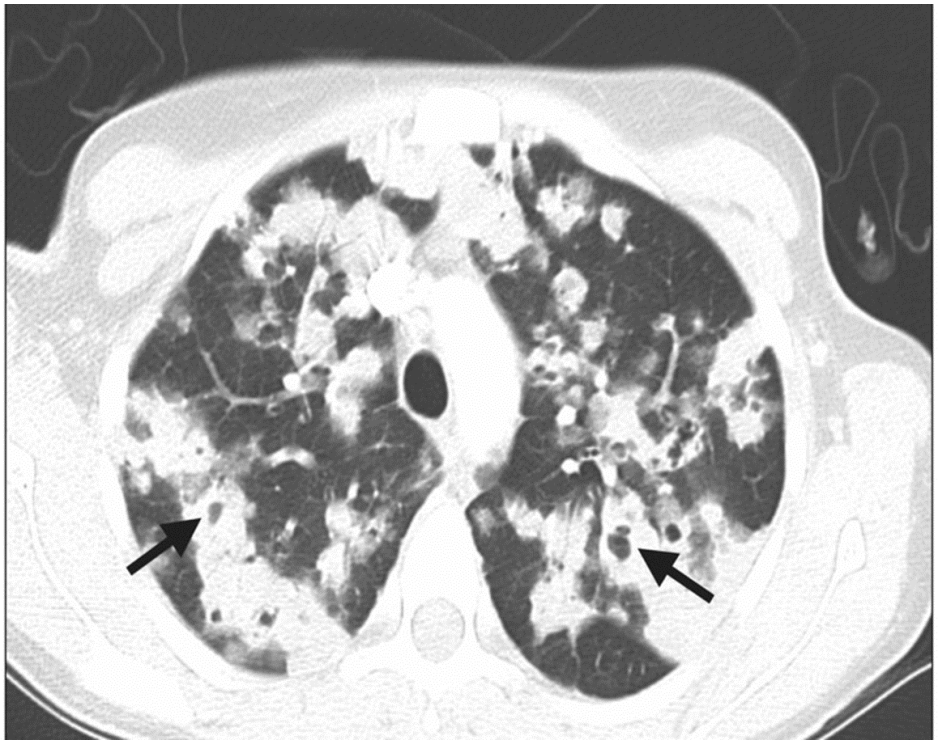
Case Study # 10



Map of the United States showing county of residence (lifetime) of naval recruits with positive histo-

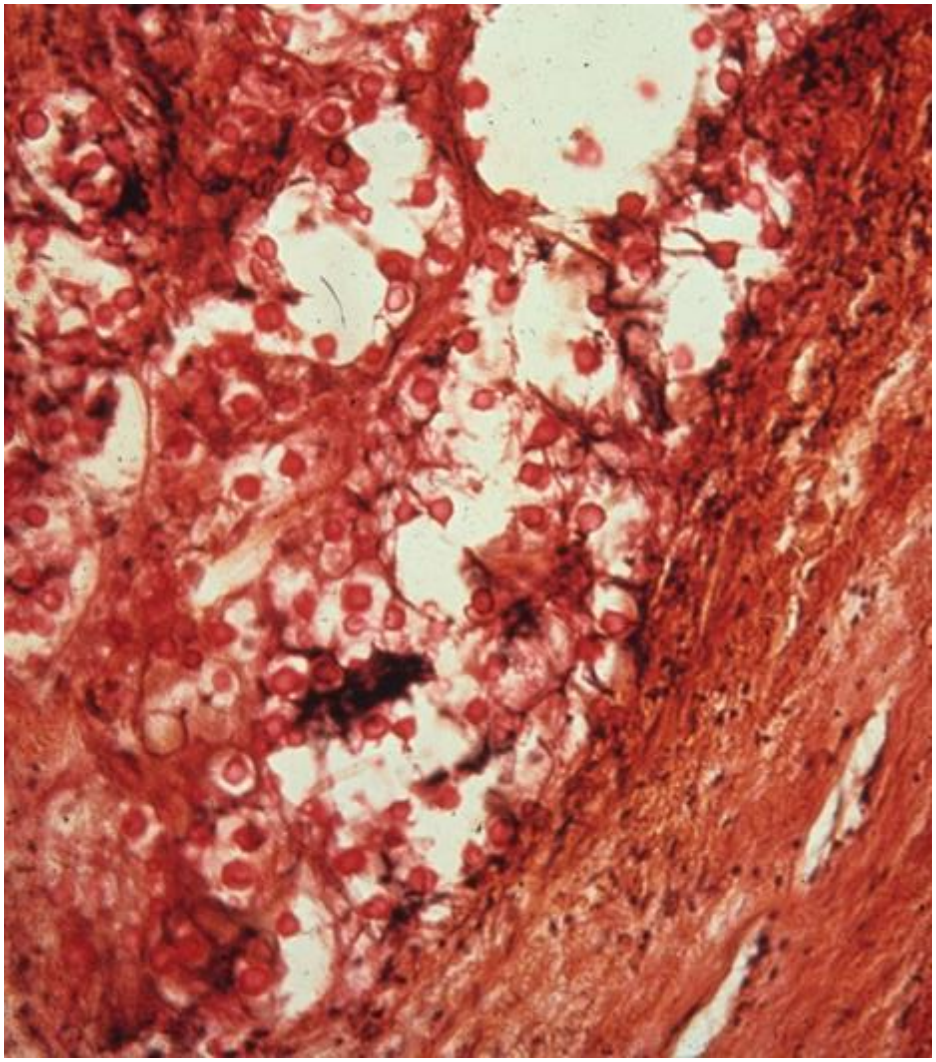
Case Study # 11

- 53 yo HIV infected patient who has been completely non-compliant with treatment
- Presents with pleuritic chest pain and severe dyspnea
- Has also had headache for past 3 weeks
- Chest CT shows multiple nodular lesions
- Patient undergoes emergency bronchoscopy

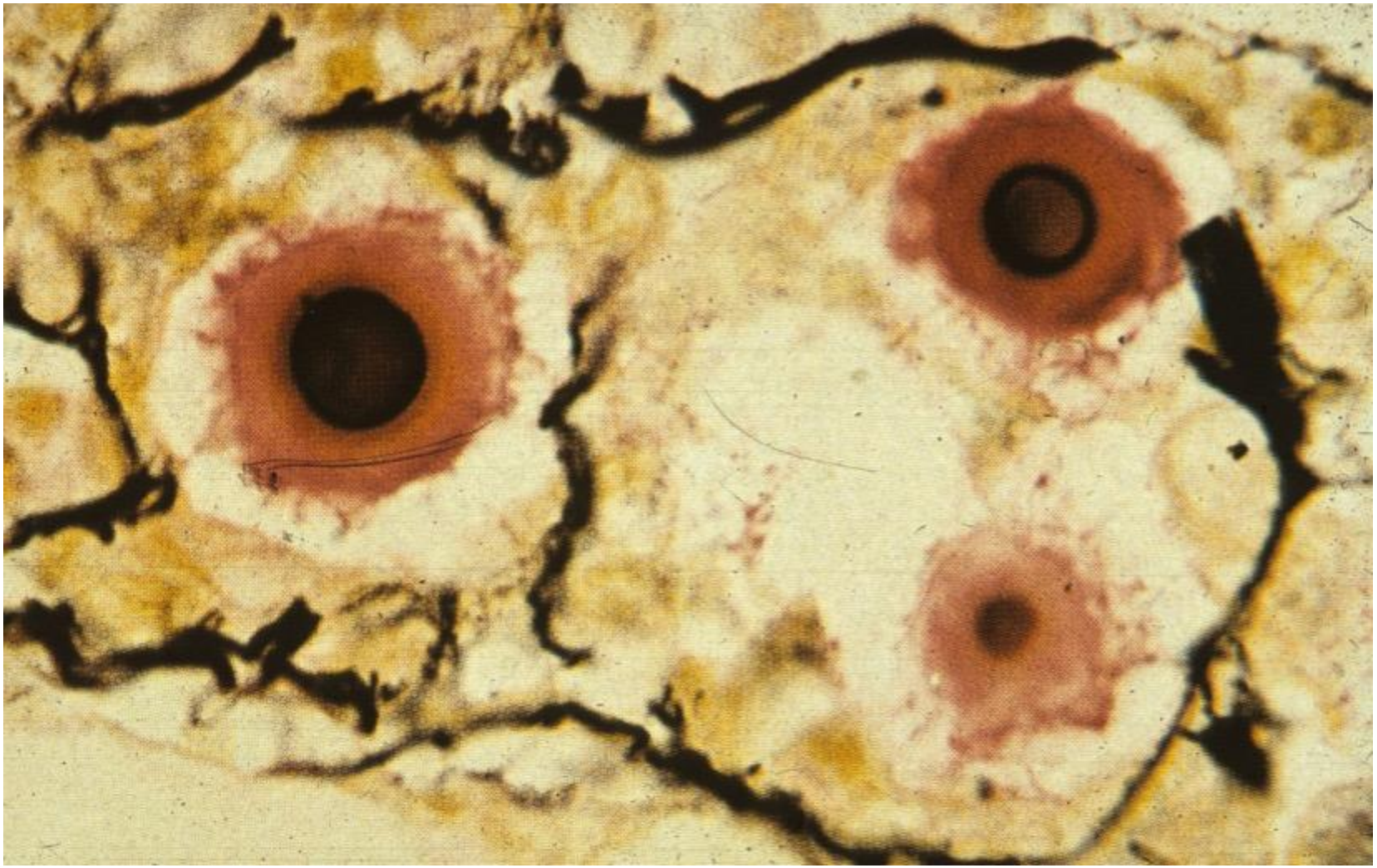


Case Study # 11

- Bronchoscopy is performed for diagnostic purposes.
- Results of the **mucicarmine** stain of the transbronchial biopsy is seen on the following slide.



High Power Mucicarmine Stain



Case Study # 11 - Answer

- Pulmonary cryptococcosis
- *Cryptococcus neoformans* or *C. gattii*
- The polysaccharide capsule stains with mucicarmine stain
- Can be seen easily on India Ink
- Treatment: Liposomal amphotericin B + 5-fluorocytosine (5-FC) x 2 weeks then long-term oral fluconazole
- This may be modified . . . Next slide . . .

The NEW ENGLAND JOURNAL of MEDICINE

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Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

J.N. Jarvis, D.S. Lawrence, D.B. Meya, E. Kagimu, J. Kasibante, E. Mpoza, M.K. Rutakingirwa, K. Ssebambulidde, L. Tugume, J. Rhein, D.R. Boulware, H.C. Mwandumba, M. Moyo, H. Mzinganjira, C. Kanyama, M.C. Hosseinipour, C. Chawinga, G. Meintjes, C. Schutz, K. Comins, A. Singh, C. Muzoora, S. Jjunju, E. Nuwagira, M. Mosepele, T. Leeme, K. Siamisang, C.E. Ndhlovu, A. Hlupeni, C. Mutata, E. van Widenfelt, T. Chen, D. Wang, W. Hope, T. Boyer-Chammard, A. Loyse, S.F. Molloy, N. Youssouf, O. Lortholary, D.G. Lalloo, S. Jaffar, and T.S. Harrison, for the Ambition Study Group*

This trial showed that a single high dose of liposomal amphotericin B given with flucytosine and fluconazole was noninferior to the current WHO recommended standard of care for cryptococcal meningitis and offers a practical treatment for the management for HIV-associated cryptococcal meningitis that is easier to administer and associated with fewer drug-related adverse effects. Continued efforts to ensure access to liposomal amphotericin B and flucytosine are needed to enable the implementation of this treatment.

Case Study # 12

- 52 year old woman presents with 5 week history of severe oral pain, inability to eat and 30-lb weight loss
- Past history of injection heroine use – shares needles with multiple people
- Oral exam on next slide

Diagnosis

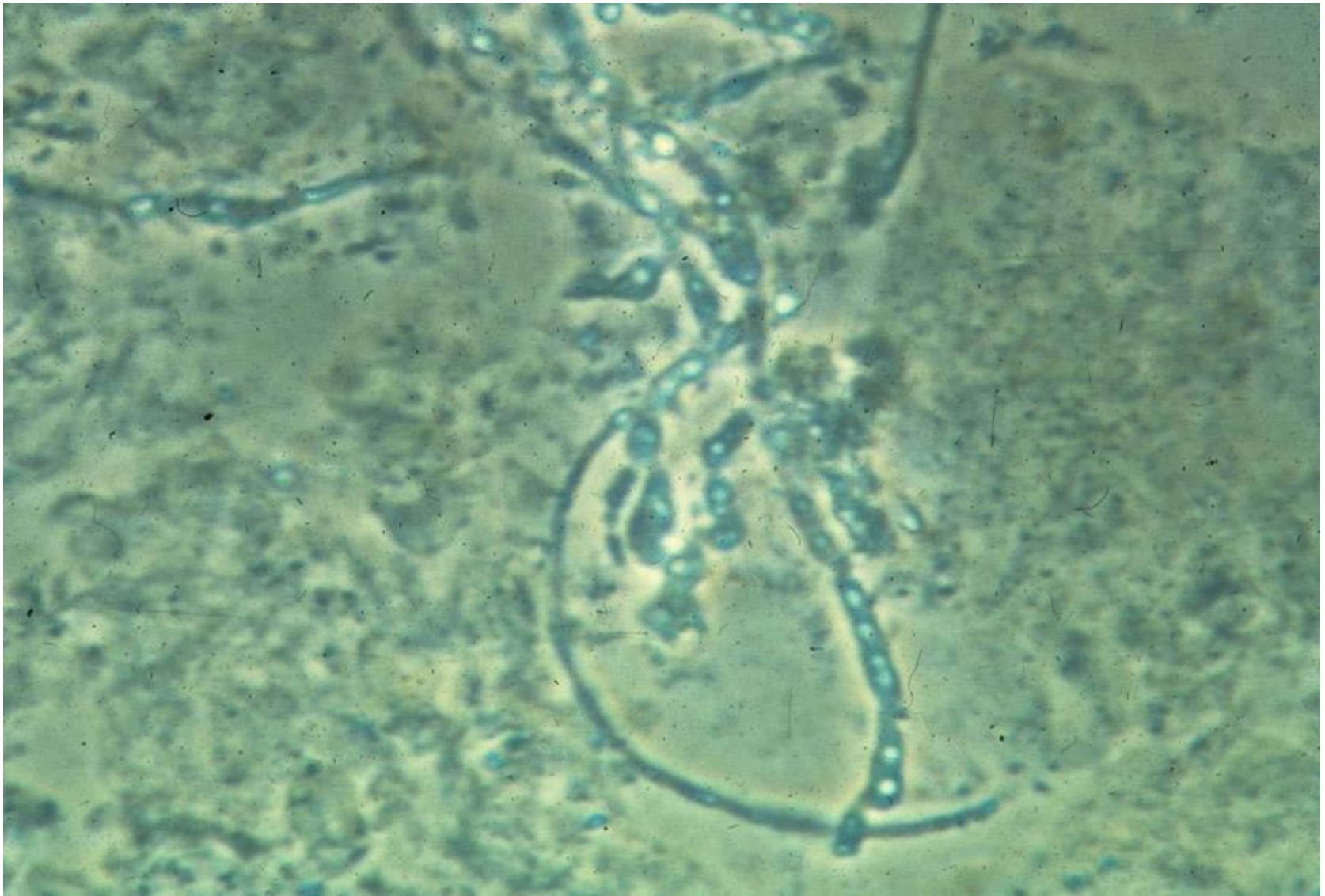
- Severe oral candidiasis as one of presenting manifestations of HIV/AIDS
- Always has esophageal candidiasis
- Therefore, topical therapy not effective
- Use high-dose fluconazole (400-800 mg) intravenously

Case Study # 12 - Alternate

- 59 year old woman with known COPD who has not sought medical care for years
- Seen by her physician who places her on inhaled oral corticosteroids
- 3 weeks later she returns to office with severe left and right buccal pain
- Oral exam on next slide

Case Study # 12

KOH preparation of scrapings



Case Study # 12 Alternate - Answer

- Oral candidiasis in a patient on inhaled corticosteroids
- She was not instructed on correct manner in which to inhale steroids into lung
- She basically sucked the spray into mouth when asked to show how she takes the medication

Case Study # 13

- 38 year old man in Cincinnati, OH who presents to his physician with skin lesion of about 2-3 months duration
  - Gradual growth from smaller size
  - No pain or any other symptoms
  - No other lesions elsewhere on body
- No other symptoms noted

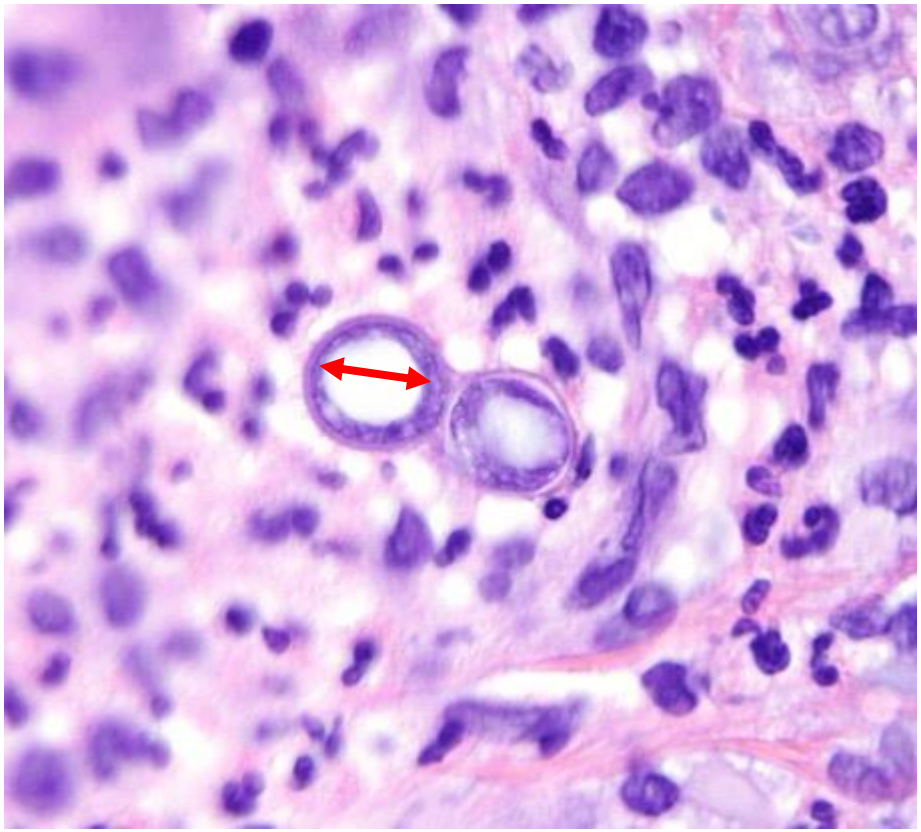
Case Study # 13

Case Study # 13

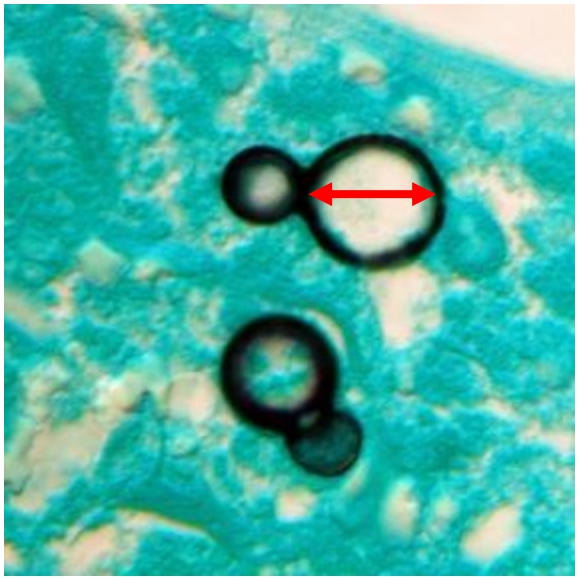
Case Study # 13

- Local biopsy is performed
- Following slide is the silver stain of the tissue at 400X power

Blastomycosis in Tissue
(12 µm diameter arrow)



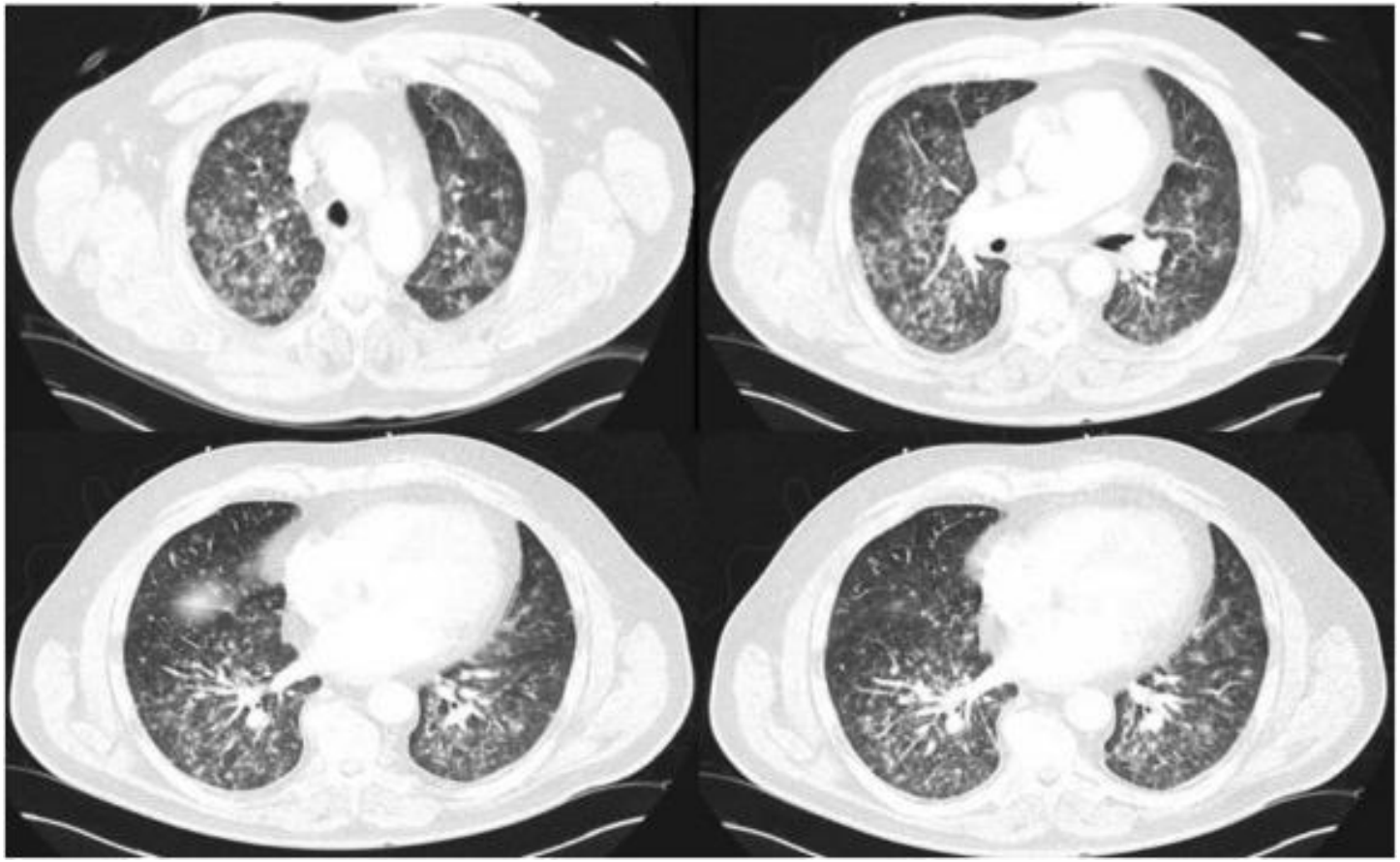
H & E Stain



Silver Stain

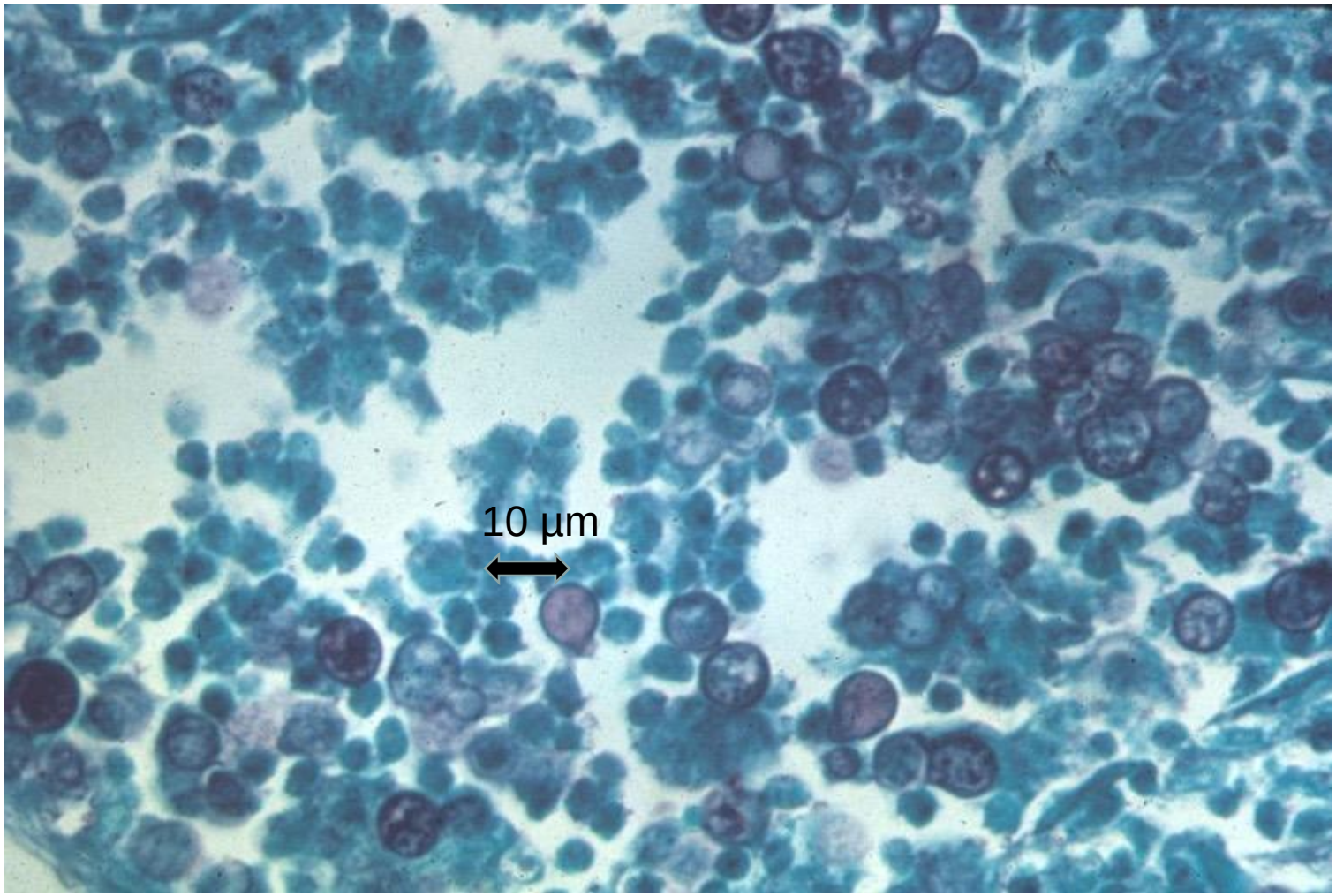
Blastomycosis on CT

Bilateral reticulonodular alveolar and interstitial opacities of pulmonary blastomycosis

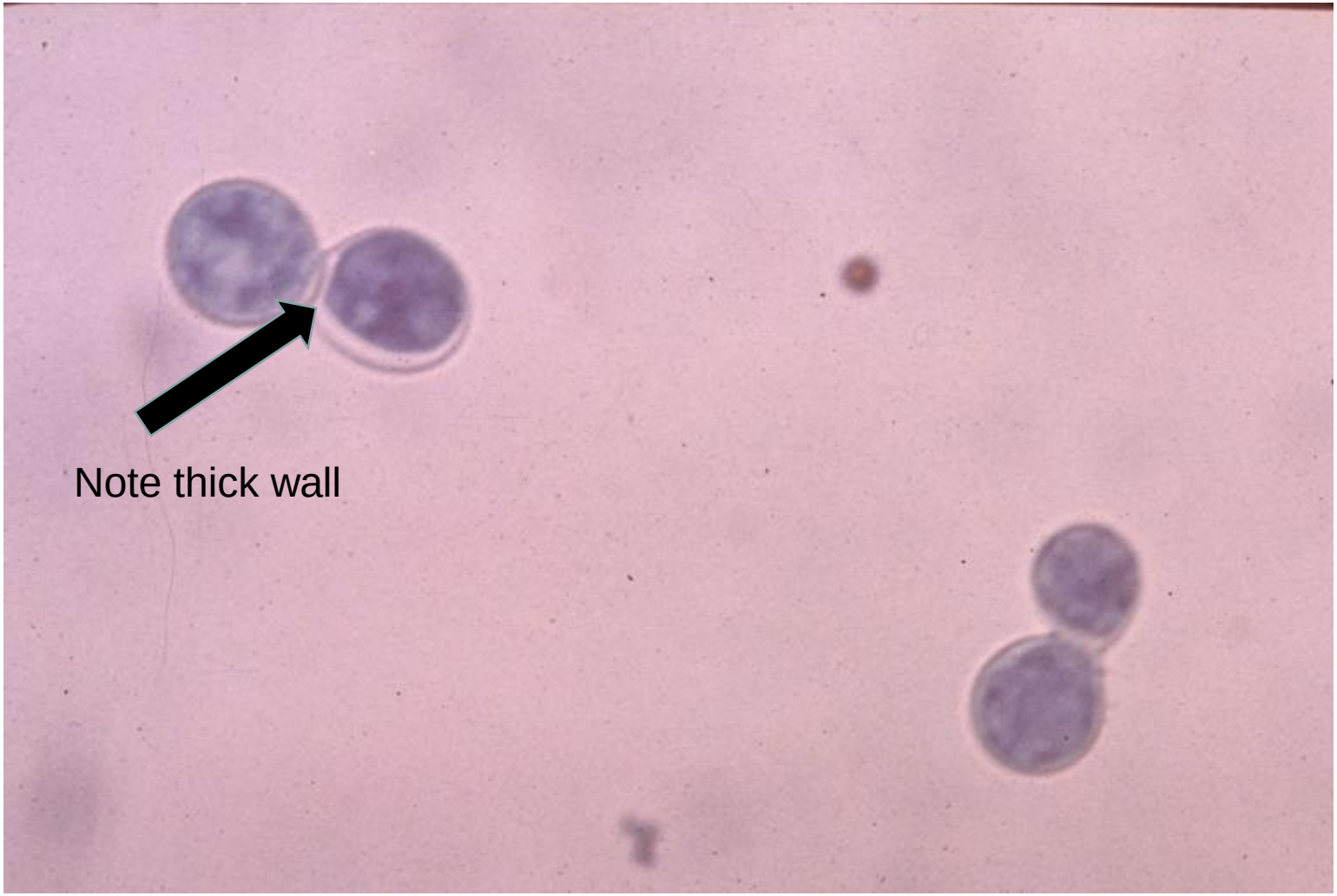


Case Study # 13

Silver Stain of Blasto in Lung Biopsy



Lactophenol Cotton Blue Image of Blastomycosis



Case Study # 13

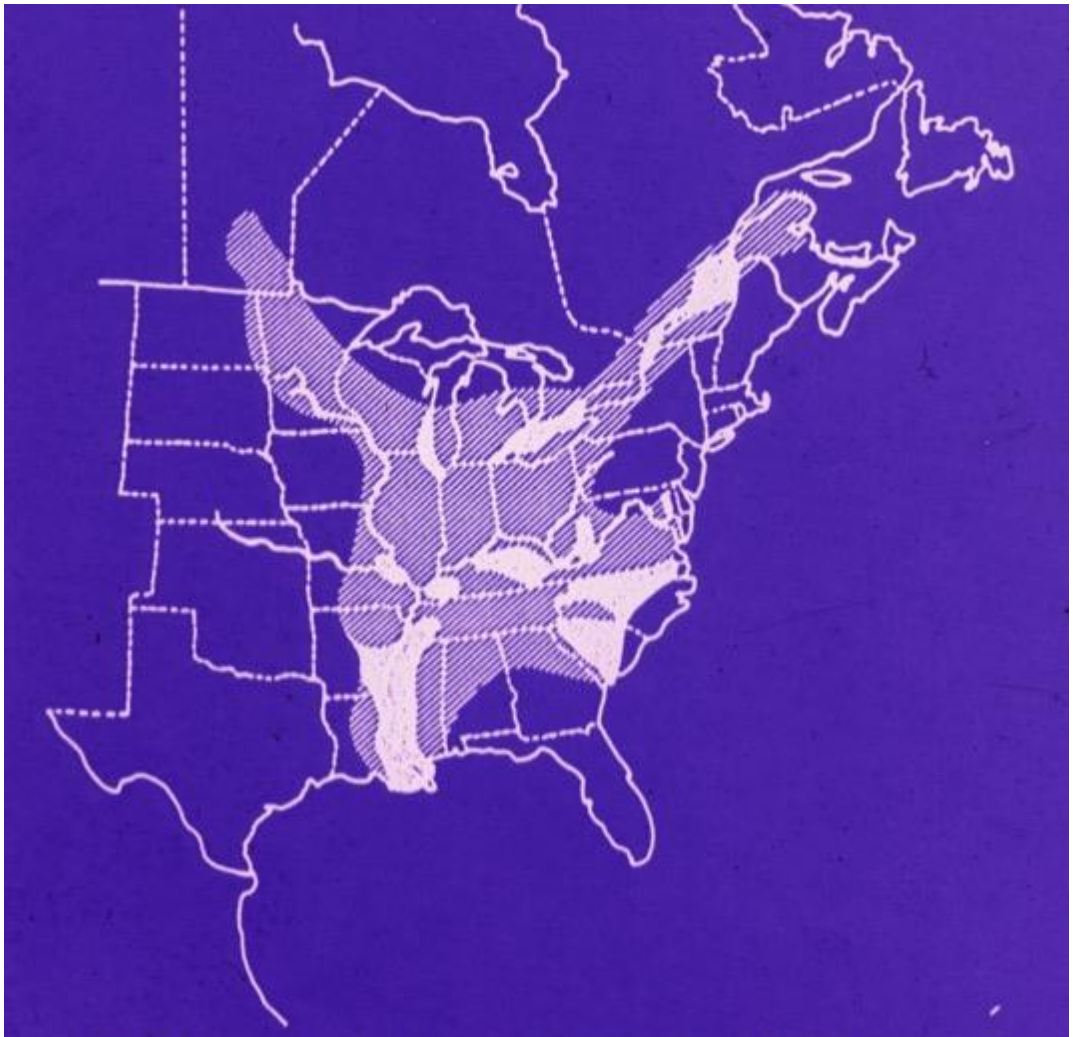


FIG. 17. Distribution of blastomycosis endemicity in North America. Reprinted from reference 54a with permission of the publisher.

Case Study # 13
Blasto Skin Lesion

Case Study # 13
Chronic Refractory Blasto

Case Study # 13
Chronic Refractory Blasto

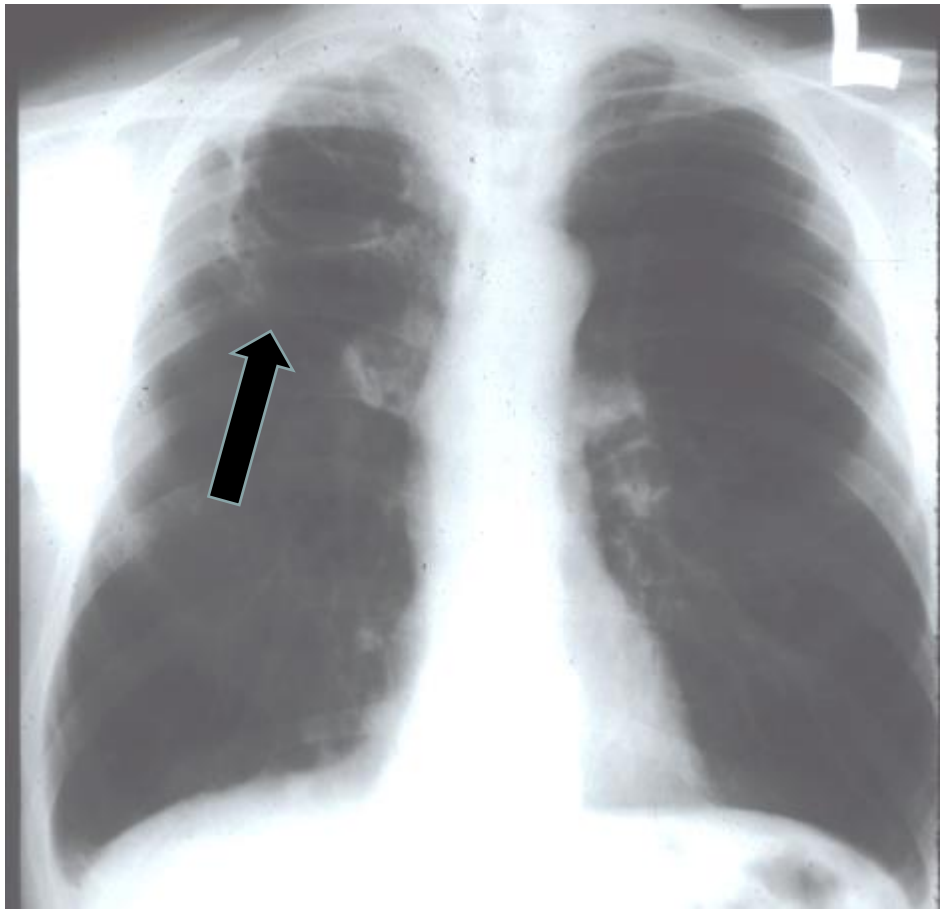
Case Study # 13 - Answer

- Blastomycosis
- Caused by *Blastomyces dermatitidis*
- Inhaled into lungs and can cause disease there and/or disseminated disease
- Frequently goes to skin, ergo its name: *dermatidis*

Case Study # 14

- 62 year old man who is a farmer from SE Michigan
- Presents to the hospital with:
  - low-grade fever
  - productive cough
  - hemoptysis
  - 30-pound weight loss over 6 months
  - right upper lobe cavitary lesion on CXR

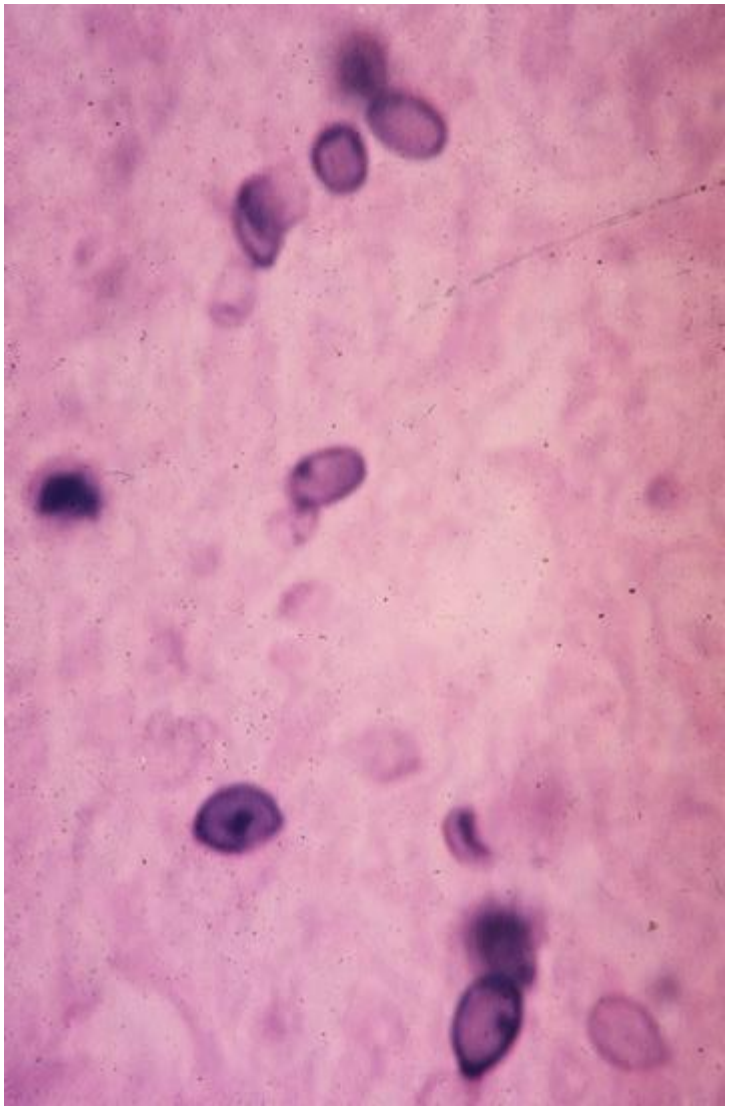
Case Study # 14
CXR ➔ Thin-Walled Cavity



Case Study # 13

Bronchoscopy Results

- AFB smear: negative
- MTb-PCR: negative
- H&E Stain shown
- Organisms are 2-3 μm in diameter



Case Study # 14 - Answer

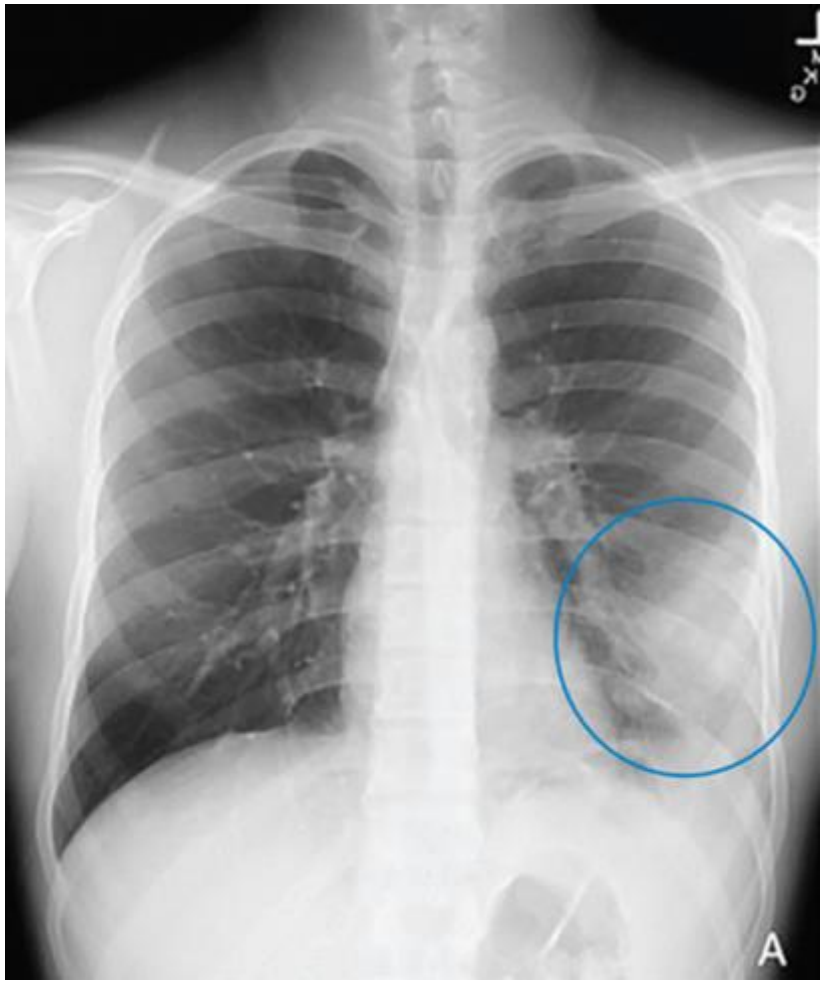
- Diagnosis: Chronic cavitary histoplasmosis
- Remember it as: “If it looks like TB, smells like TB, and tastes like TB, but all acid-fast studies and cultures are negative, think of chronic cavitary histo.”

Case Study # 14

FIG. 3. Distribution of histoplasmosis endemicity in the Americas. The highest incidences are in the finely stippled areas of North and Central America. Reprinted from reference 54a with permission of the publisher.

Case Study # 15

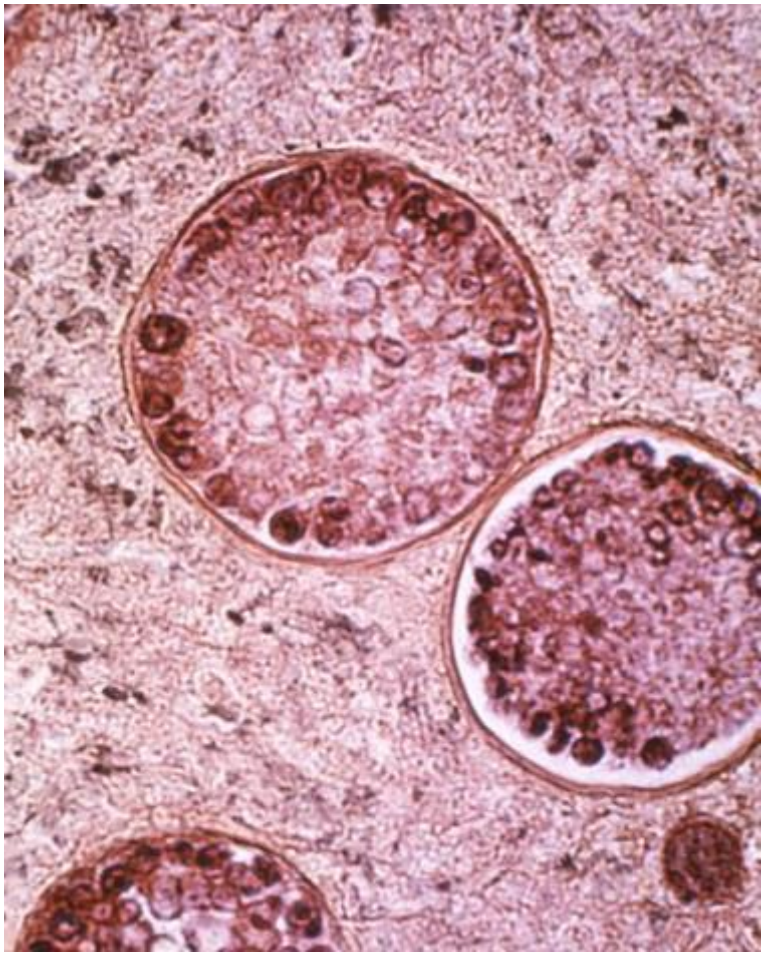
- 55 year old man who returns to Ohio from trip the spending summer in Arizona
- He had just retired and was bored so he volunteered at Philmont Scout Ranch in Cimarron, NM for 6 weeks
- 2 weeks after returning, he noted onset of:
  - Dyspnea
  - Dry, non-productive cough
  - Left lower pleuritic chest pain



Case Study # 15

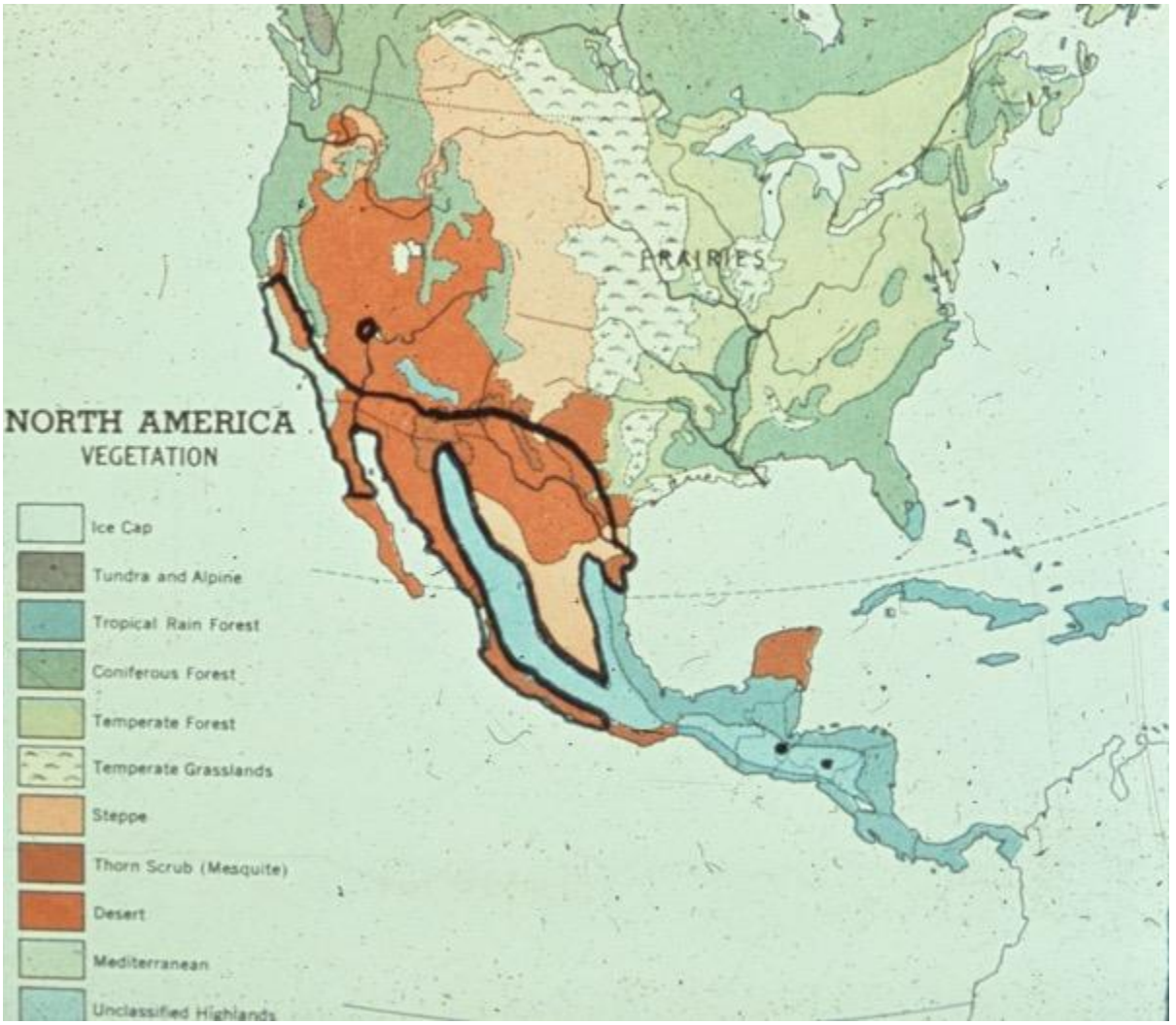
- Patient admitted to the hospital
- Bronchoscopy performed and the following slide is PAS stain of the transbronchial biopsy:

Spherule diameter = 20-80 µm;
Endospore diameter = 2-5 µm



Case Study # 15

Case Study # 15



Case Study # 15

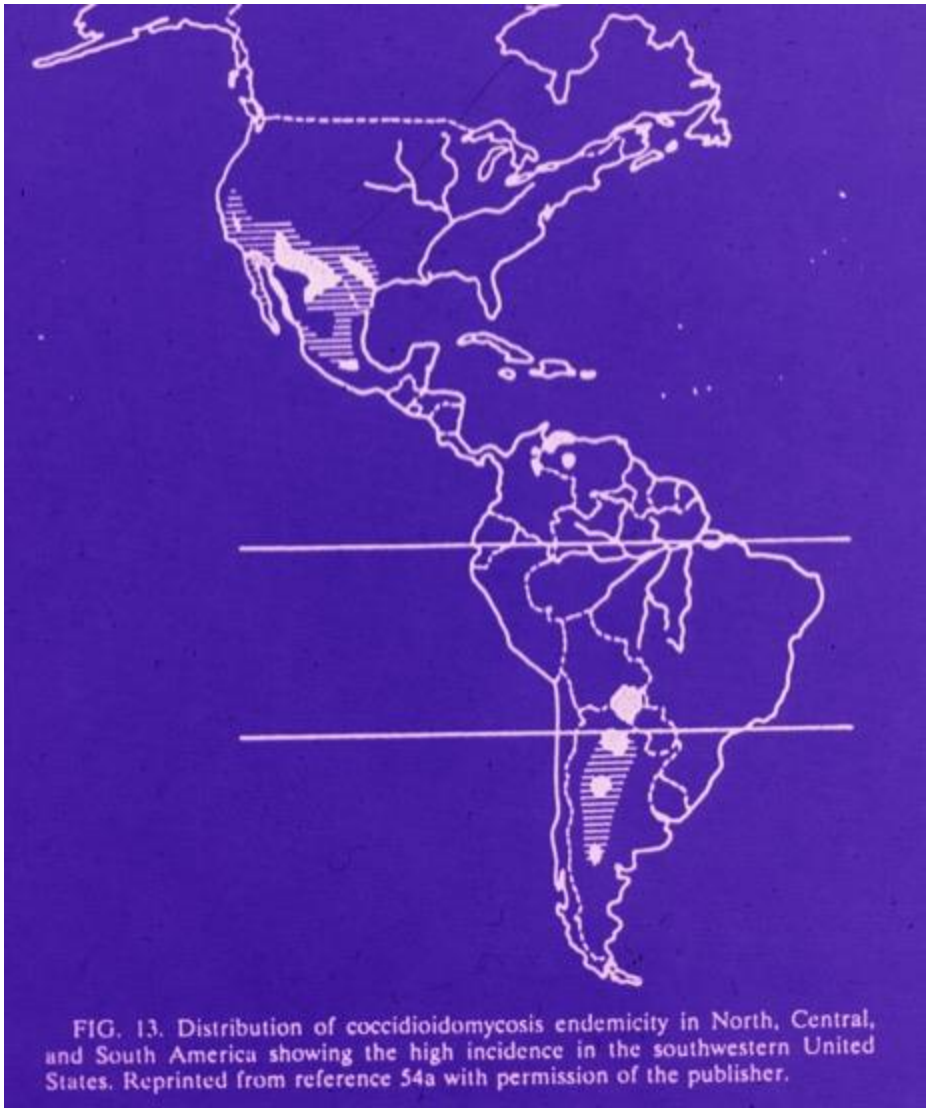
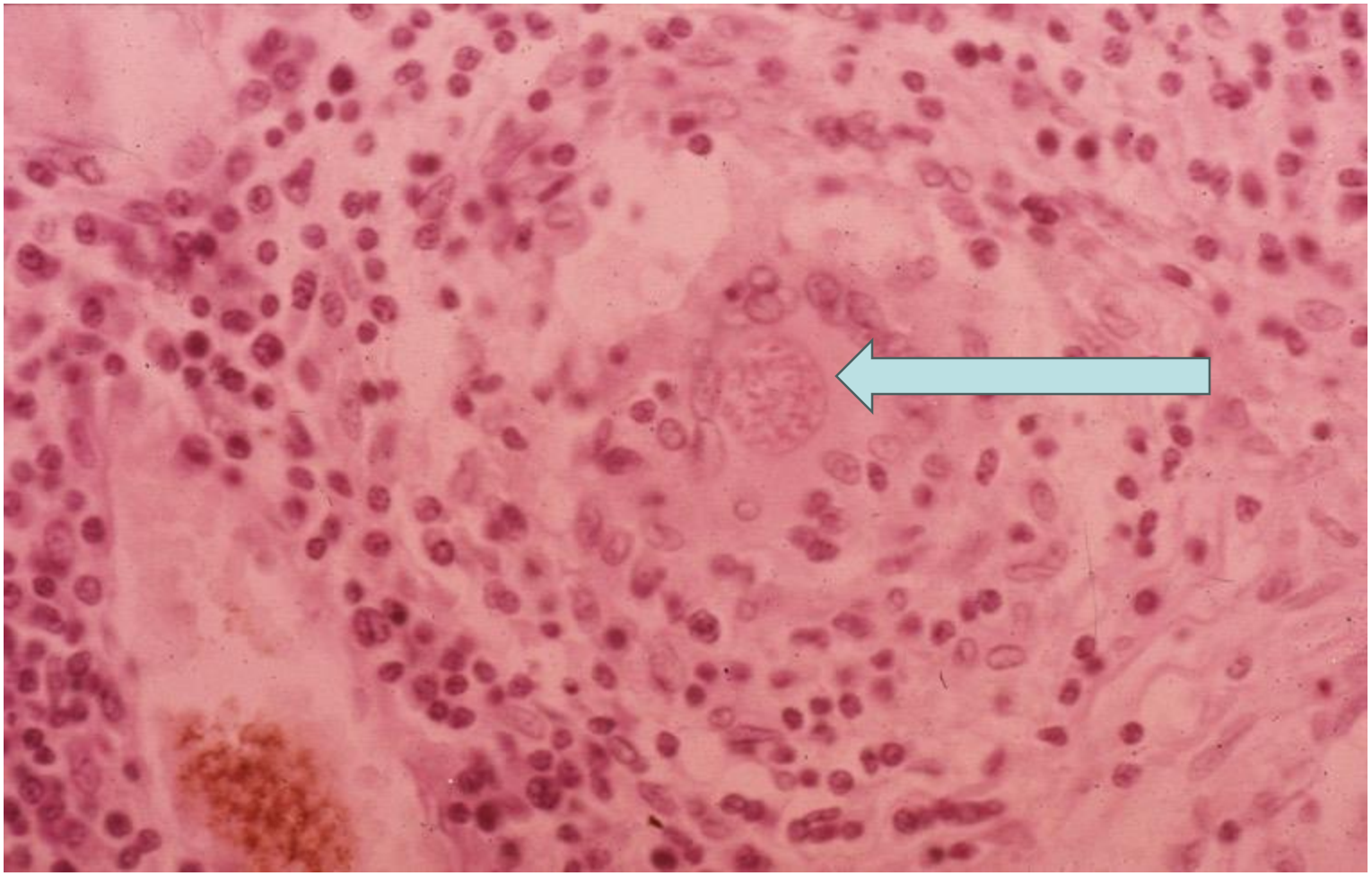


FIG. 13. Distribution of coccidioidomycosis endemicity in North, Central, and South America showing the high incidence in the southwestern United States. Reprinted from reference 54a with permission of the publisher.

Case Study # 15
Most Feared Complication: CNS Disease



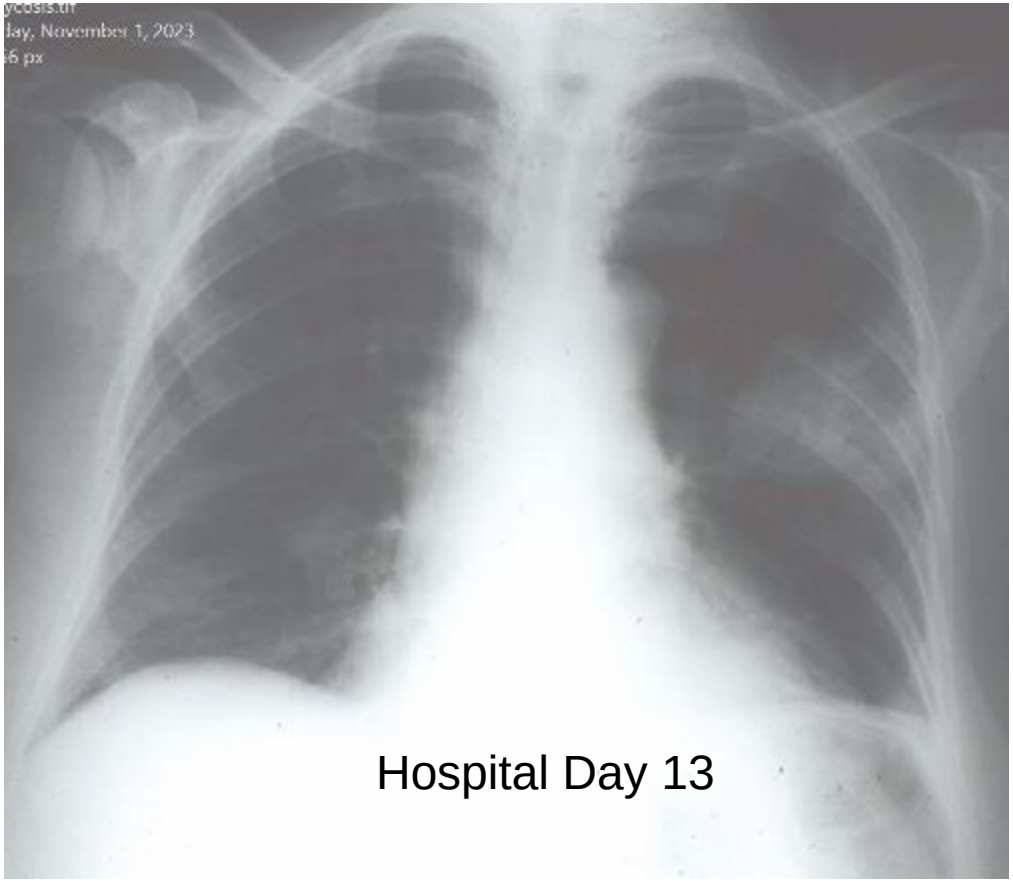
Arrow pointing to a spherule inside a multi-nucleated giant cell

Coccidioidomycosis - Treatment

- Fluconazole
- Itraconazole
- Voriconazole
- Intra-thecal amphotericin B for severe CNS disease

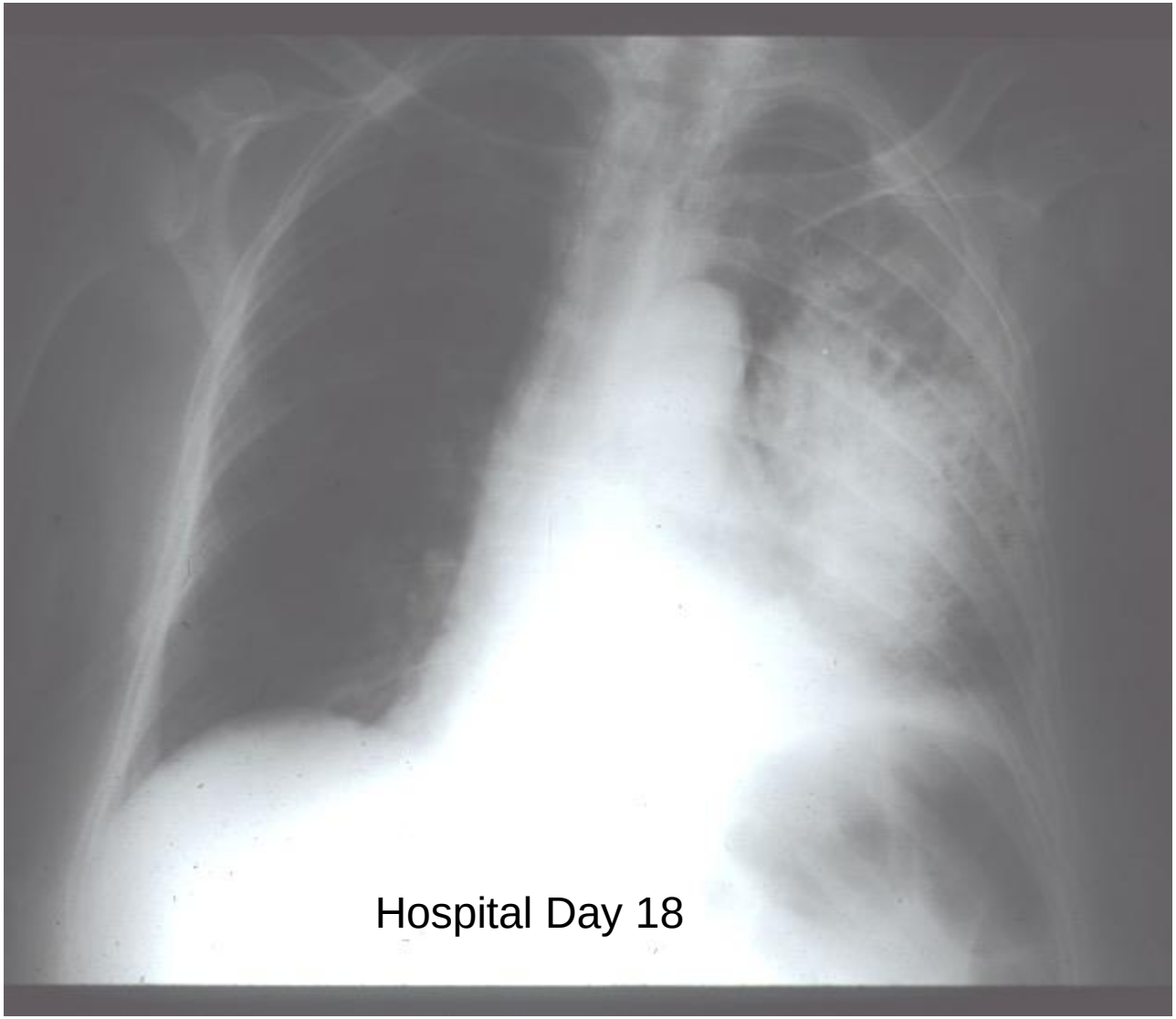
Case Study # 16

- Patient with AML s/p chemotherapy
- Has been on broad-spectrum antimicrobial therapy (Cefepime + Vancomycin) for neutropenic fever for 13 days
- On Day 13, he develops new fever, chills, pleuritic chest pain and hemoptysis with persistent neutropenia (ANC < 20)

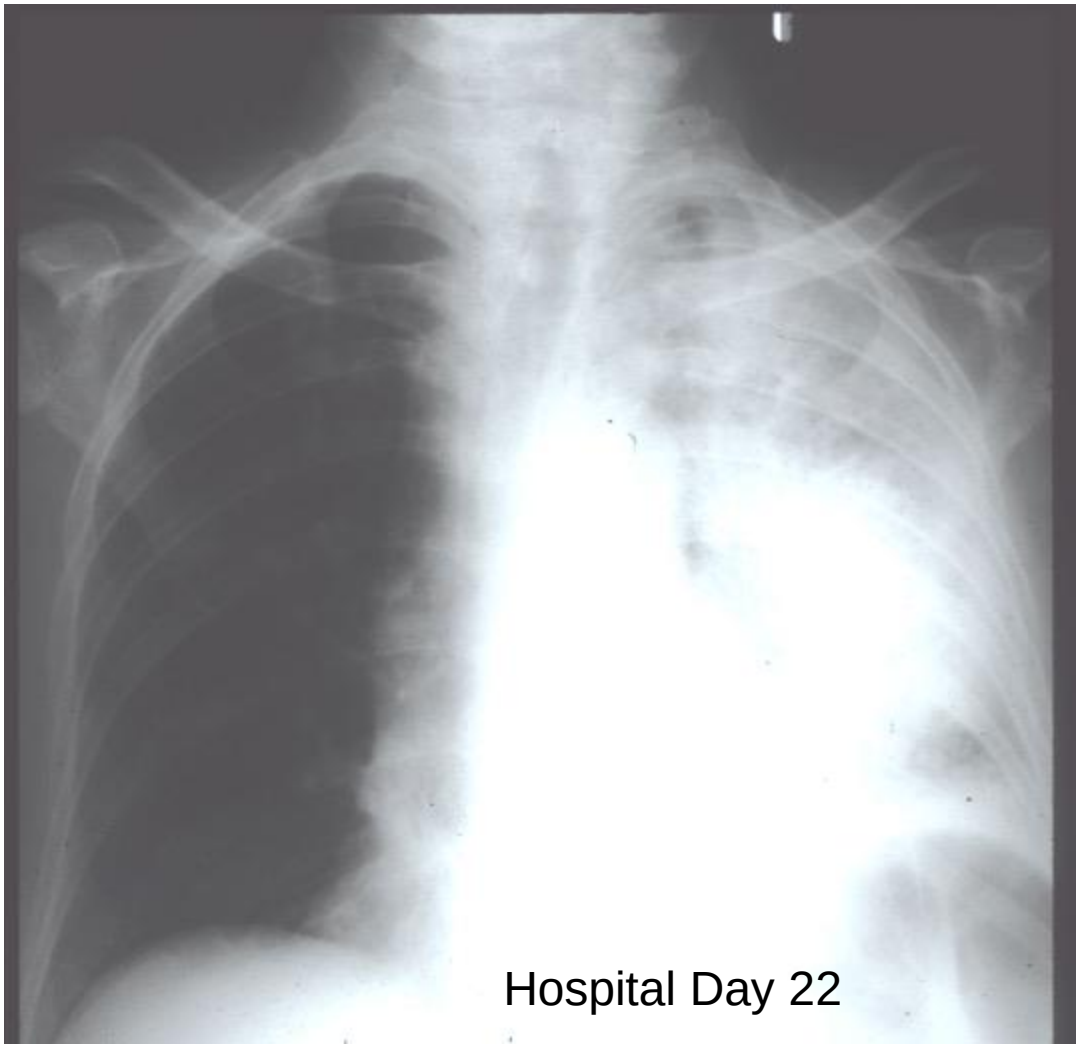


Hospital Day 13

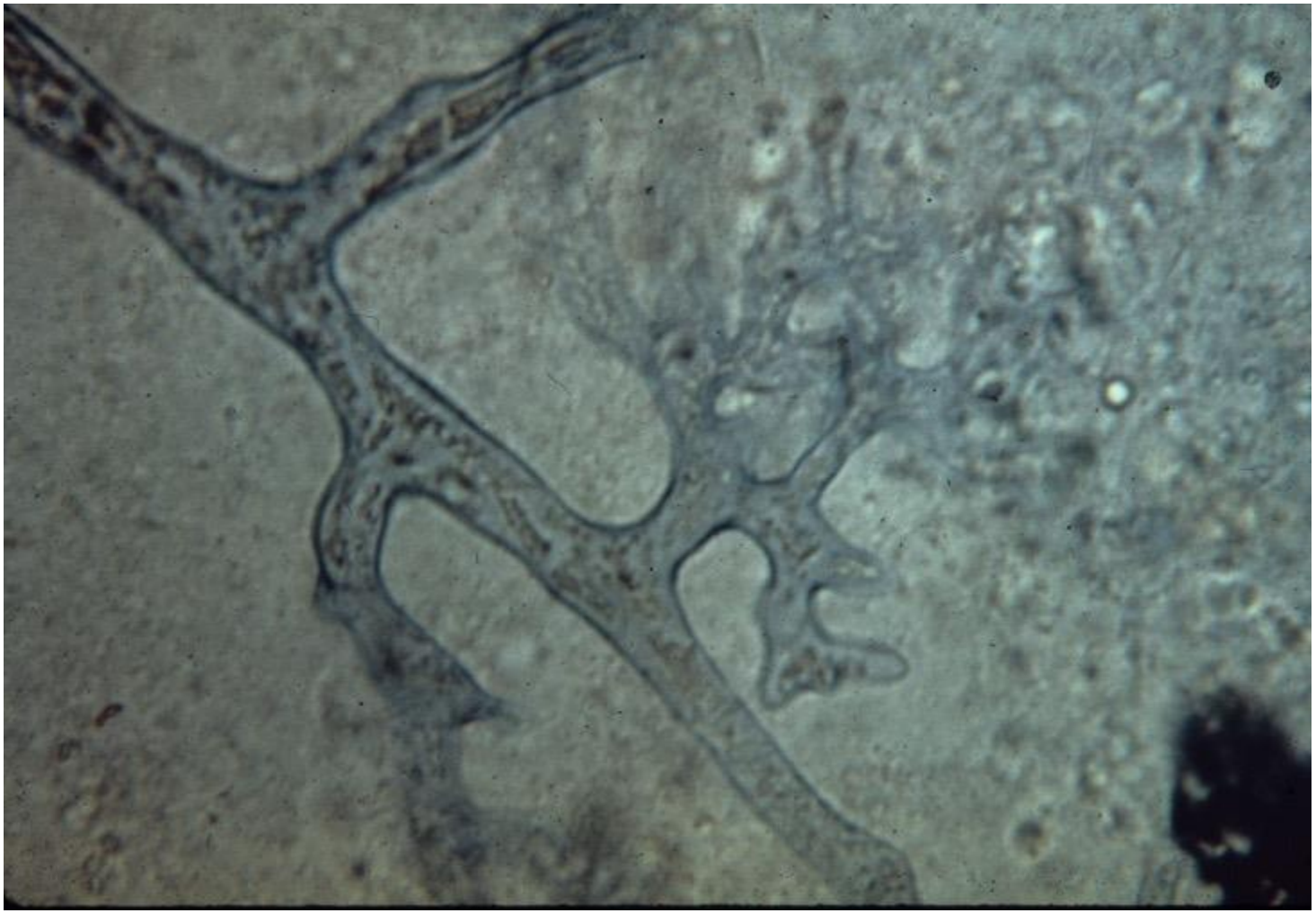
Case Study # 16



Case Study # 16



Case Study # 16
Lung Tissue from Autopsy



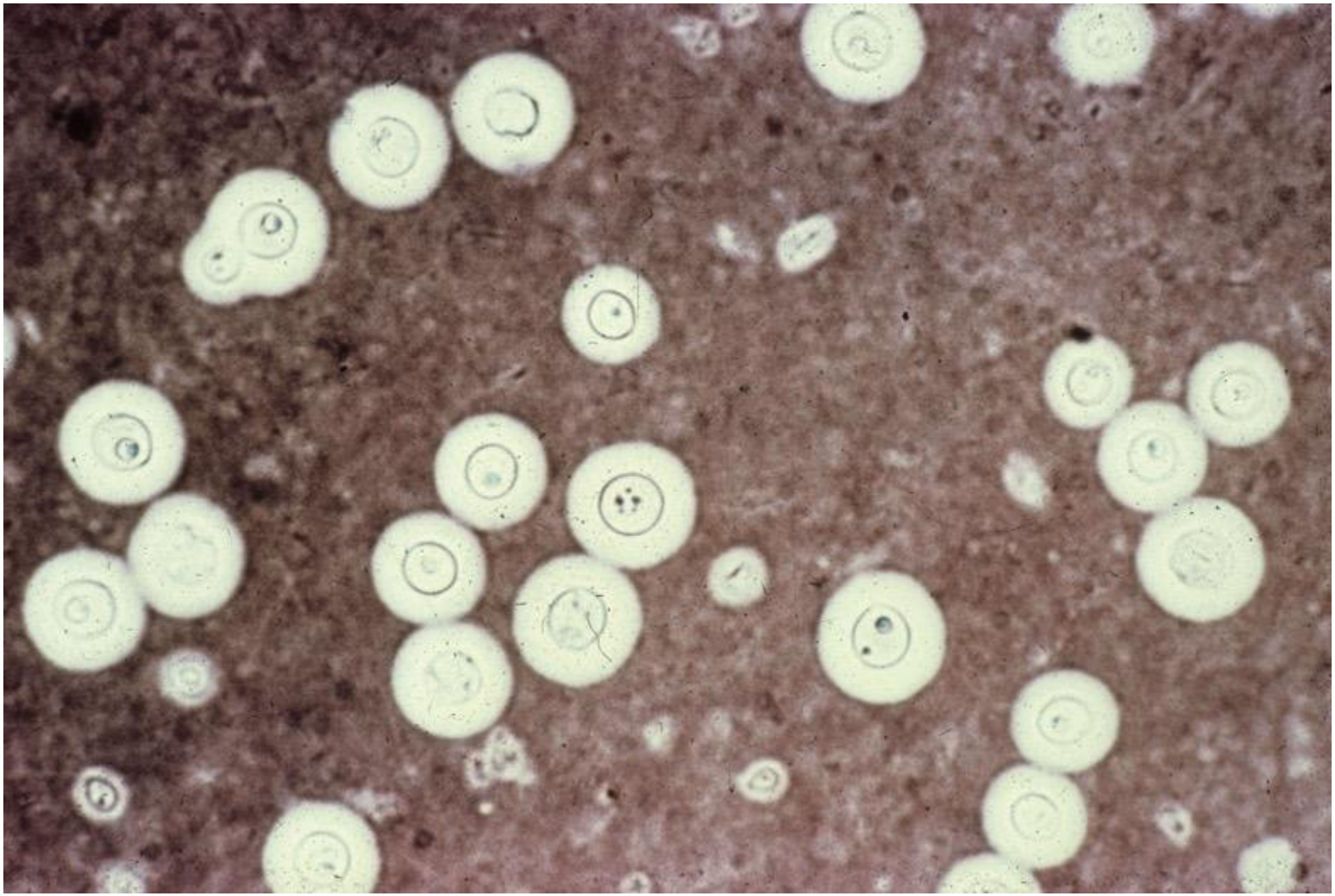
Case Study # 16 - Answer

- Acute invasive mucormycosis causing pulmonary infarct by vasculoinvasive characteristic of this group of fungi
  - *Mucor*
  - *Absidia (Lichthiemia)*
  - *Rhizopus*
  - Others

Case Study # 17 A

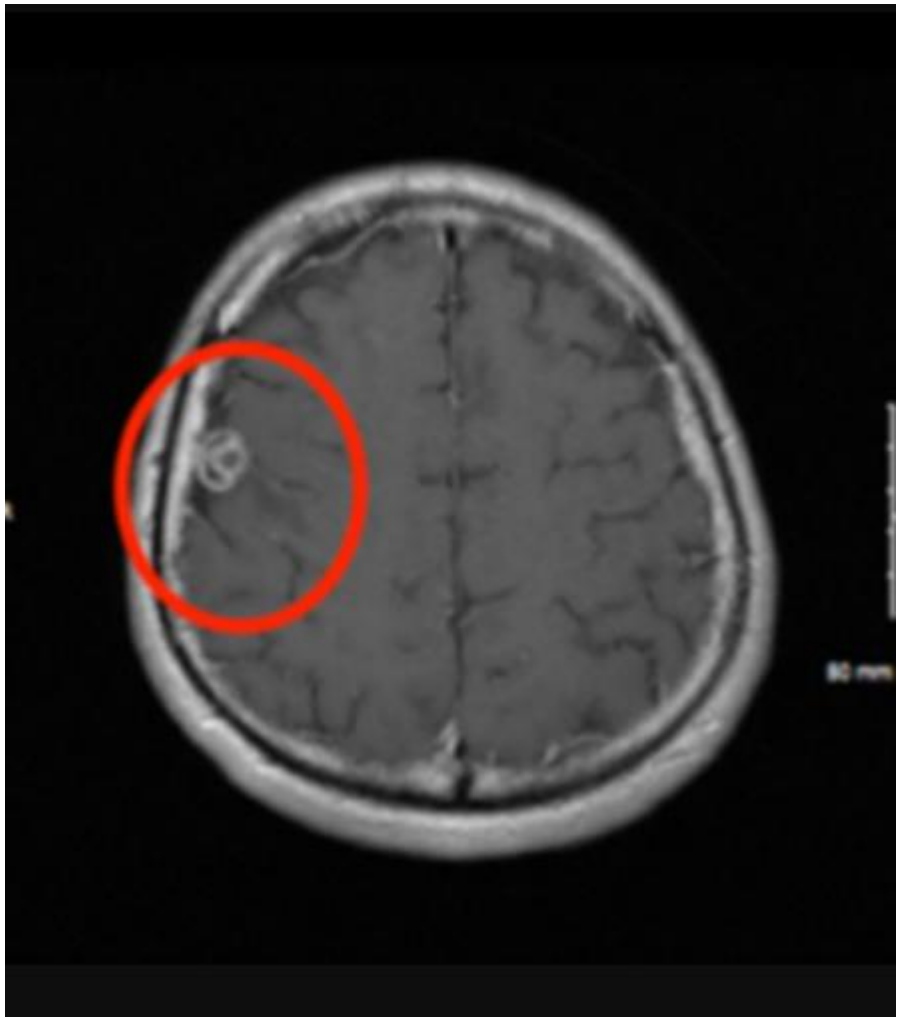
- 23 year old patient with known HIV disease
- New onset of headache during past week
- Seen in ED and after CT scan is negative, an LP is done
- India ink preparation is shown on next slide

Case Study # 17 A



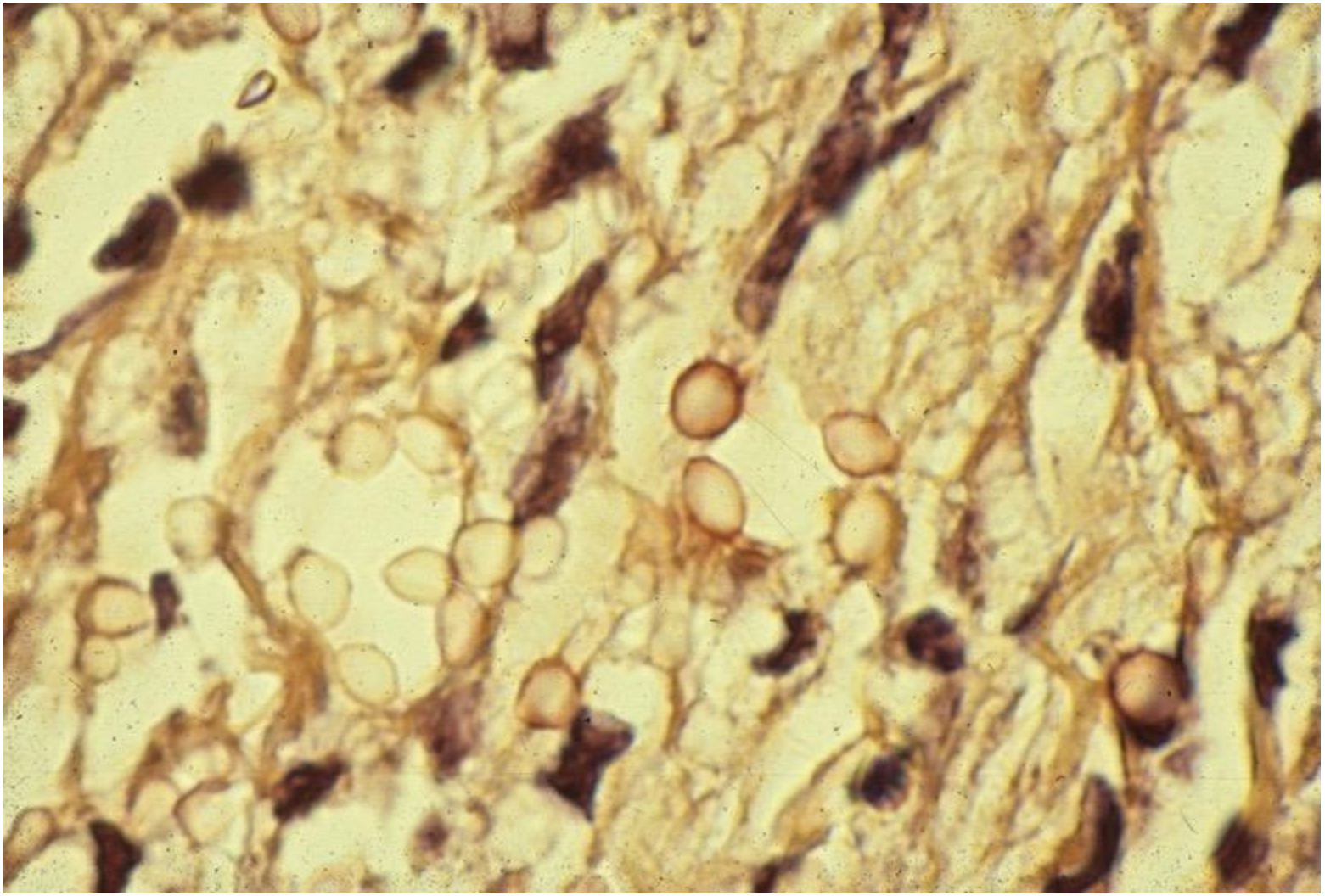
Case # 17 B

- 39 y.o. man presenting with
  - Headache
  - Numbness of left upper lip
  - Difficulty with word finding
- HIV-negative
- No other illnesses
- Brain biopsy done



Case Study # 17 B

Mucicarmine stain of brain bx



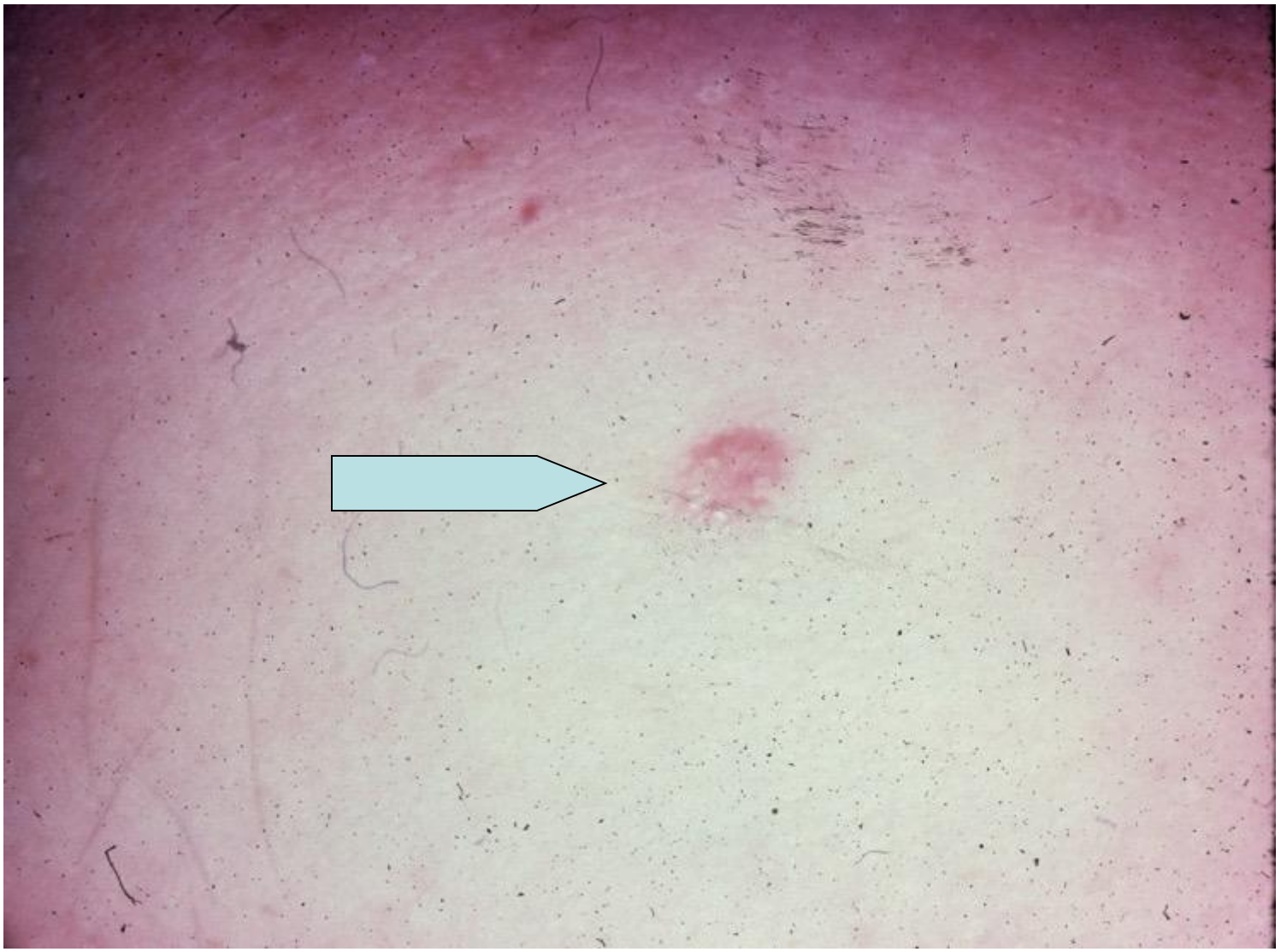
Case Study # 17 - Answer

- 17 A slide is India ink prep showing *Cryptococcus neoformans*
- 17 B slide shows mucicarmine stain of brain biopsy in patient B with “cryptococcoma” – mucicarmine stains cryptococcal capsule.

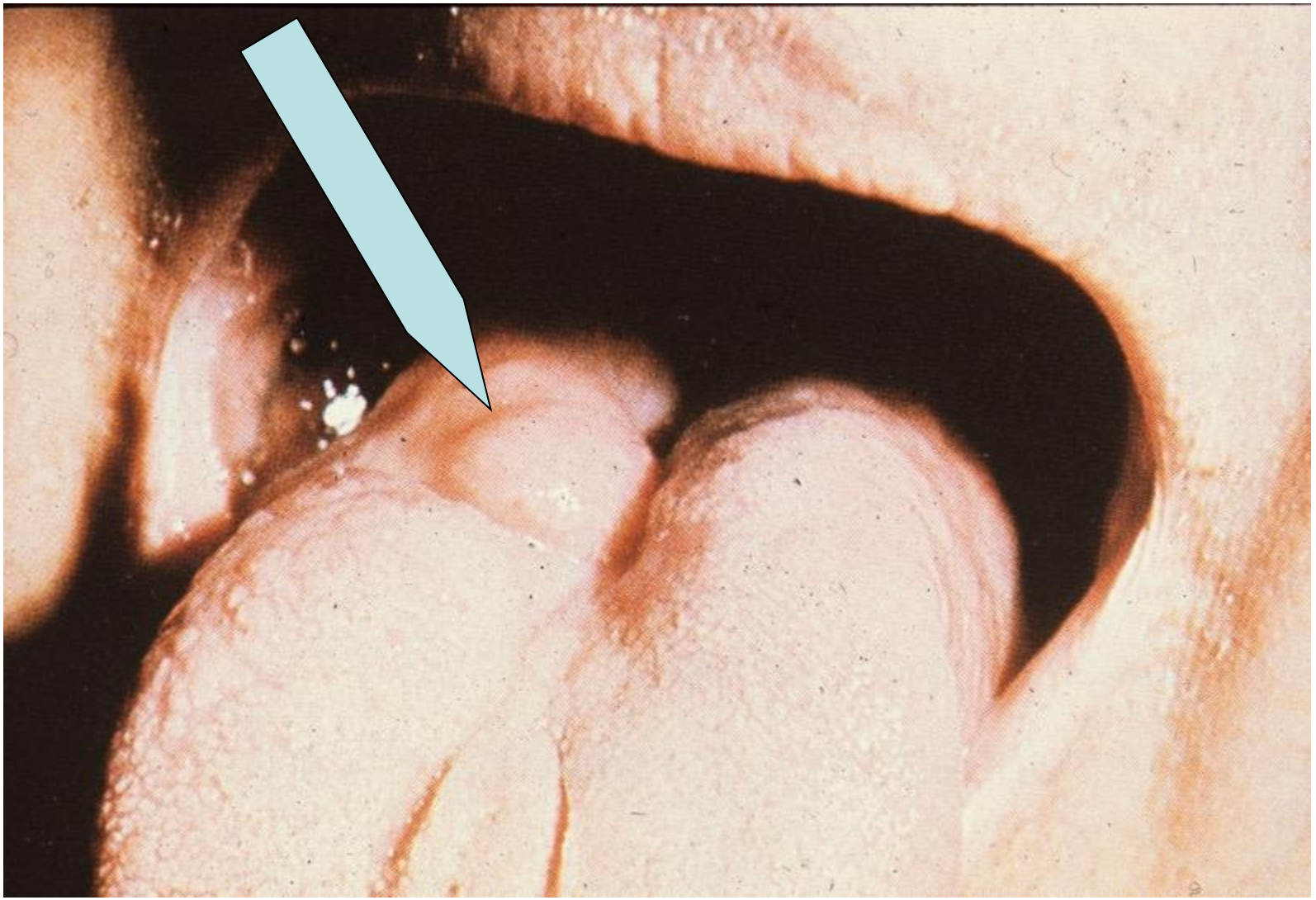
Case Study # 18

- All of following slides are manifestations of **disseminated Histoplasmosis** in various patients

Case Study # 18



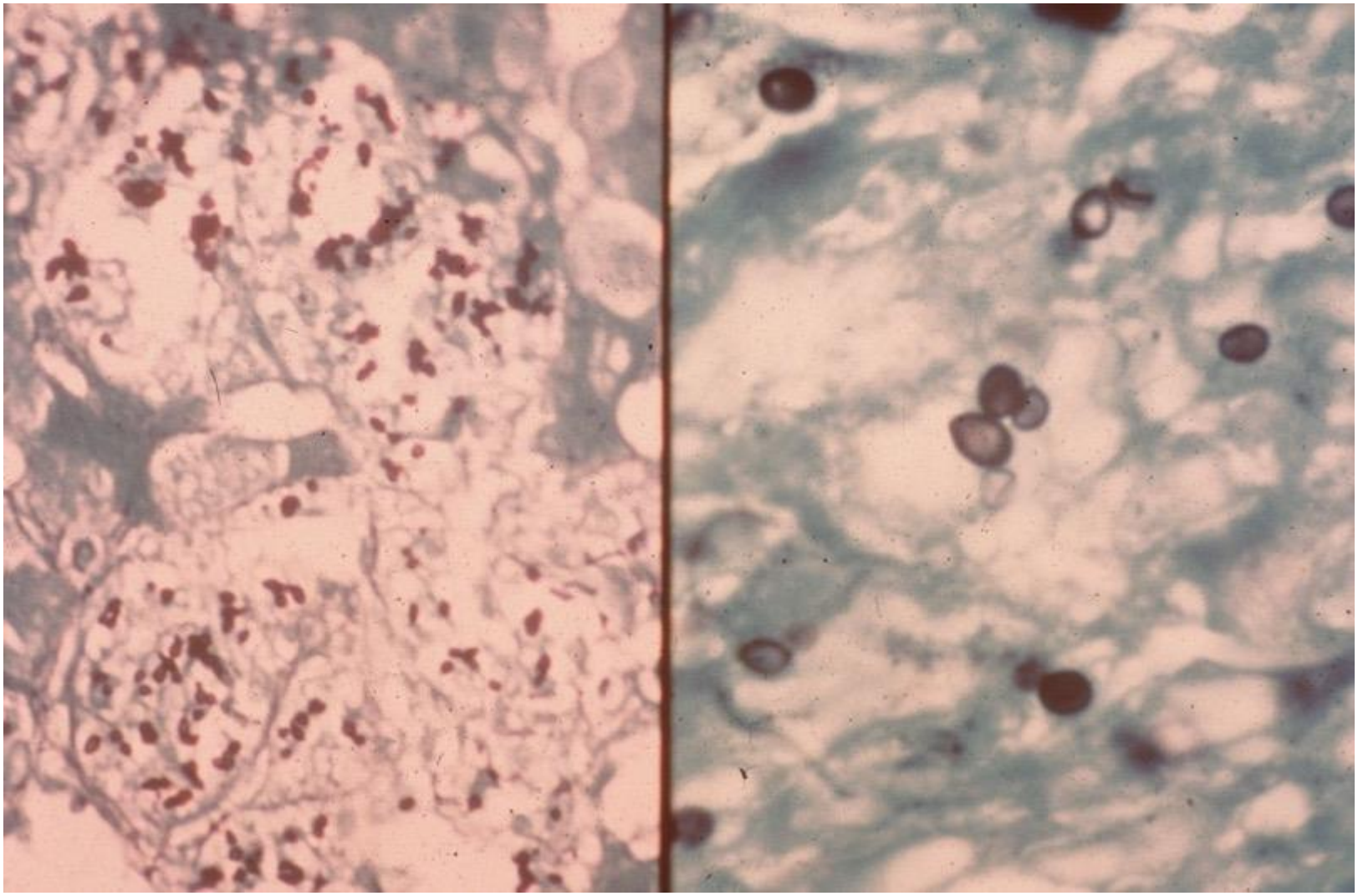
Case Study # 18



Case Study # 18

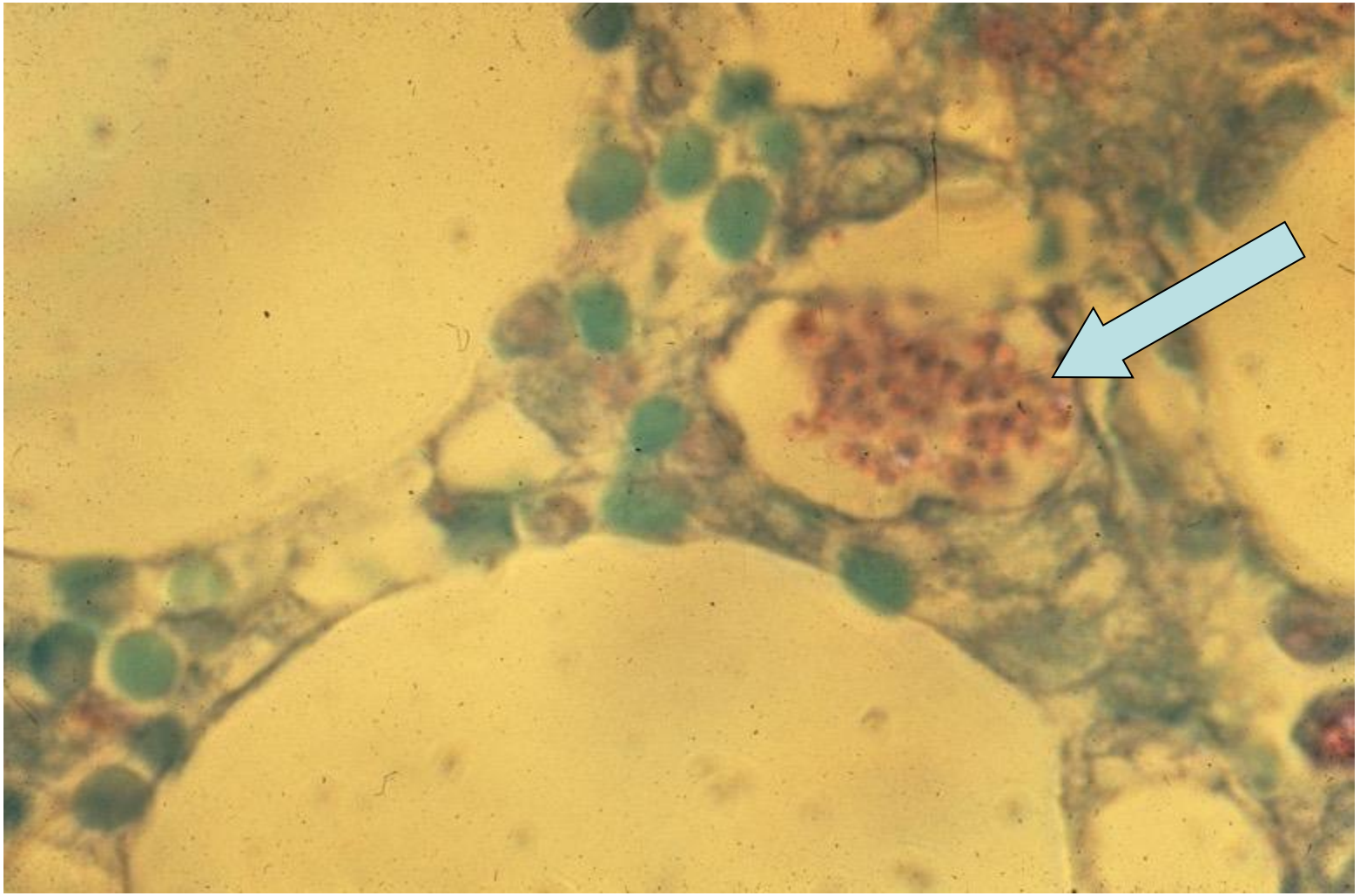
Silver stain of liver biopsy

(400X) (1000X)



Case Study # 18

Bone Marrow Bx – 400x Power



Case Study # 18 - Answer

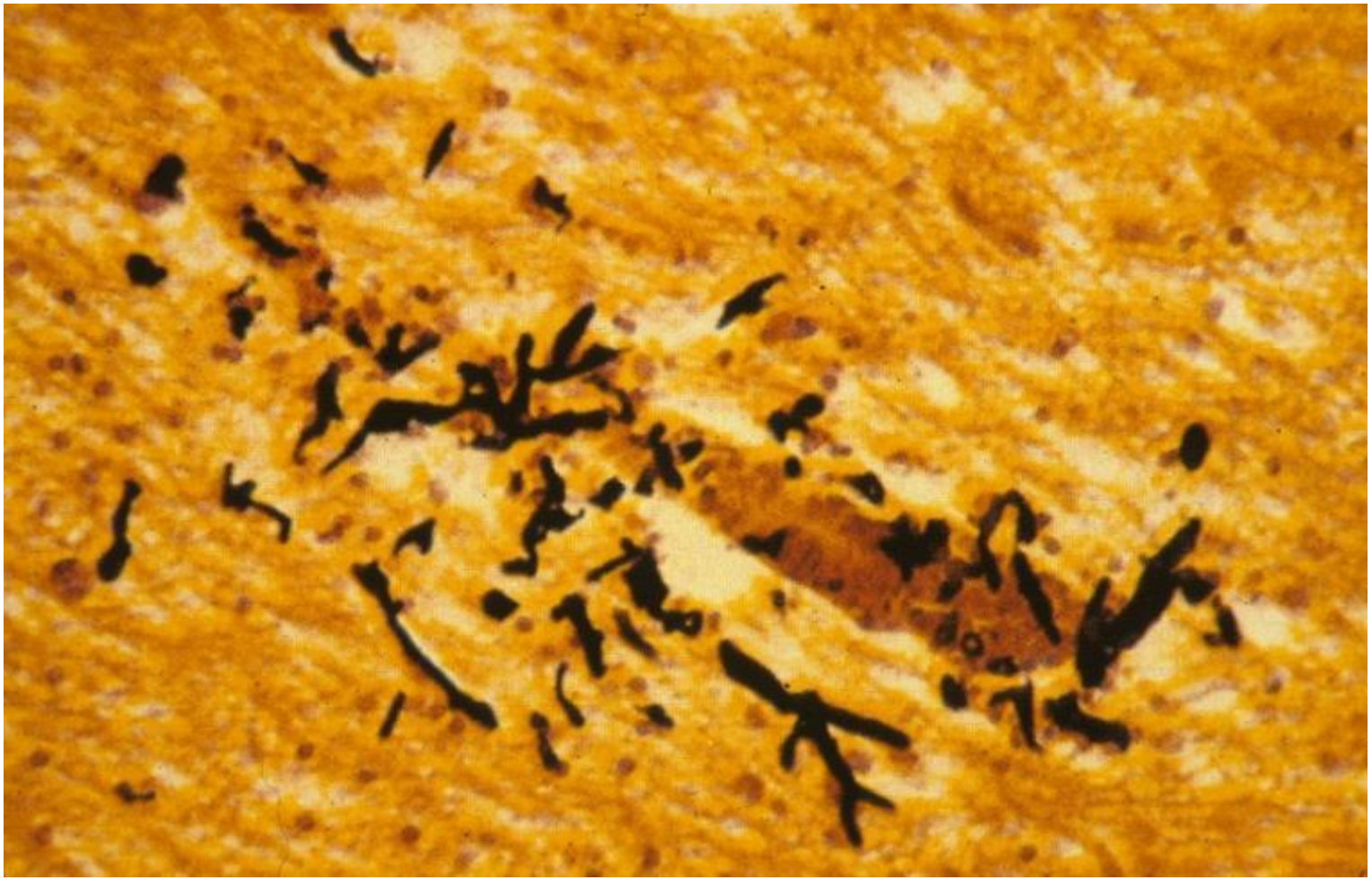
- Skin and tongue changes of disseminated histoplasmosis in an alcoholic patient with cirrhosis and ascites
- GMS stain of histoplasmosis in liver biopsy in a patient with disseminated histoplasmosis
- Histo bodies in reticuloendothelial areas of bone marrow in patient with disseminated histoplasmosis

Case Study # 19 A

- 9 year old child with ALL and severe neutropenia on antibiotic therapy
- Overnight develops facial lesion as seen on next slide

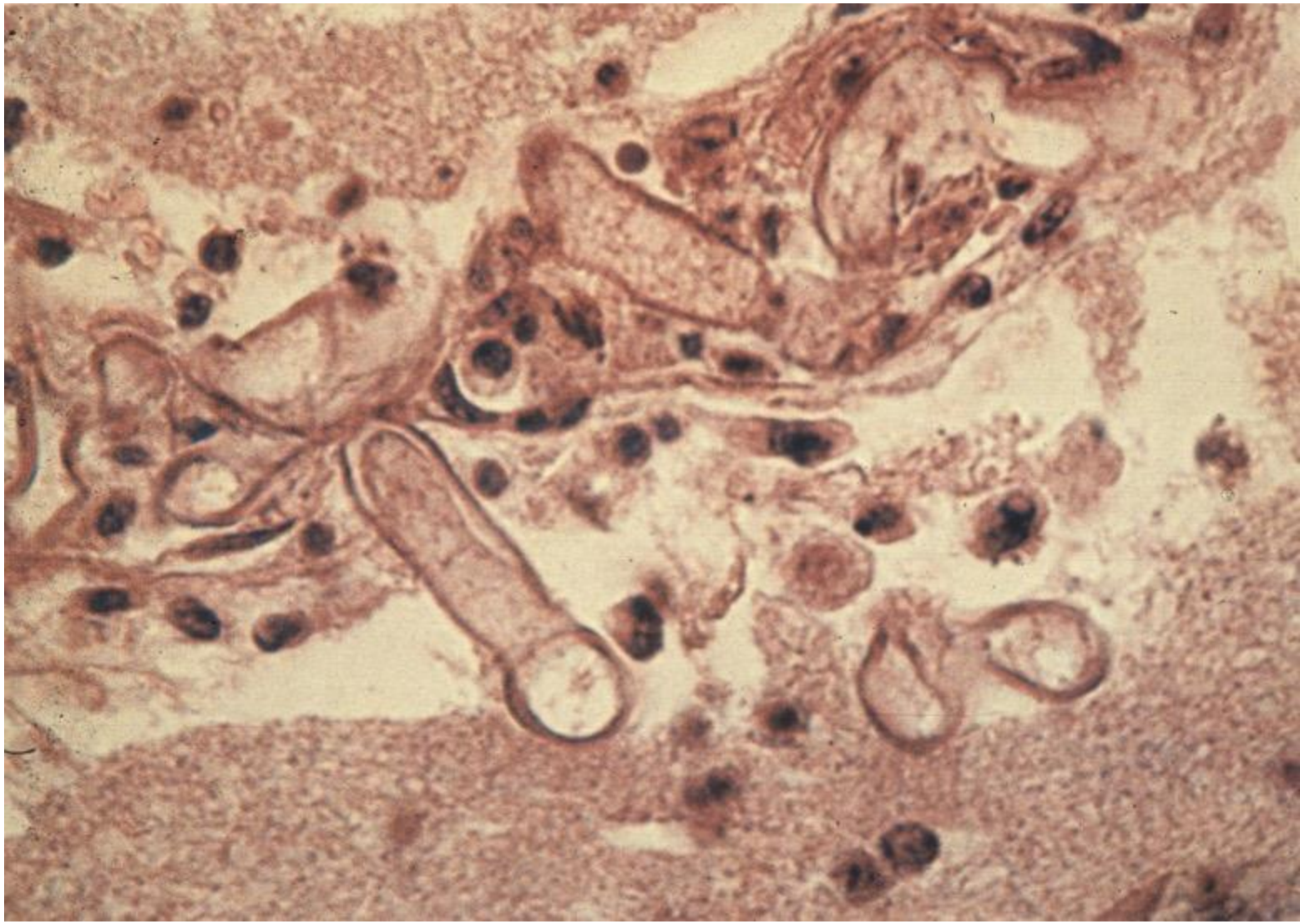
Case Study # 19 A

Case Study # 19 A
Surgical Biopsy – Silver Stain



Case Study # 19 A

H&E ➔ Non-septate hyphae



Case Study # 19 A - Answer

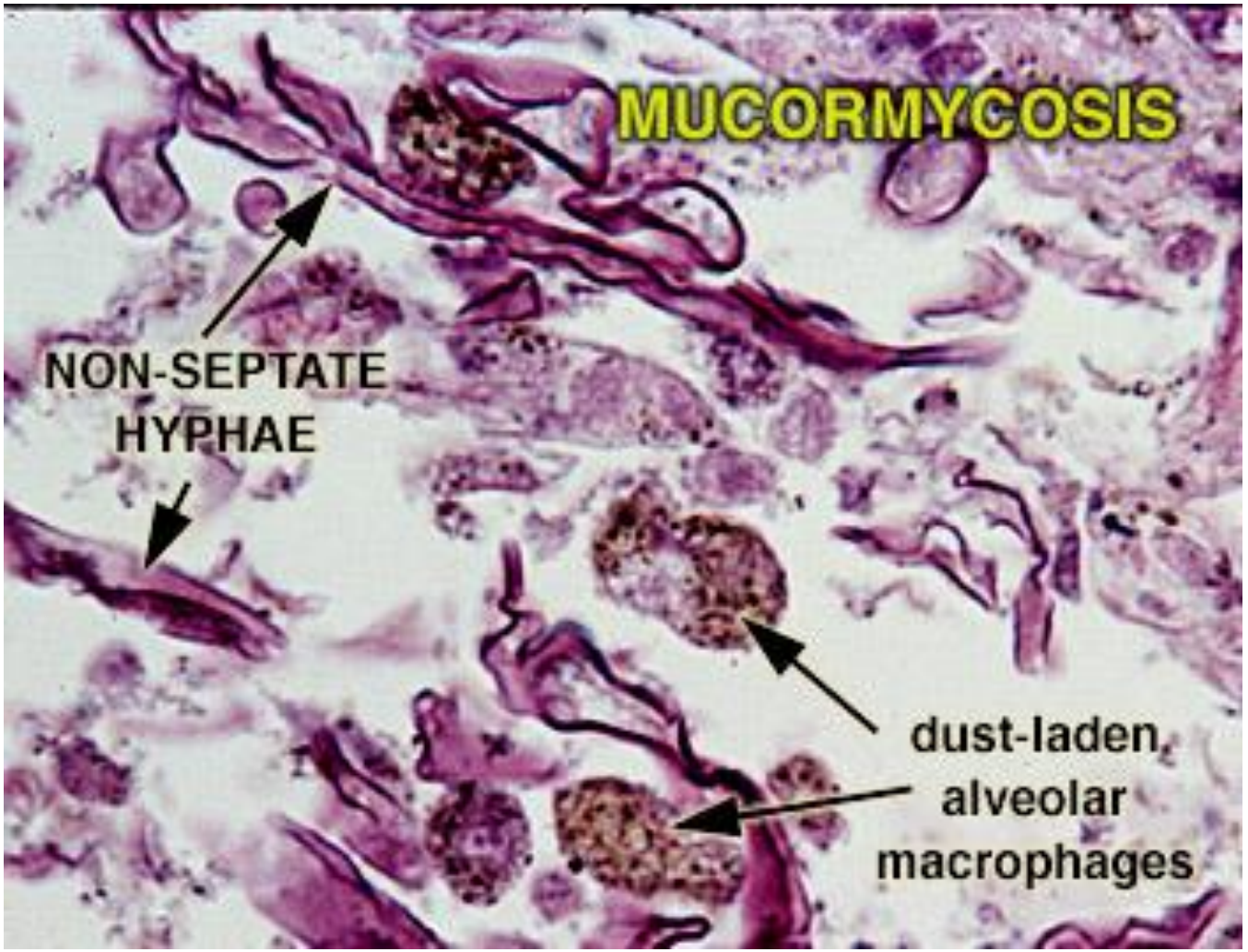
- Diagnosis is rhinocerebral mucormycosis
- Therapy is surgical debridement and amphotericin B treatment
- Need neurosurgeon, ENT surgeon, and an ophthalmologist for this operation

Case Study # 19 B

- 63 y.o. woman with diabetic ketoacidosis
- Develops eye swelling last 12 hours

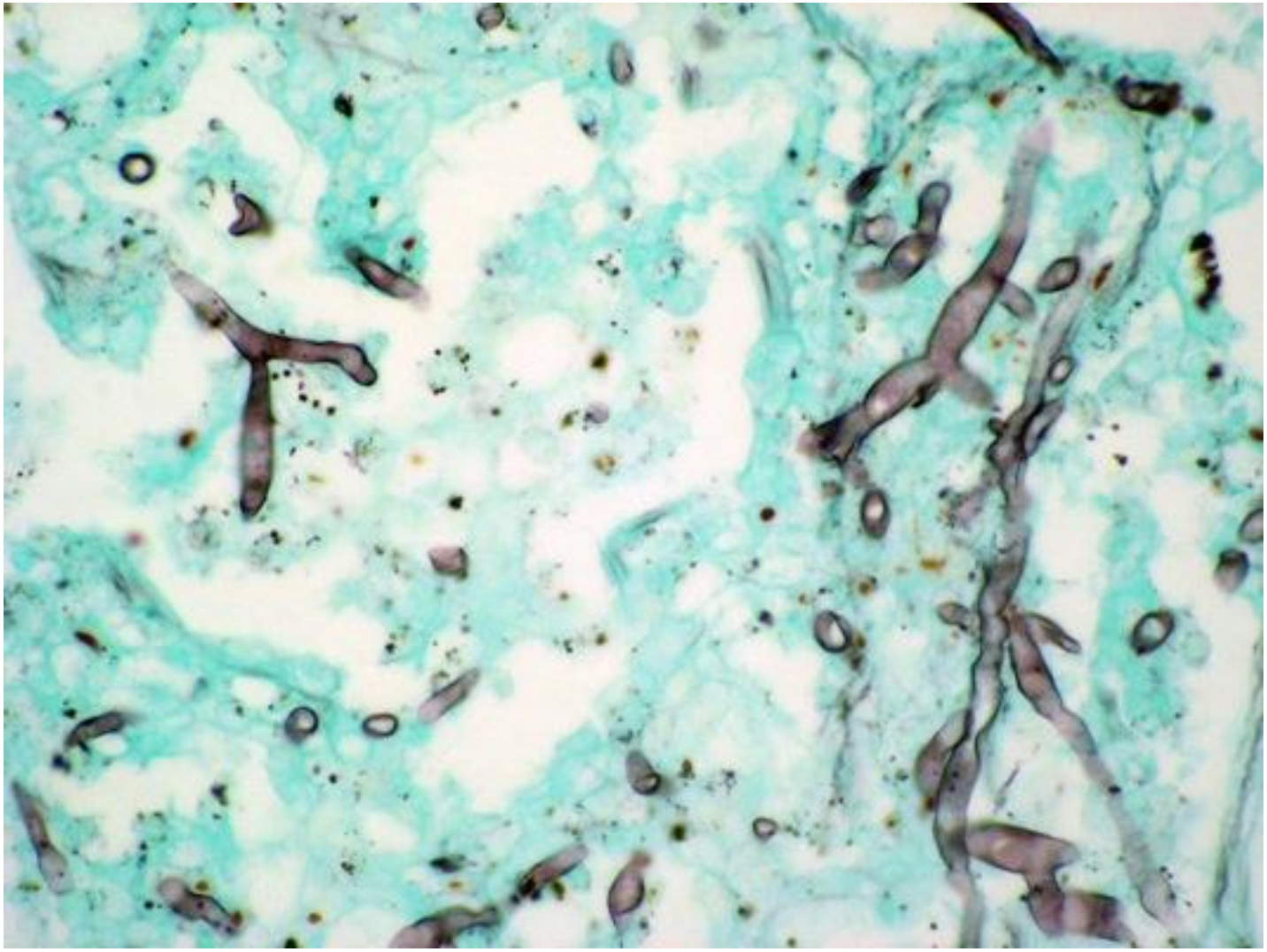
Case Study # 19 B

PAS Stain



Case Study # 19 B

Methenamine Silver Stain



Case Study # 19 B- Answer

- Rhinocerebral mucormycosis complicating diabetic ketoacidosis
- Non-septate hyphae in tissue as shown

Case Study # 20

- 54 y.o. man with known HIV disease, lost to follow-up for 2 years comes to ED with SOB
- Seven days earlier, he had first noticed significant shortness of breath with minimal exertion
- Symptoms increased in severity to dyspnea at rest
- He had lost 13 pounds during the preceding 3-4 months

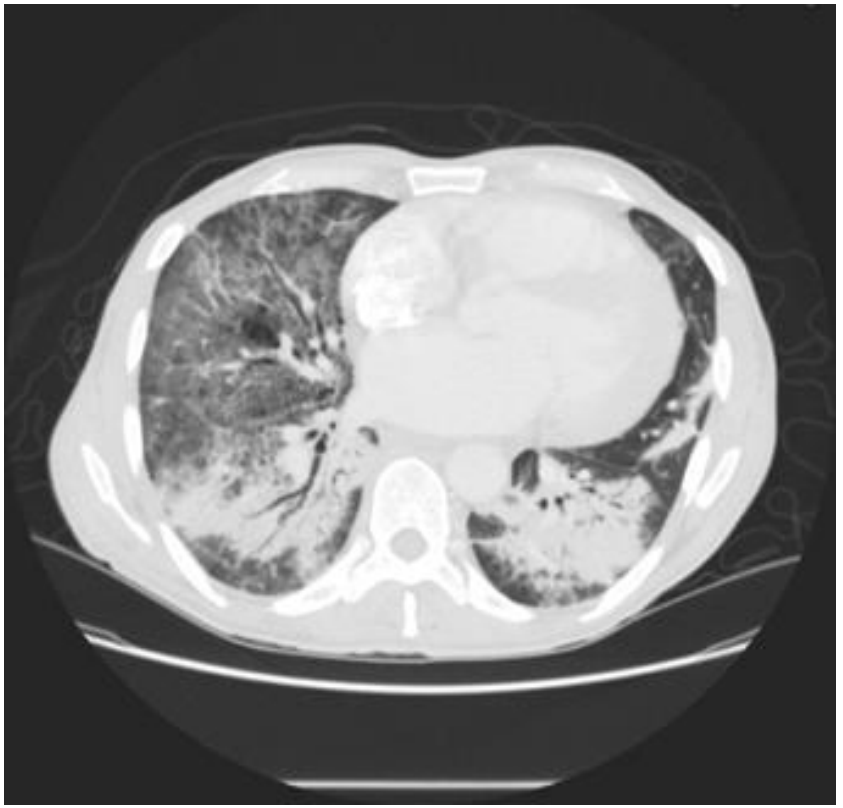
Case Study # 20

- Thirteen months earlier, the CD4 T-lymphocyte count was 215 cells/mm^3 and the plasma HIV RNA level was 177,000 copies per milliliter
- He was lost to follow-up until the current presentation. He had never taken antiretroviral medications
- EXAM➔He was thin and appeared in moderate respiratory distress. The blood pressure was 110/71 mm Hg, pulse 97 beats per minute, respirations 24-40 breaths per minute, and oxygen saturation 93% while breathing 60% oxygen administered by face mask. The temperature was 98.6°F (37.0°C).

Case Study # 20

Chest X-Ray

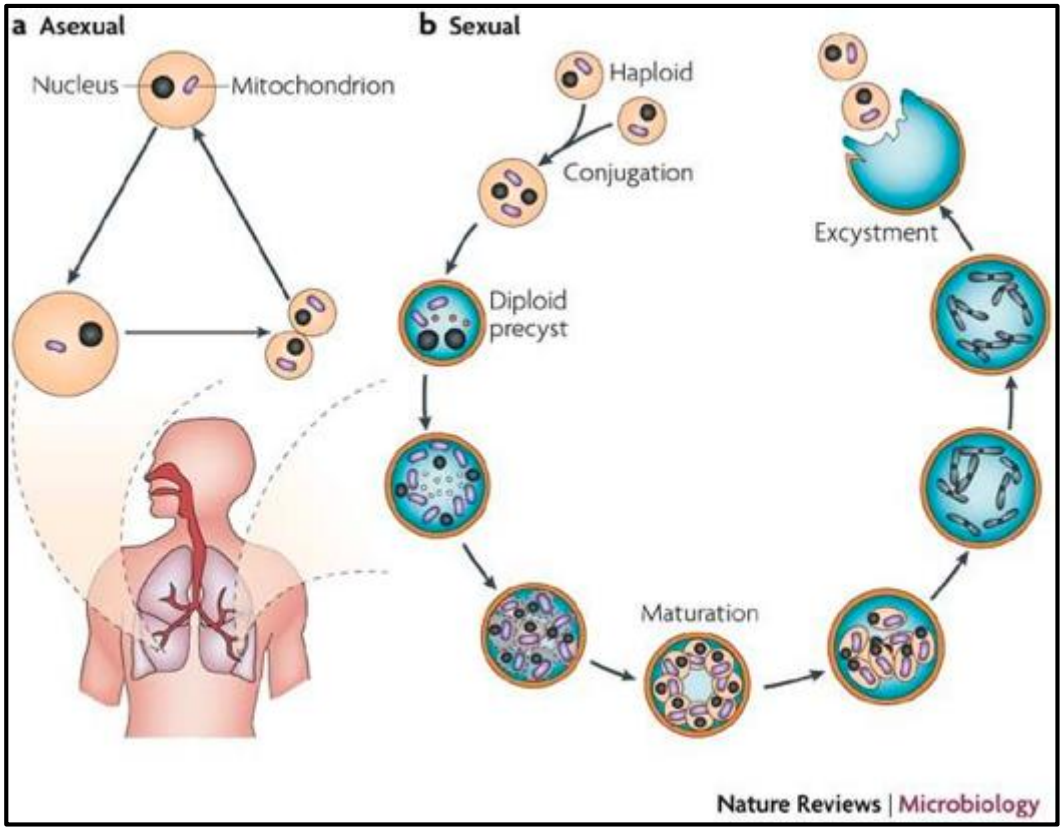
Case Study # 20



Pneumocystis jirovecii Pneumonia

Gomori Methenamine Silver Stain

Pneumocystis Life Cycle



Case Study # 20 - Answer

- It was initially thought to be protozoal; however, detailed analysis of *Pneumocystis* has led to its identification as a fungus.
- Subsequent research indicated that *Pneumocystis* is host-specific; that is, a strain that infects rats does not appear to be the same as that which infects humans.
- Consequently, the name of the human pathogen was changed from *Pneumocystis carinii*, which was isolated from rats, to *Pneumocystis jiroveci,* and then to *Pneumocystis jirovecii* [Walzer and Smulian 2005].

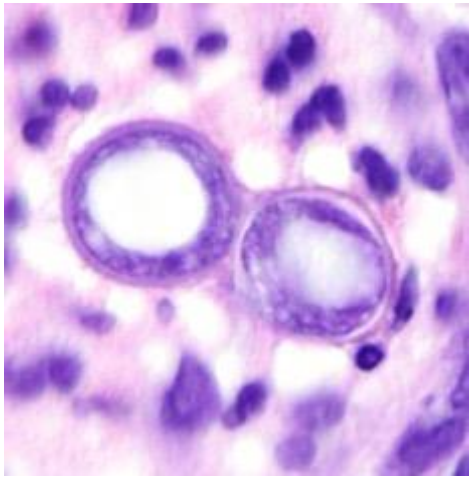
Why *Pneumocystis Was* Reclassified as Fungus (Previously in Protozoa)

- Despite lack of ergosterol and lack of growth in culture, it was reclassified as a fungus because:
  - rRNA and mitochondrial sequence are homologous to fungi
  - Ultrastructural features similar to those of fungi
  - Presence of ß-1,3 D-glucan in cell wall
  - Favorable activity of glucan synthesis inhibitors vs. *Pneumocystis*
  - Existence of lamellar cristae in its mitochondria
  - Presence of elongation factor-3 which is unique to fungi
  - Presence of thymidylate synthase and dihydrofolate reductase as distinct proteins in a fashion homologous to *Saccharomyces cerevisiae* as opposed to these being a single protein in protozoa
  - Cross-reactivity of its monoclonal antibodies with fungi
  - Similarity between its sporogenous state and the ascospore formation in some yeasts

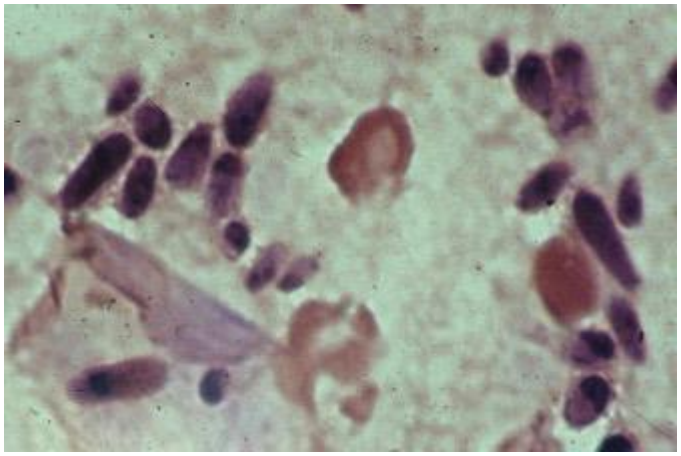
Case Study # 20 - Answer

- Treatment: Trimethoprim-sulfamethoxazole 5 mg/kg of TMP component every 6-8 hours and steroids (prednisone 40 mg bid initially)
- His pulmonary status gradually improved over the course of his admission.
- At the time of discharge, he was comfortable at rest while breathing ambient air, and was able to perform activities of daily living without significant difficulty.

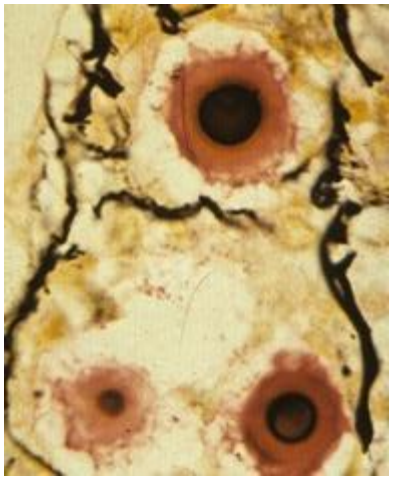
Yeast in Tissue



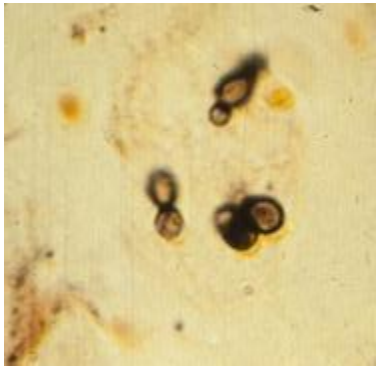
Blastomycosis: 10-12 µm



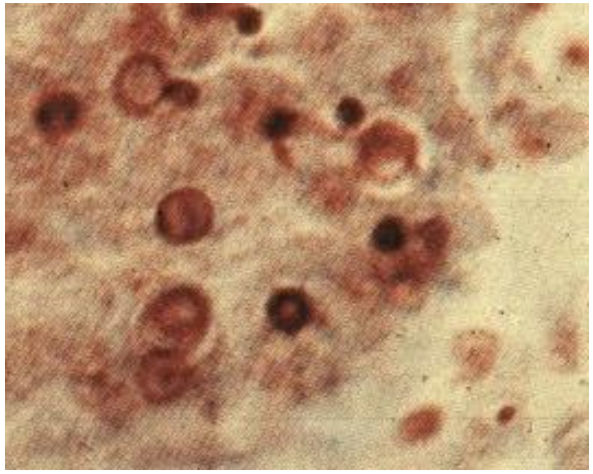
Candidiasis: 6-8 µm



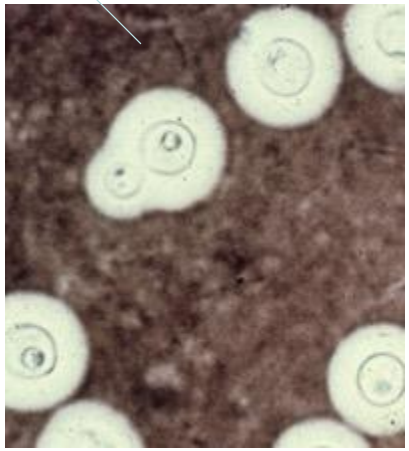
Cryptococcosis: 6-8 µm
Mucicarmine Stain



Histoplasmosis: 2-5 µm

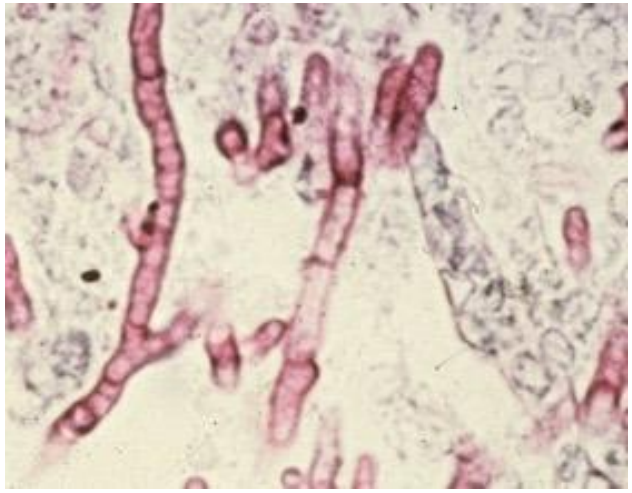


Sporotrichosis: 6-8 µm

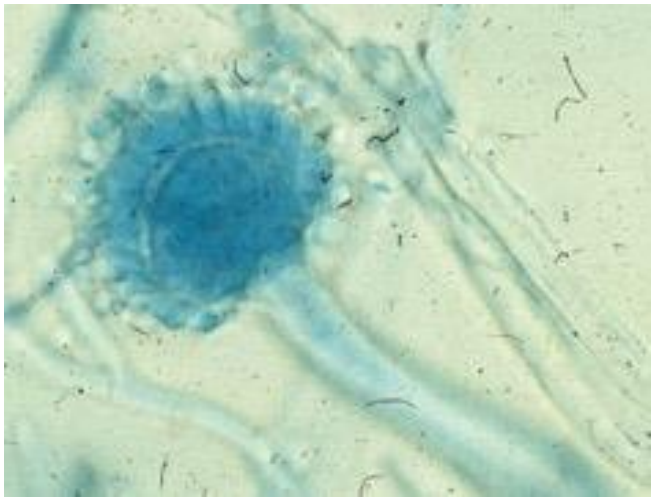


Cryptococcosis: 6-8 µ
India Ink Prep (CSF)m

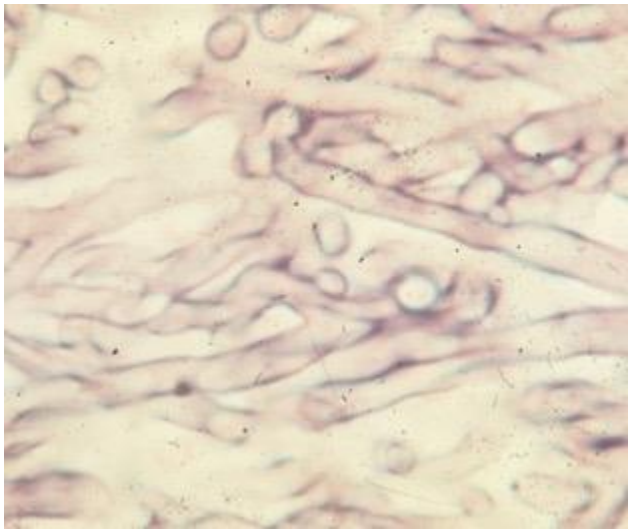
Hyphal Forms in Tissue and Vasculo-Invasive



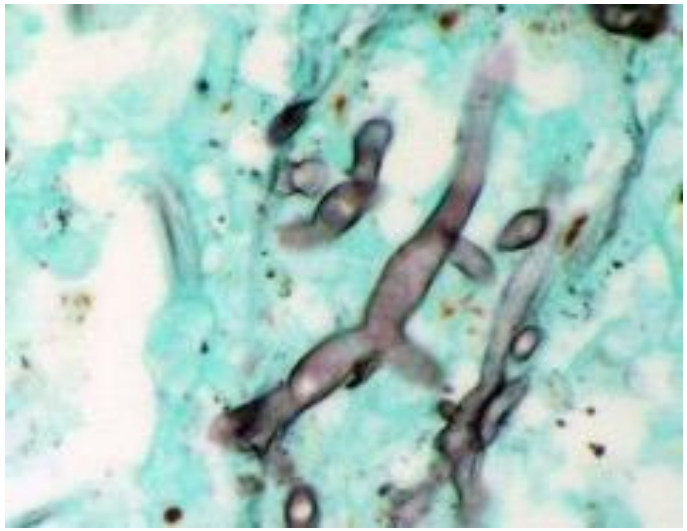
Aspergillosis: Septate Hyphae
H & E Stain (2-5 µm)



Aspergillus in Culture:
“Fruiting Heads” (50 µm)

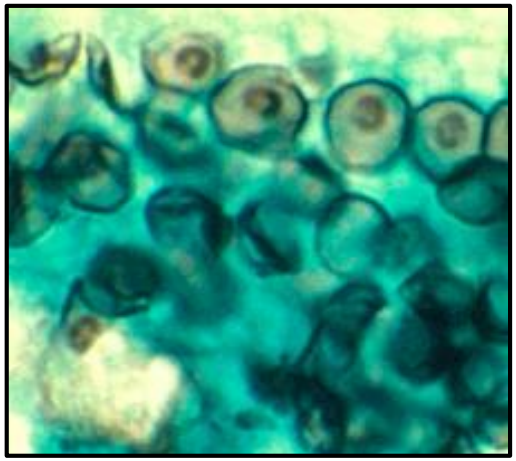


Mucormycosis: Non-Septate Hyphae
H & E Stain (7-30 µm)

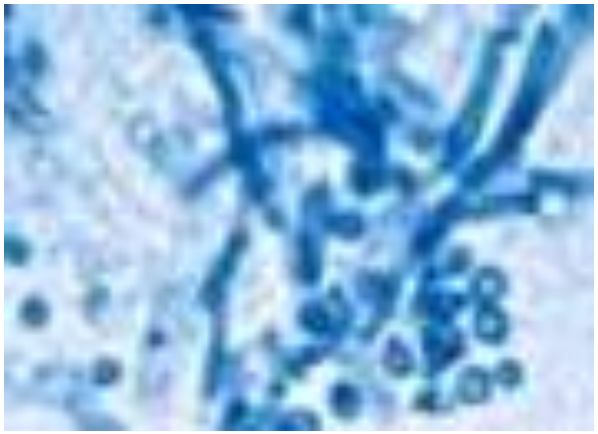


Mucormycosis: Non-Septate Hyphae
Silver Stain (7-30 µm)

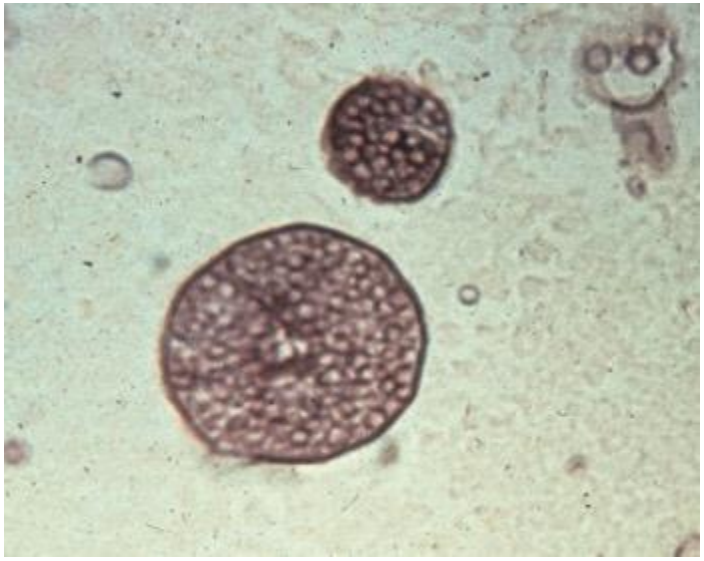
Other Forms



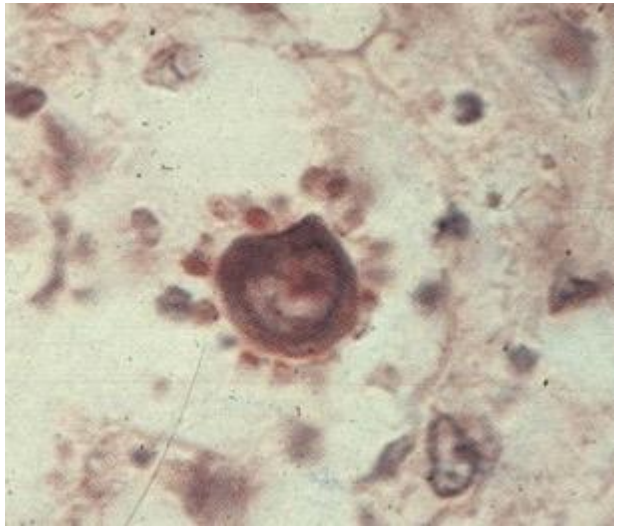
Pneumocystis: 5-8 µm



Malassezia furfur: 2,5-6 µm



Coccidioides Spherule: 20-80 µm



Paracoccioides: 4-60 µm