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LAB SERVICES

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I Can Really Dance

The patient is a 90 year old Caucasian gentleman who was admitted to the hospital after experiencing right-sided weakness and progressive, involuntary, right-sided movement that started after he had a fall three months earlier.

He told physicians that his leg would occasionally “kick” and that currently both his right leg and arm would “flop” uncontrollably. His personal physician had prescribed steroids and there have been only minimal improvements in his symptoms.

Both his past medical history and social history were noncontributory.

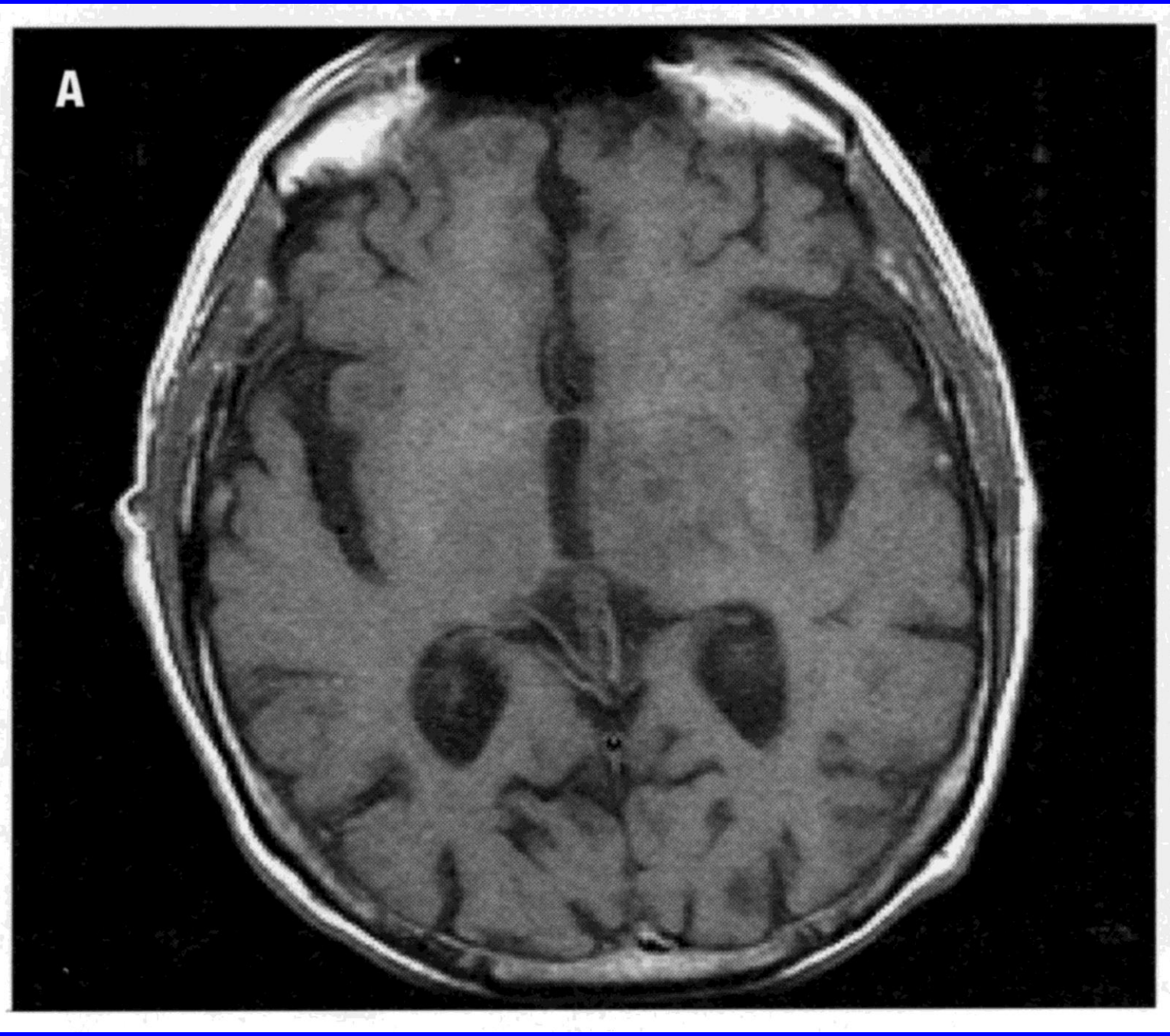
On physical examination, he was in no acute distress. On neurologic examination, he leaned to the right, dragged his right foot, had a pronator drift of his right arm, and increased deep tendon reflexes in his right leg. Sensations were intact and the cranial nerves were normal. He had no appreciable lymphadenopathy or hepatosplenomegaly.

Laboratory Results

		Normal
• CBC	Within normal limits	
• Liver function tests	Within normal limits	
• Blood:		
◦ Bacterial culture	Negative	Negative
◦ Fungal culture	Negative	Negative
◦ *Histoplasma* Ab by RID	Negative	Negative
◦ HIV 1,2 Ab	Negative	Negative
◦ CF Ab:		
• *Coccidioides*	Negative	Negative
• *Blastomyces*	Negative	Negative
• *Histoplasma*	Negative	Negative
• Urine:		
◦ Bacterial culture	Negative	Negative
◦ Fungal culture	Negative	Negative
◦ *Histoplasma* antigen	Negative	Negative

		Normal
• Sputum:		
Bacterial culture	Negative	Negative
Fungal culture	Negative	Negative
• Cerebrospinal fluid:		
Cell count	<1	0-5 cells/µL
RBC count	0	0 cells/µL
Total protein	61	15-45 mg/dL
Glucose	52	40-70 mg/dL
VDRL	Negative	Negative
Bacterial culture	Negative	Negative
Fungal culture	Negative	Negative
Histoplasma antigen	Negative	Negative

MRI Cerebral Studies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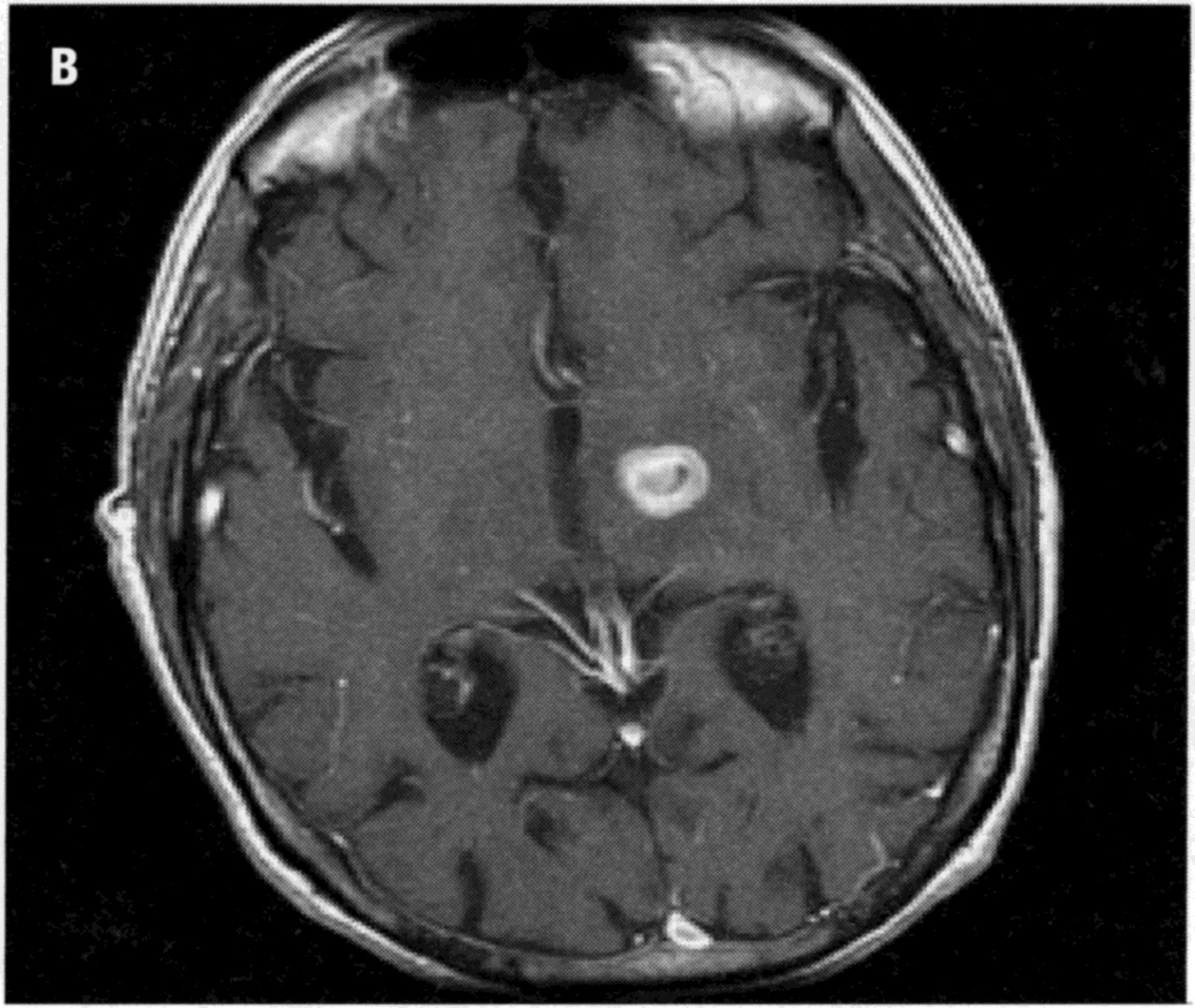
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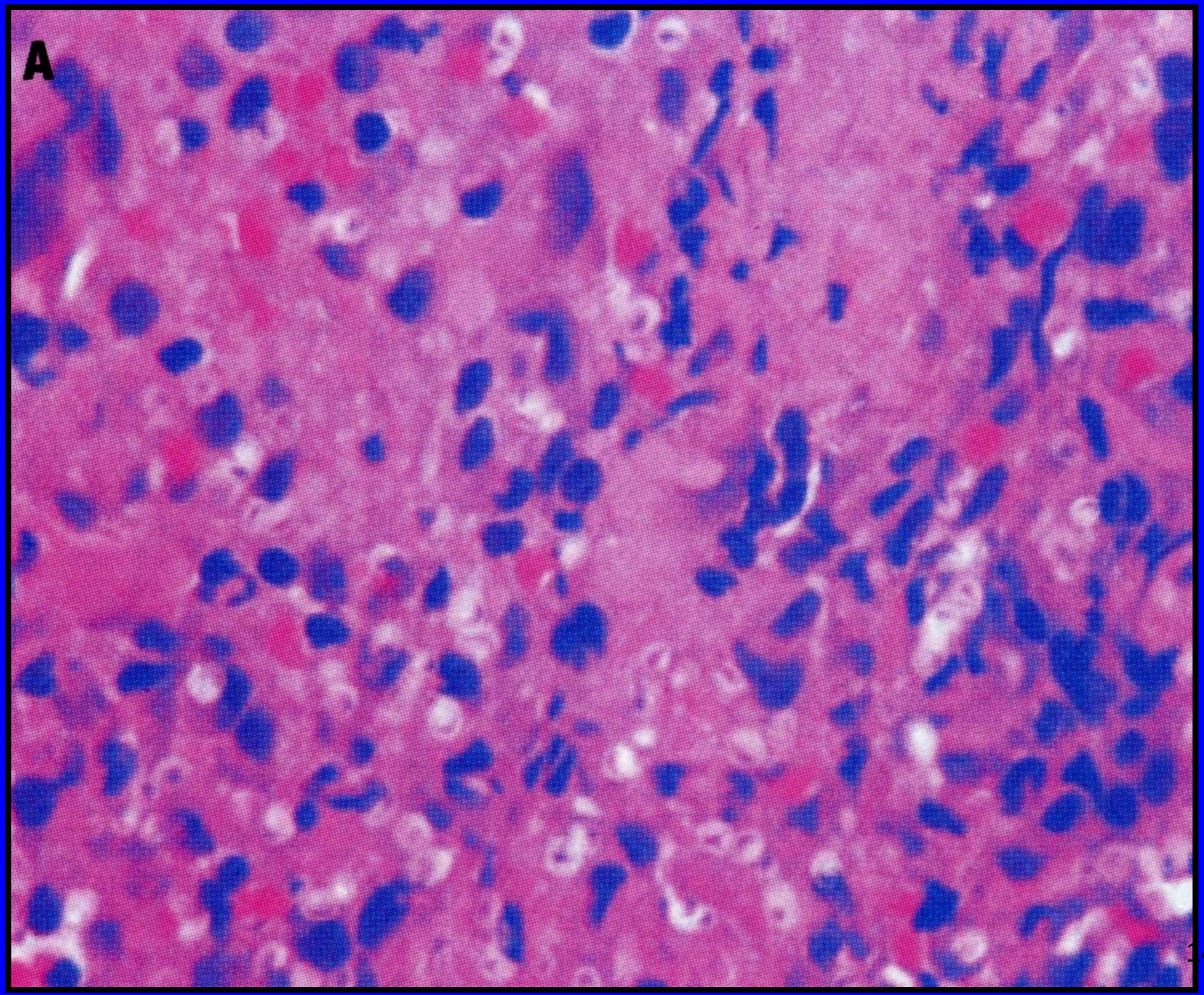
CT examination of his chest, abdomen, and pelvis had evidence of an enlarged prostate, splenomegaly, and a suspicious lung nodule.

Electromyographic findings were normal. A brain biopsy of the enhancing thalamic lesion was performed.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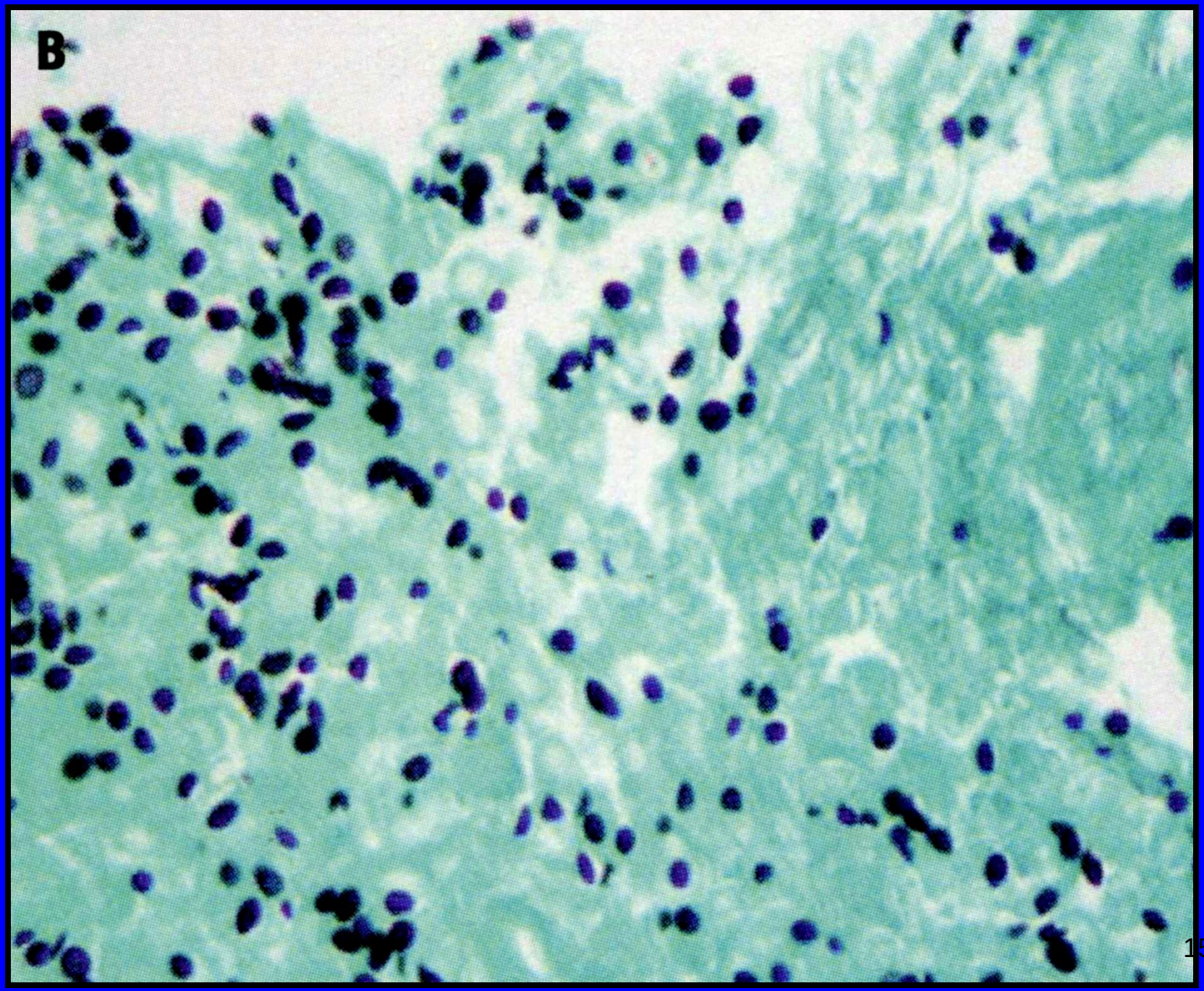
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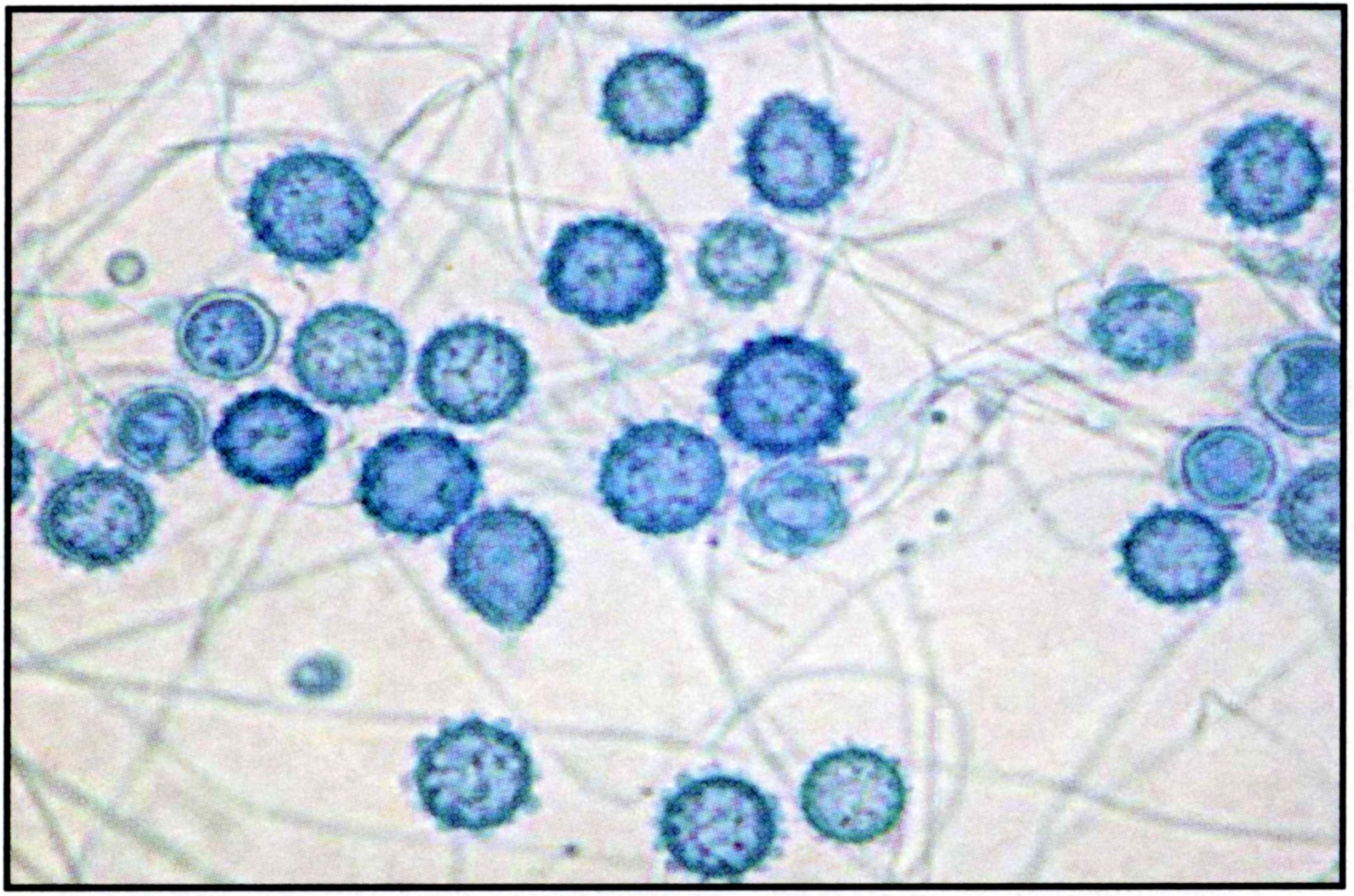
Diagnosis

Histoplasmosis

Histoplasmosis is the most common endemic mycosis in North and Central America. In the United States, it is found primarily in the soil of the Mississippi River and Ohio River valleys. It is also found in east Texas and in central America. Factors that promote *Histoplasma* growth in soil include acidic, porous soil rich in bird and bat droppings.

Histoplasma is a dimorphic fungus that grows as a mold or mycelial phase at 25˚C and as a yeast in tissue or 37˚C in the laboratory. The mycelial form grows as a white, fluffy colony with abundant, delicate hyphae with characteristic macro- and microconidia.



Disruption of *Histoplasma*-contaminating soil facilitates the aerosolization of the conidia, explaining the increased incidence of the disease among construction workers, agriculture workers and spelunkers. Immunocompromised individuals are also at a higher risk for the disease in endemic areas.

Inhaled conidia travel to the lung where they germinate into the yeast form. These forms invade and reproduce within macrophages and are disseminated to extra-pulmonary sites. Person-to-person transmission does not occur. More than 50% of persons living in endemic areas are skin-test positive for *Histoplasma* exposure. Most infections are asymp-tomatic or are self-limited.

Symptomatic histoplasmosis presents several weeks after exposure and is characterized by flu-like symptoms. A patchy infiltrate and enlarged hilar or mediastinal lymph nodes can be present on chest x-ray. In immunocompromised individuals and those exposed to high levels of *Histoplasma*, the symptomatic presentation can be life threatening. These patients are also more likely to develop chronic pulmonary and disseminated histoplasmosis.

Chronic pulmonary disease is characterized by cavitary lung lesions and enlarged hilar and mediastinal lymph nodes. Acute and chronic dissemination can occur (1 in 2,000 infections). Chronic progressive disseminated histoplasmosis is an often fatal disease and occurs mostly in elderly men with no history of immunosuppression. CNS histoplasmosis is not common but can occur in 10-20% of chronic disseminated cases. Chronic meningitis is the most frequent CNS manifestation and most cases are a result of reactivation of latent *Histoplasma* infections.

Definitive laboratory diagnosis of histoplasmosis requires culture of the organism, exoantigen testing, demonstration of antibodies to H and M antigens, and staining of tissue samples (i.e., biopsies) using GMS and PAS stains.

Growth of *Histoplasma* can take up to six weeks. Adjuvant tests (i.e., DNA amplification, complement fixation, immunodiffusion, and antigen testing allow for more rapid diagnosis).

One of the difficulties with antibody testing, is that the immunosuppressed individual may not be able to produce antibodies to *Histoplasma* antigens.

The enzyme immunoassay for the detection of *Histoplasma* antigen is 90% sensitive in acute persistent disseminated disease or in an acute, higher-titer inoculation. The sensitivity of *Histoplasma meningitis* ranges from 40-67% with CSF-based assays, 38% with serum based assays, and 71% with urine based assays.

Treatment of symptomatic patients is either itraconazole or amphotericin B (more severe infections). Fluconazole is a second-line alternative if the patient creatinine levels increase. Most patients with disseminated disease will respond to therapy. An exception is those patients with chronic pulmonary histoplasmosis due to the severe pulmonary destruction that is present with this disease.

The Case of the Louisville Slugger

The patient is a 74 year old Caucasian gentleman from Louisville, Illinois who was admitted to Memorial Medical Center with a history of a chronic cough. A chest CT scan had been performed and there was evidence of progressive lung disease. When questioned the slugger said he had had no associated fever, chills, or night sweats.

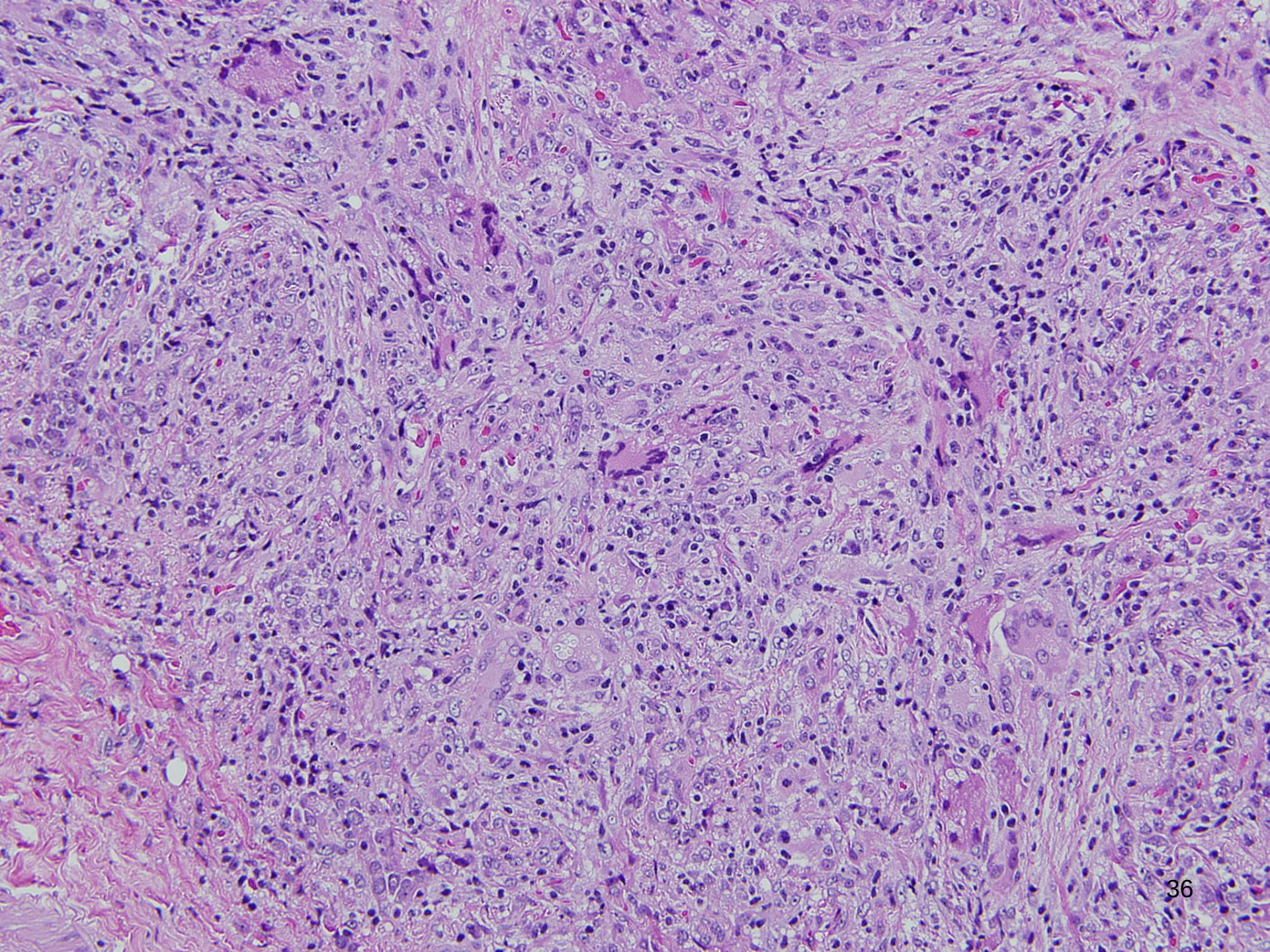
The patient's past medical history was significant for chronic rheumatoid arthritis for which he had taken long term immuno-suppressive agents, including methotrexate and prednisone. Currently he is taking Remicade. In addition, he also had a 20 pack/year smoking history. His father had been diagnosed with pulmonary tuberculosis and the slugger had had numerous Tbc skin tests which had always been negative.

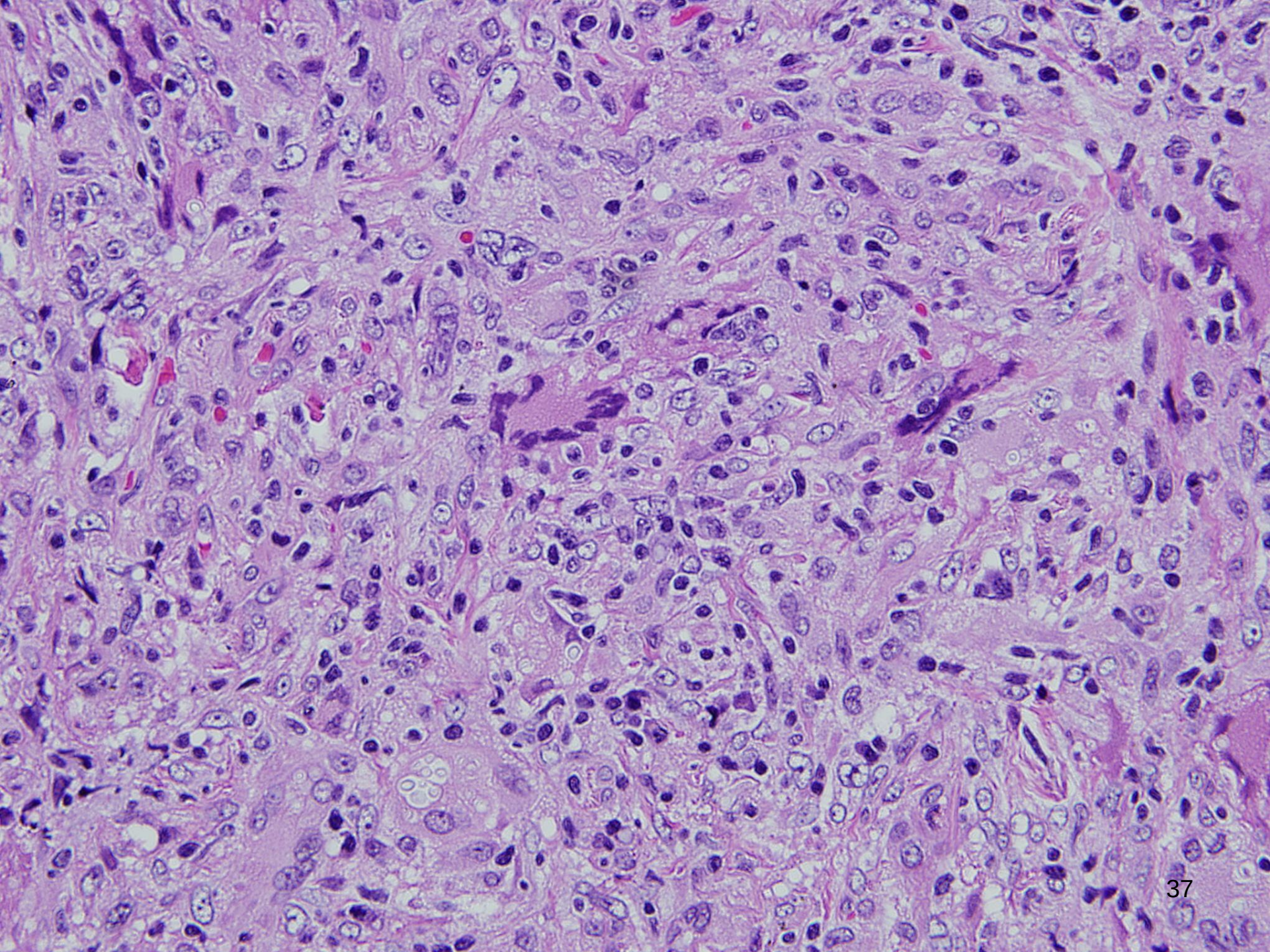
A chest film performed at the time of admission had evidence of multifocal areas of consolidation in both the middle and right lower lobes.

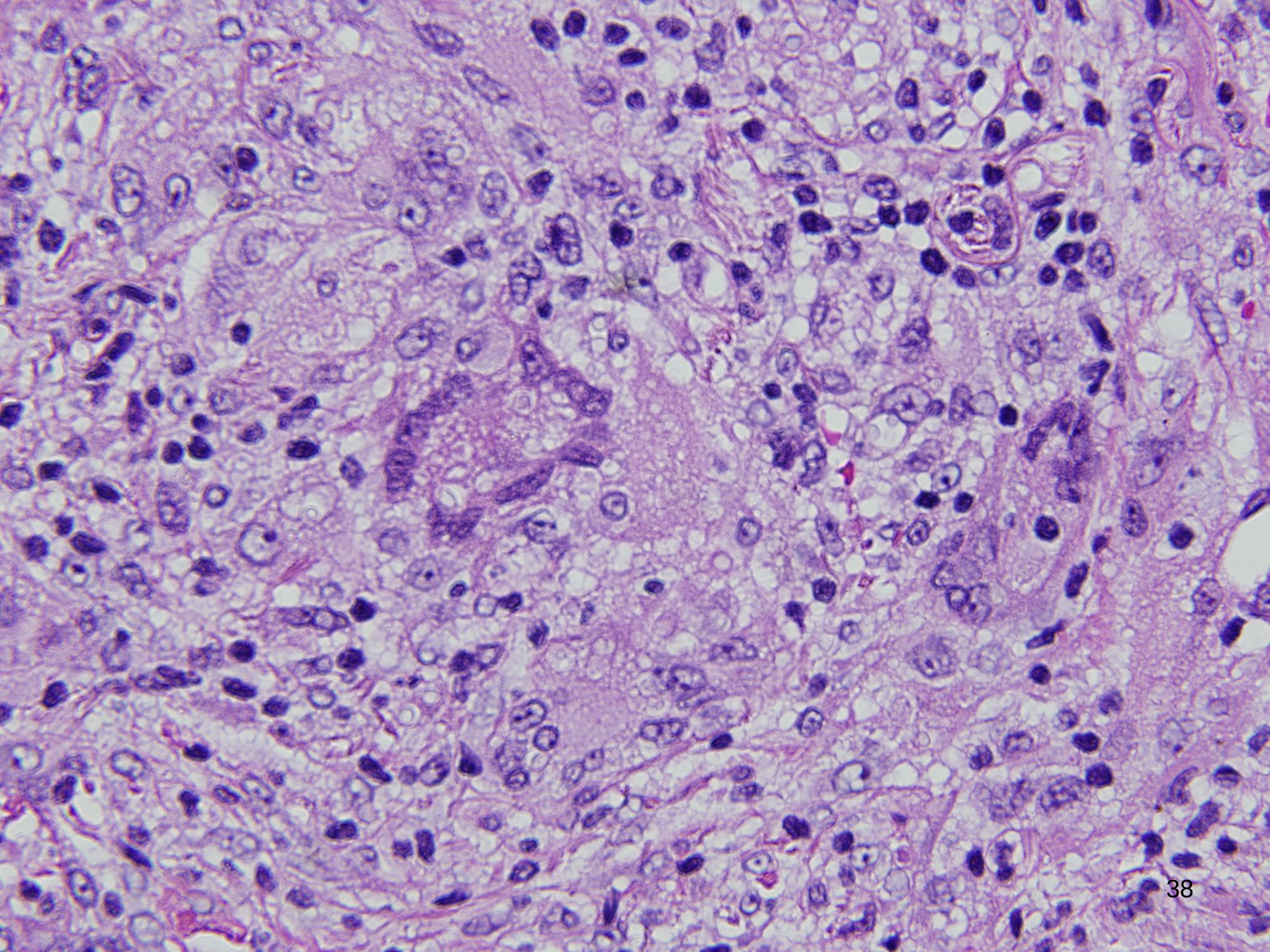
Laboratory Studies

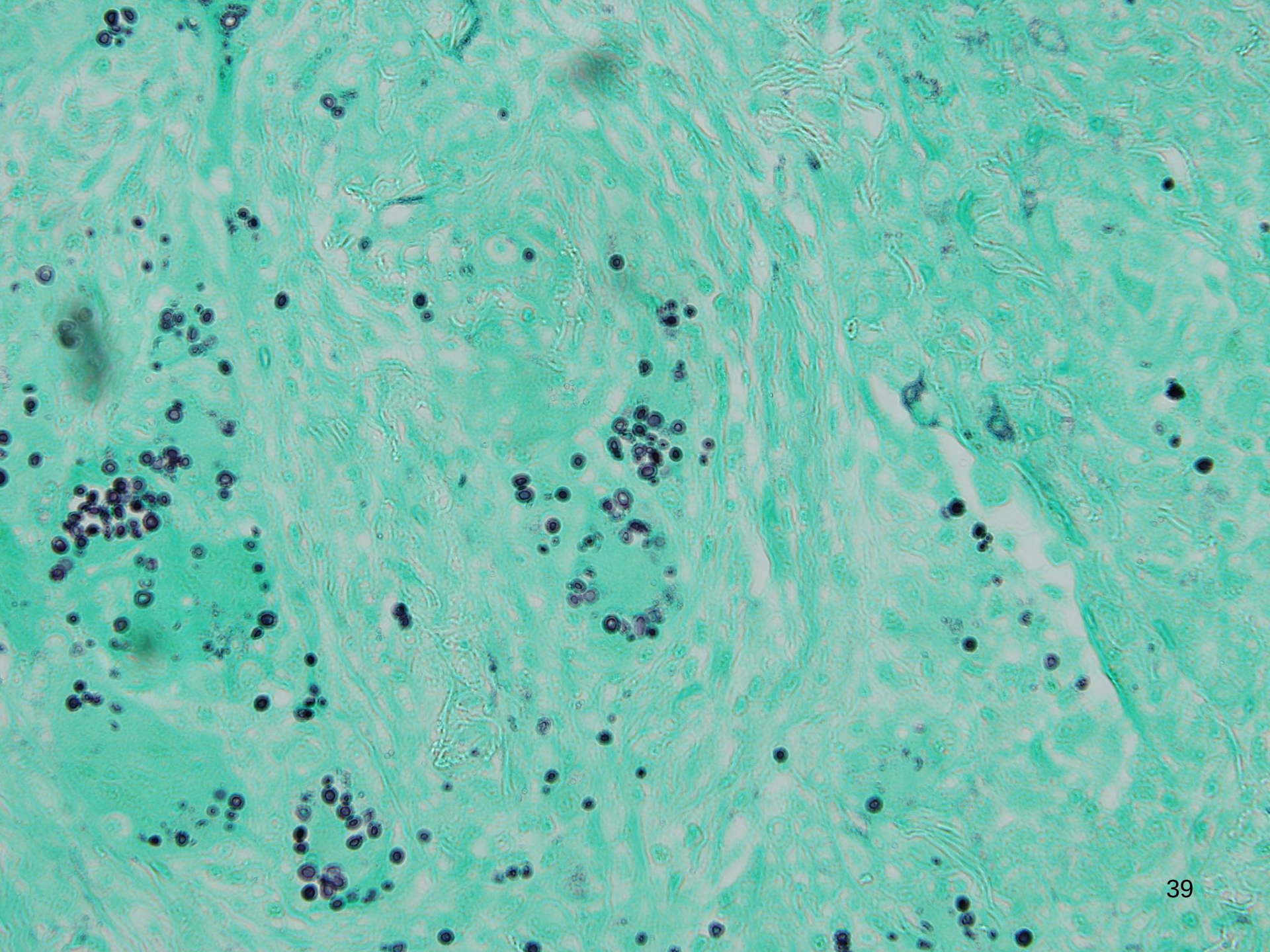
		Normal
• Hemoglobin	9.7 g/dL	14-18
• Hematocrit	29%	42-52
• RBC	3.35 x 10^6/µL	4.7-6.1
• WBC	8.3 x 10^3/µL	3.4-9.4
• Neutrophils	81%	47-67
• *Histoplasma* yeast & mycelial antibodies	Negative	Negative

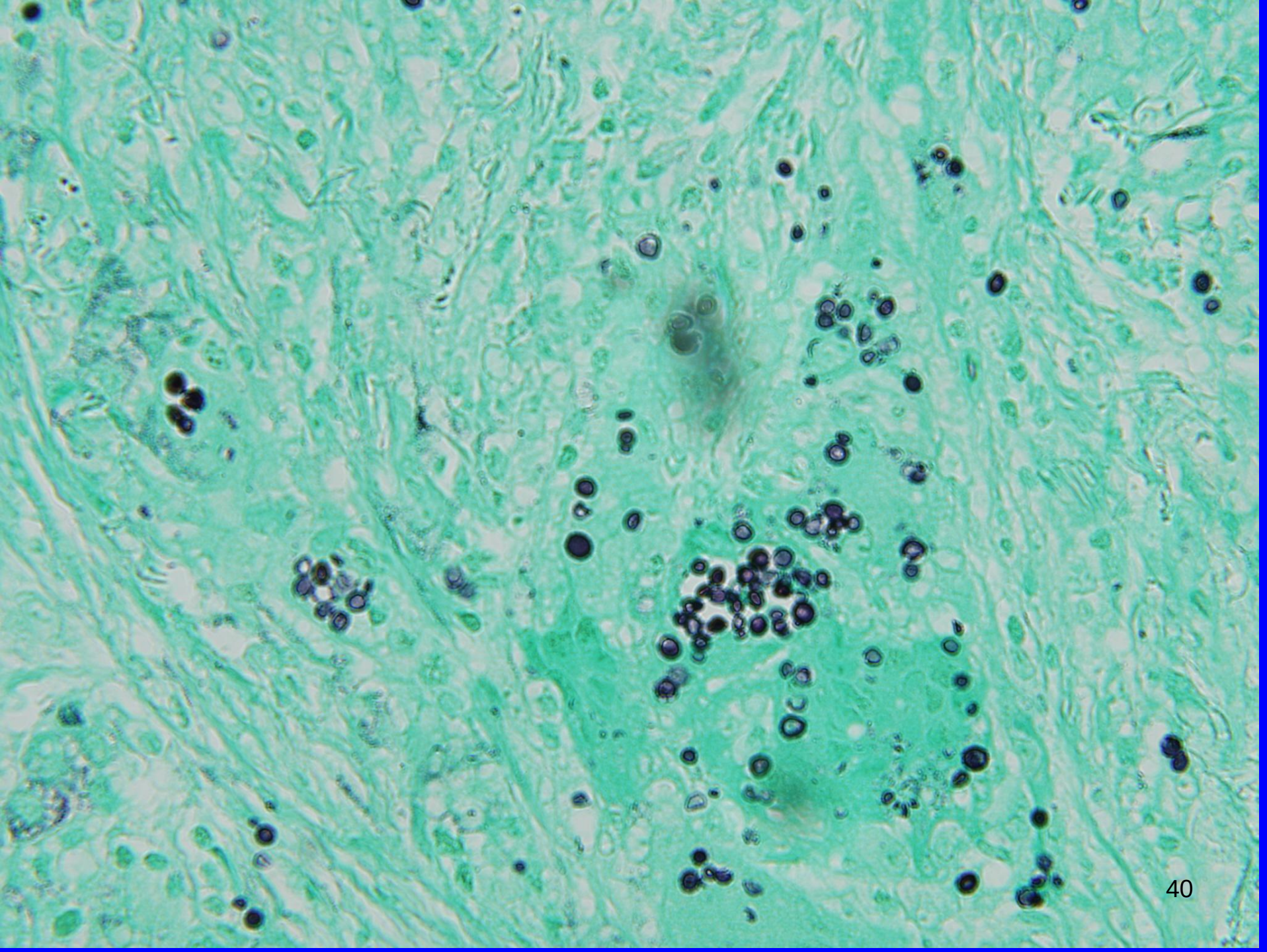
Bronchoscopy was performed and Gram stains, fungal stains, and bacterial and fungal cultures were all negative. Wedge biopsies were then performed on the right middle and lower lobes.

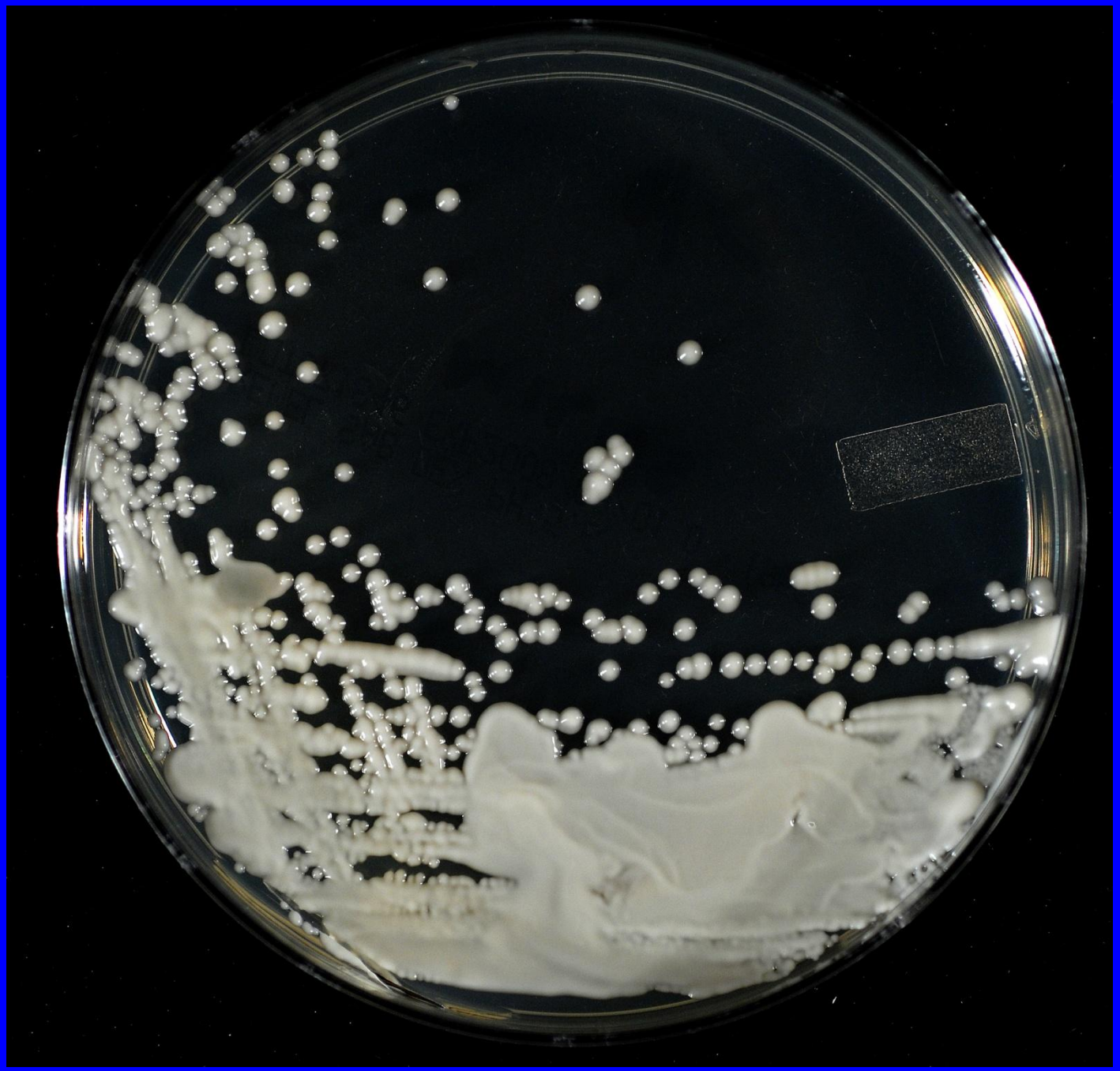












Pathologic Diagnosis

Pulmonary cryptococcosis (capsule deficient organisms)

Cryptococcosis is an infection caused by a yeast-like fungus *Cryptococcus neoformans*. Typically in the host (i.e. patient) and on certain culture media, a large (characteristic) capsule surrounds the yeast cell. This organism is the only pathogenic yeast that contains this capsule and it protects the yeast from desiccation under drying conditions.

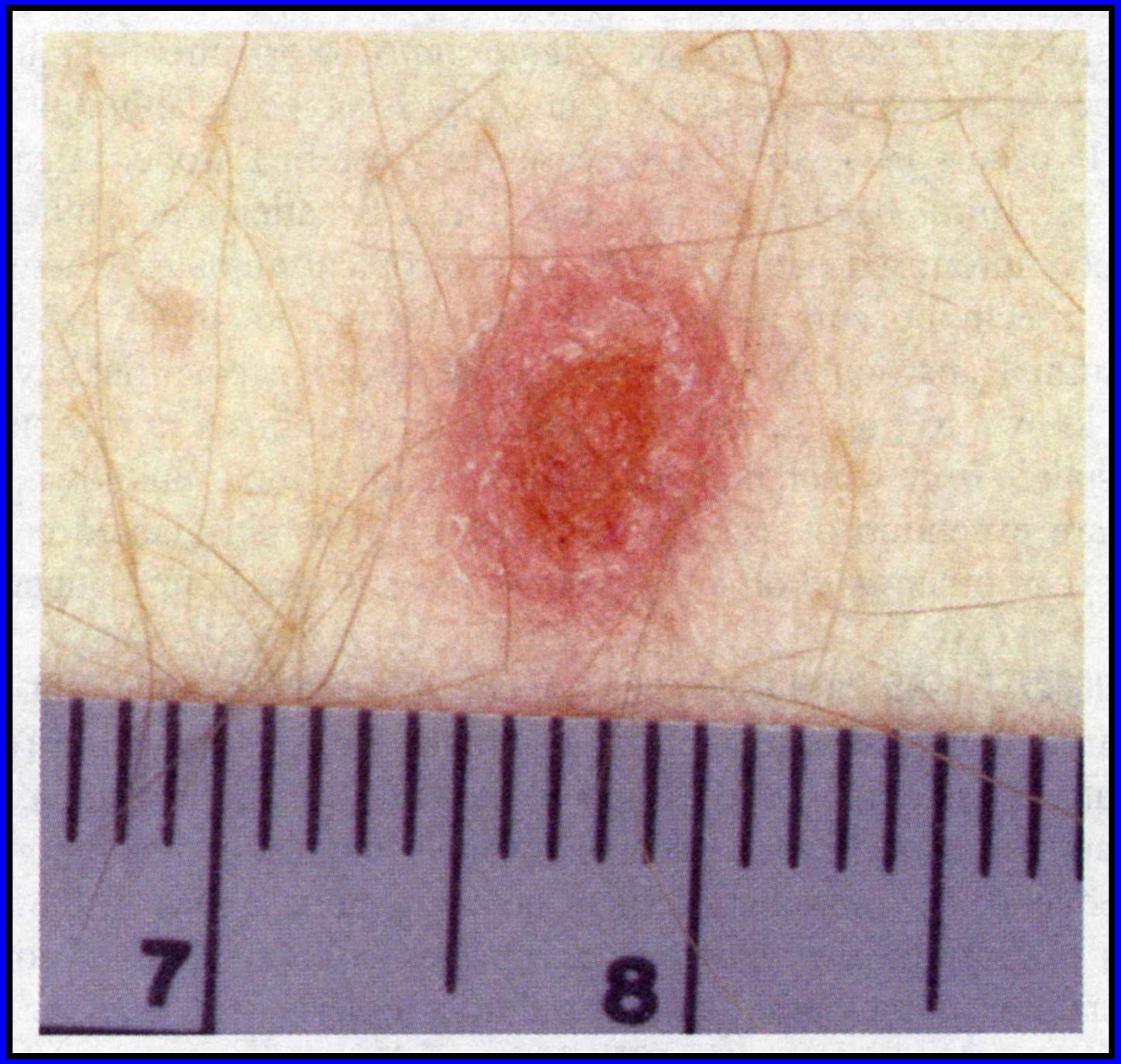
Importantly, the polysaccharide capsule contains compounds that are not recognized by phagocytes. These so-called acapsular strains (actually reduced capsular strains) of *Cryptococcus neoformans* are more easily phagocytized by macrophages and are therefore less virulent.

Weathered pigeon droppings commonly contain the organism. Typically inhalation of the fungus into the lungs introduce organisms into the body. In most people there are no signs or symptoms and if minor respiratory symptoms are present, they spontaneously resolve. At the time of exposure, silent hematogenesis spread to the brain occurs which leads to cluster of cryptococci residing in the perivascular areas of the cerebral gray matter and the basal ganglia.

Serious CNS manifestation (most often meningoencephalitis) can occur in patients with severe immuno-suppression (e. g.,50% of AIDS patients with $CD4^+$ counts below 200/µL). The remainder of patients are on chronic immunosuppressive agents, have lymphoma, or have T cell abnormalities.

Most patients with CNS involvement have cryptococcal meningo-encephalitis. This is invariably fatal without therapy and death will occur as early as two weeks to several years after the onset of symptoms. Focal lesions called cryptococcomas are more common in patients without immunosuppression.

Pulmonary cryptococcosis causes chest pain in 40% of patients and chronic cough in 20%. Fever is typically modest or is absent. Chest x-rays have evidence of one or more dense infiltrates. Cavitation, pleural effusions, and hilar adenopathy are usually not present. Ten percent of patients with disseminated infections may also have skin involvement. These lesions typically enlarge and develop a central necrotic ulcer.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Standard treatment for cryptococcosis is amphotericin (10 weeks) followed by fluconazole (6-12 months). Itraconazole is an alternative therapy.