

Granulomas in the Liver- with an emphasis on infectious etiologies

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Diagnostic yield in liver biopsies for infection in HIV+ patients

Study	Population	Outcome
Wiboonchutikul <i>et al</i> , 2015	101 HIV+ patients with FUO	Diagnostic bx: 50% Helpful bx: 12% Not helpful bx: 38%
Garcia-Ordonez <i>et al</i> , 1999	58 HIV+ patients with FUO	Diagnostic bx: 43% Helpful bx: 22% Not helpful bx: 34.5%
Roger <i>et al</i> , 1996	98 HIV+ patients with suspected mycobacterial infections	Bx led to diagnosis: 16%

Wiboonchutikul S *et al*. *Jpn J Infect Dis* 2015;68:296-300.

Garcia-Ordonez MA *et al*. *J Infect* 1999;38:94-8.

Roger PM *et al*. *Clin Inf Dis* 1996;23:1302-4.

Challenges when evaluating liver biopsies for infection

- Sampling: you are getting 1/60,000th to 1/50,000th of the liver on a needle biopsy
- Lack of access to important information
- Nonspecific inflammatory reaction patterns
 - Lack of understanding of what pathogens are associated with certain patterns
 - Lack of knowledge about available ancillary tests

“Liver biopsy interpretation is sometimes regarded as a troublesome and perplexing exercise, frustrating for pathologists and too often yielding inadequate answers for clinicians.”

– Randall G. Lee, M.D.; Diagnostic Liver Pathology

Granulomas in liver biopsies

- Present in 2-10% of liver biopsies
- BUT 13-36% have **no discoverable etiology** even after extensive workup of tissue and patient!
- Helpful things to know:
 - Immune status of patient
 - Exposure to animals
 - Foreign travel
 - Medication/drug history

Infectious Causes of Hepatic Granulomas

- Viral

- CMV, EBV, HCV

- Bacterial

- Cat scratch disease
- Mycobacteria
- Lyme disease
- Brucella
- Tularemia
- Rickettsia
- Whipple disease

- Fungal

- Histoplasmosis
- Candida

- Parasitic

- Schistosomiasis
- Ascaris
- Pinworms
- Toxoplasma
- Fasciola hepatica

Helpful morphologic features

- Type of granuloma
- Accompanying inflammatory infiltrate
- Location of granulomas
- Nature of necrosis, if present
- Is there anything in the granuloma
- Changes in background liver
- Need for special stains

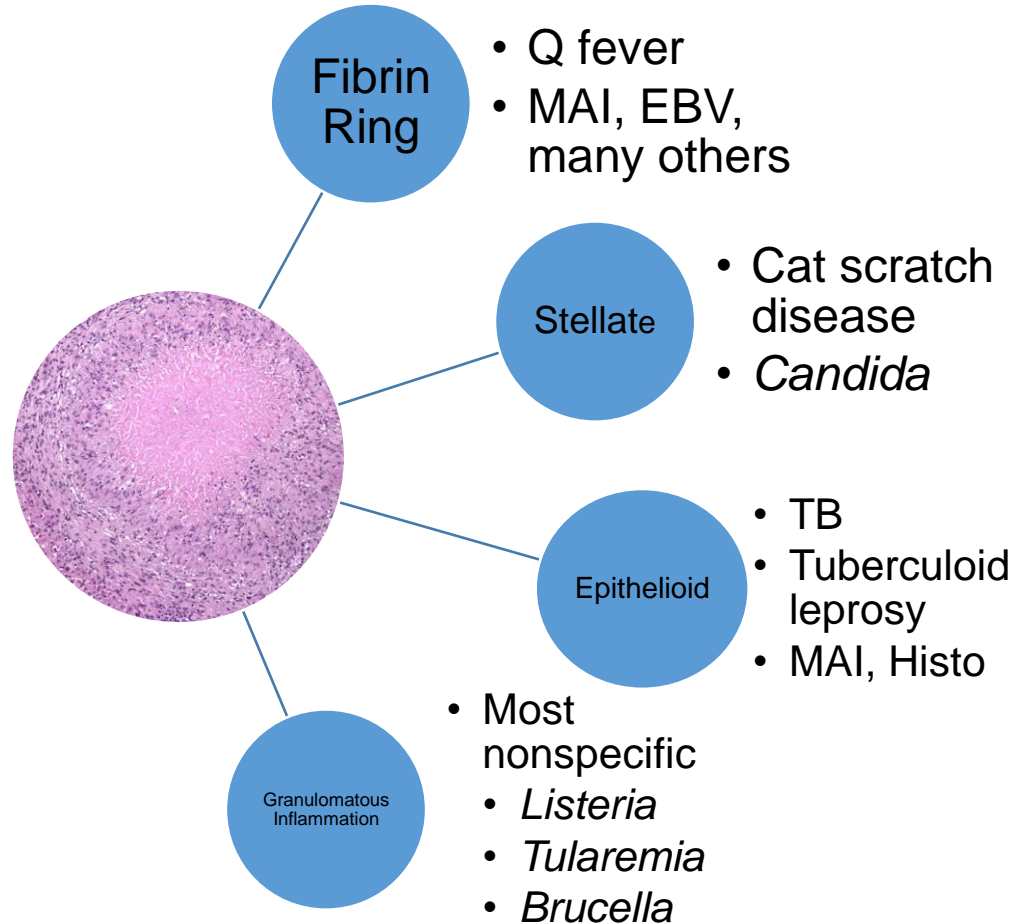
Granulomas

DDx:

Epithelioid:
Sarcoidosis

Drug
PBC
Foreign material

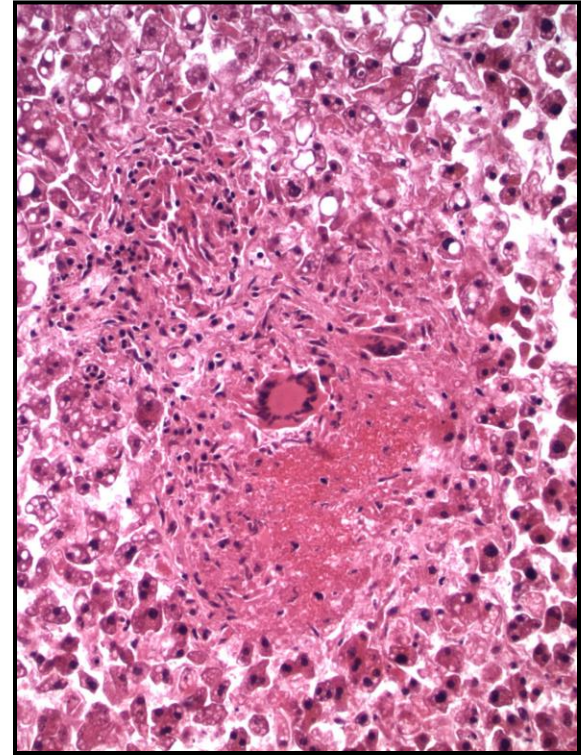
Granulomatous:
Drug



Murphy E et al. Histopathol 1991;19:91-3.
Pelligrin M et al. Hum Pathol 1980;11: 51-7.
Lamps et al. Am J Surg Pathol 1996;20:1253-9.
Hickey et al. BMC Infect Dis 2015;15:209.
Karat AB et al. Brit Med J 1971;1:307-10.
Lamps LW. Arch Pathol Lab Med 2015;139:867-75.

Morphological Classification of Granulomas

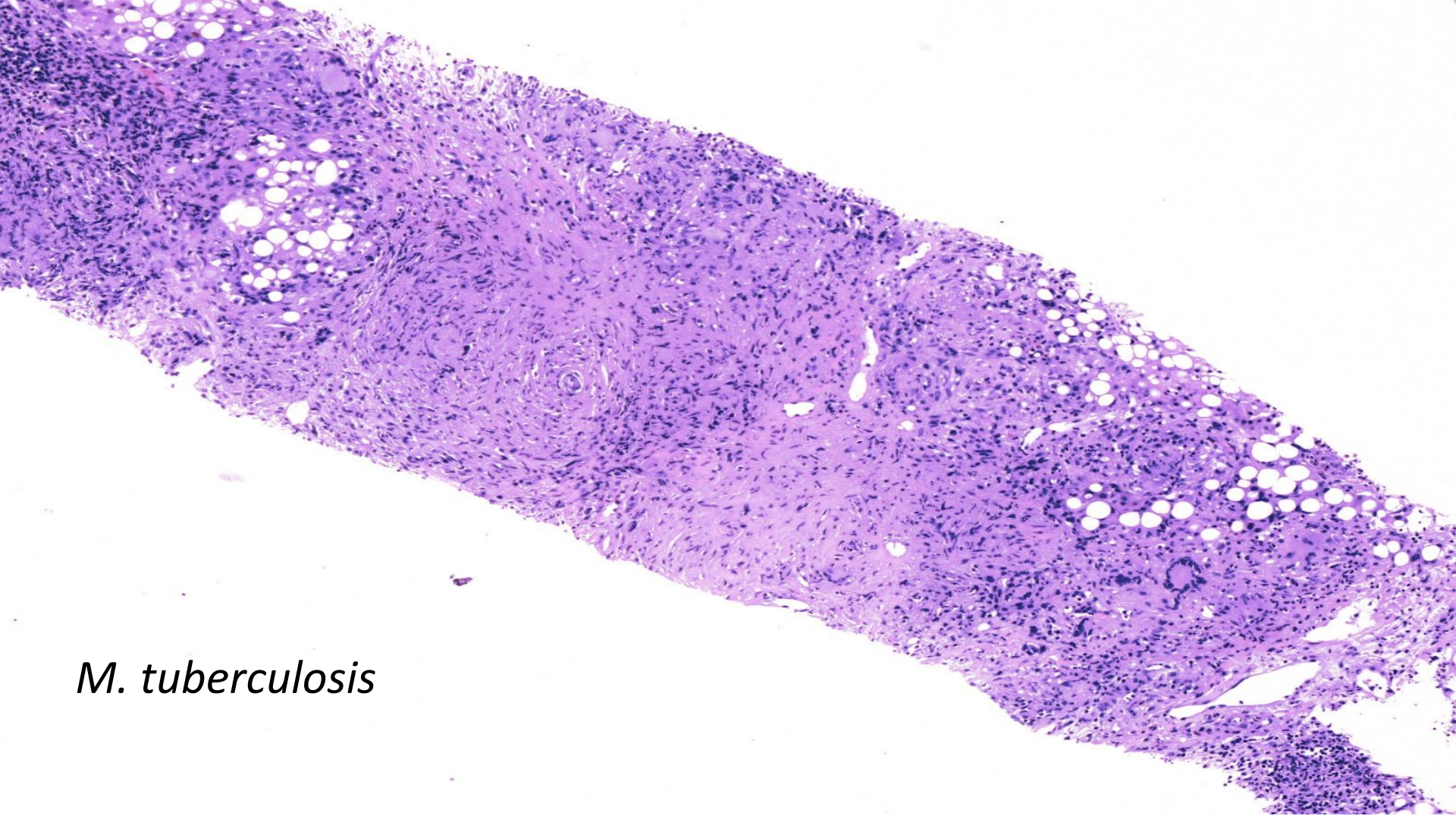
- Epithelioid
 - Discrete with distinct edges
 - +/- necrosis
 - Lack of respect for normal architecture



Courtesy Dr. Joe Misdraji

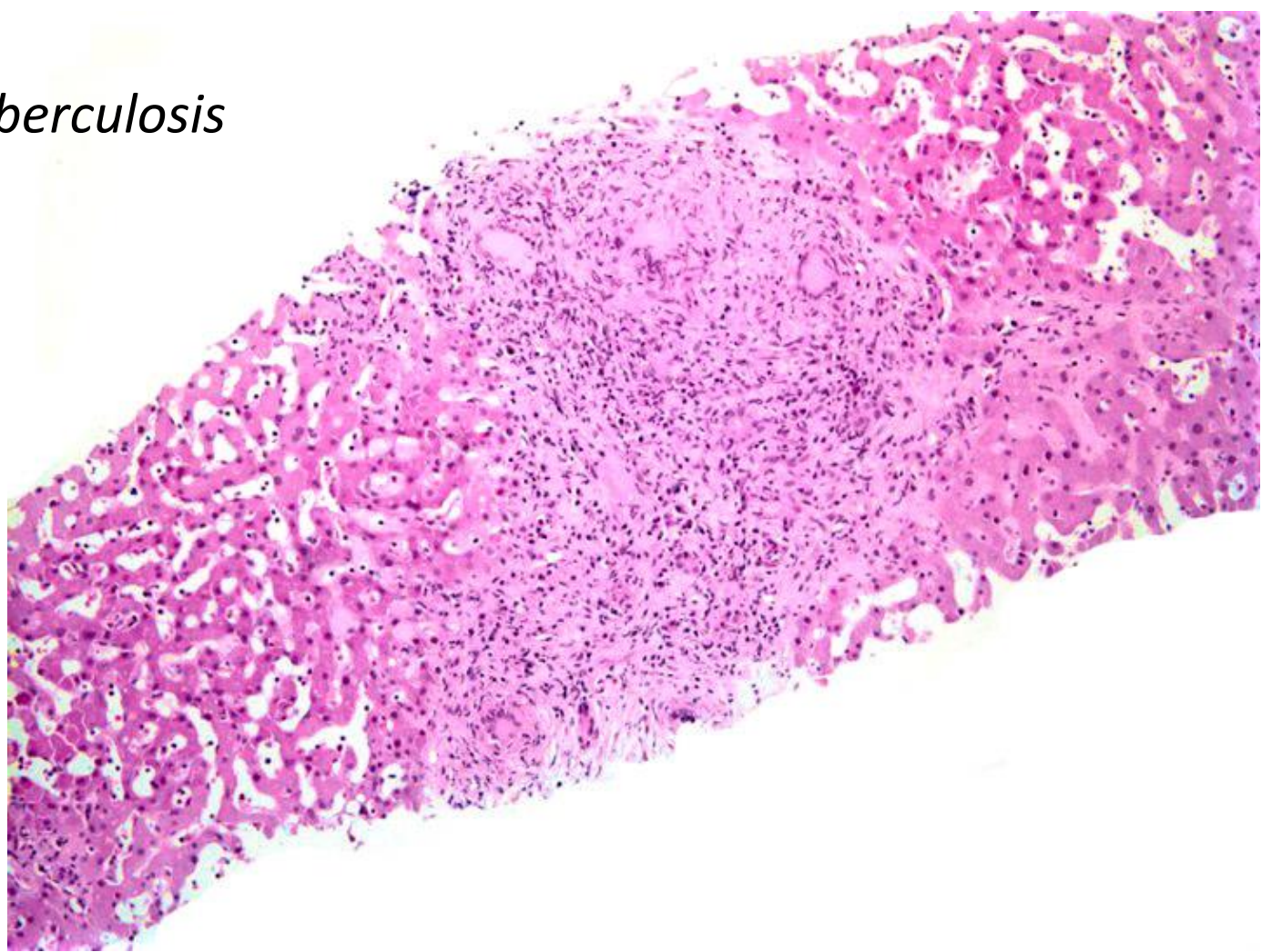
Mycobacterium tuberculosis

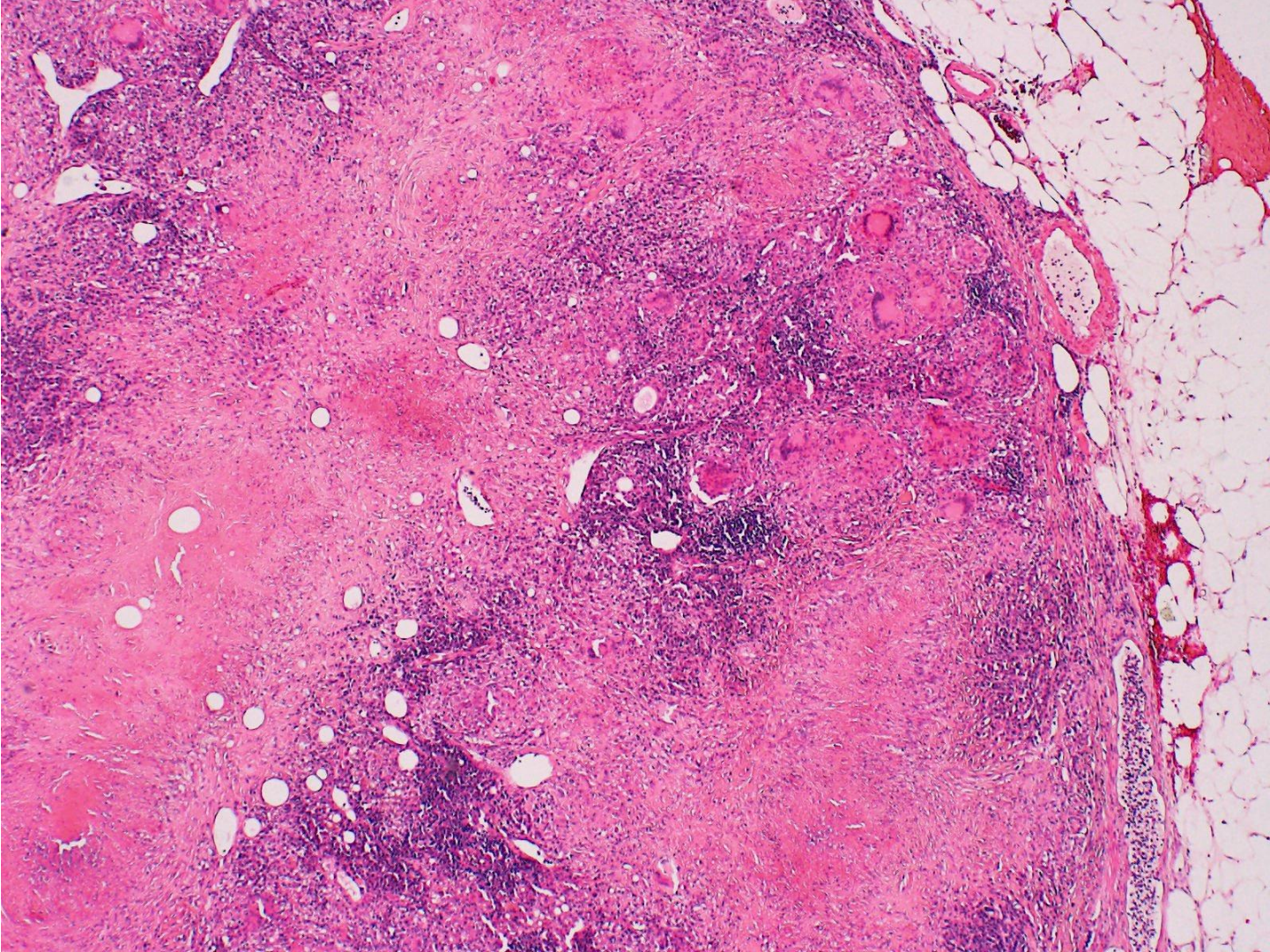
- Granulomas present in virtually all cases of miliary TB
- Signs/symptoms of liver disease may be dominant presenting feature (not lung)
- Presentation ranges from asymptomatic to fever/RUQ pain/hepatomegaly
- Diagnosis: special stains, molecular, culture

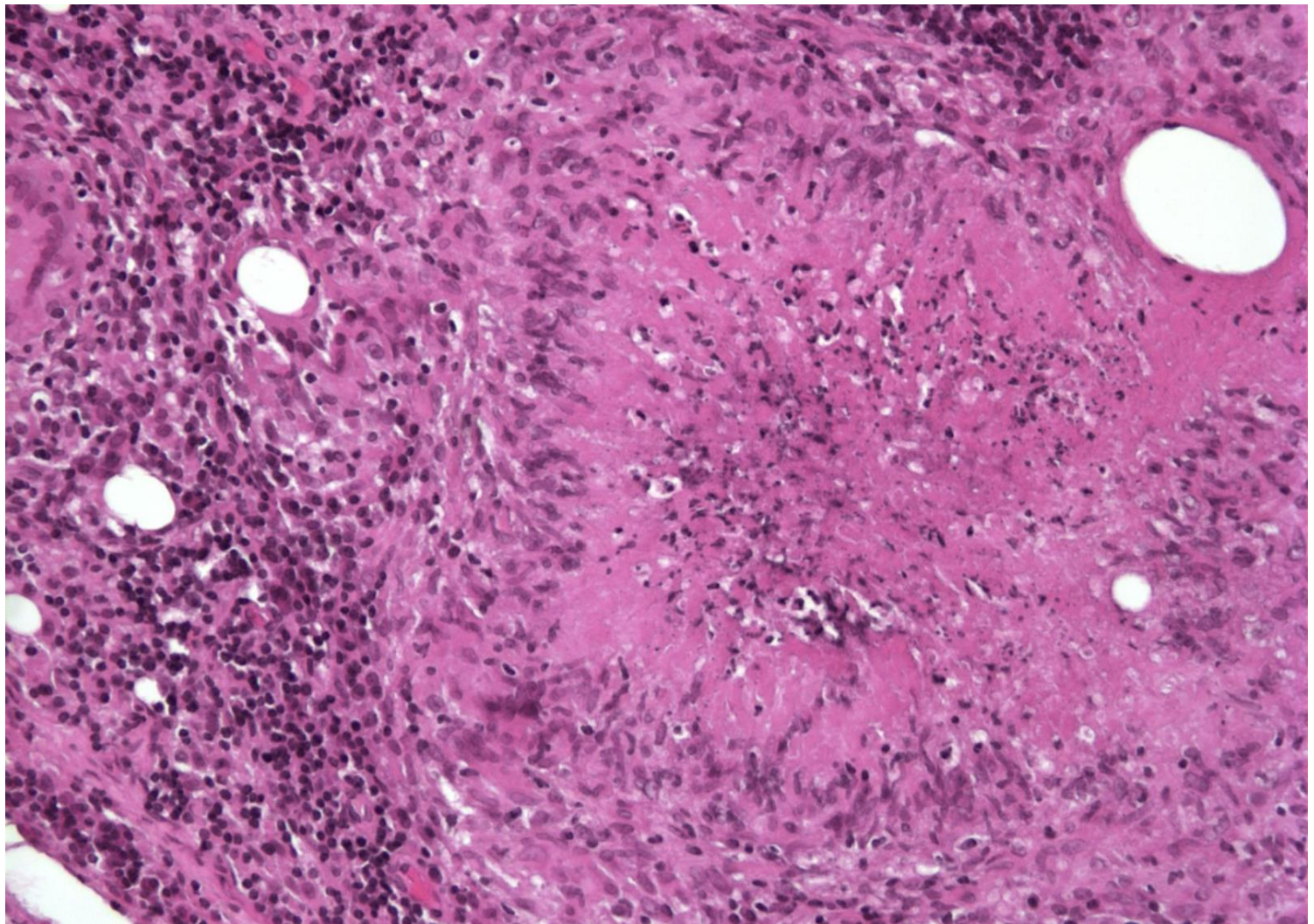


M. tuberculosis

M. tuberculosis



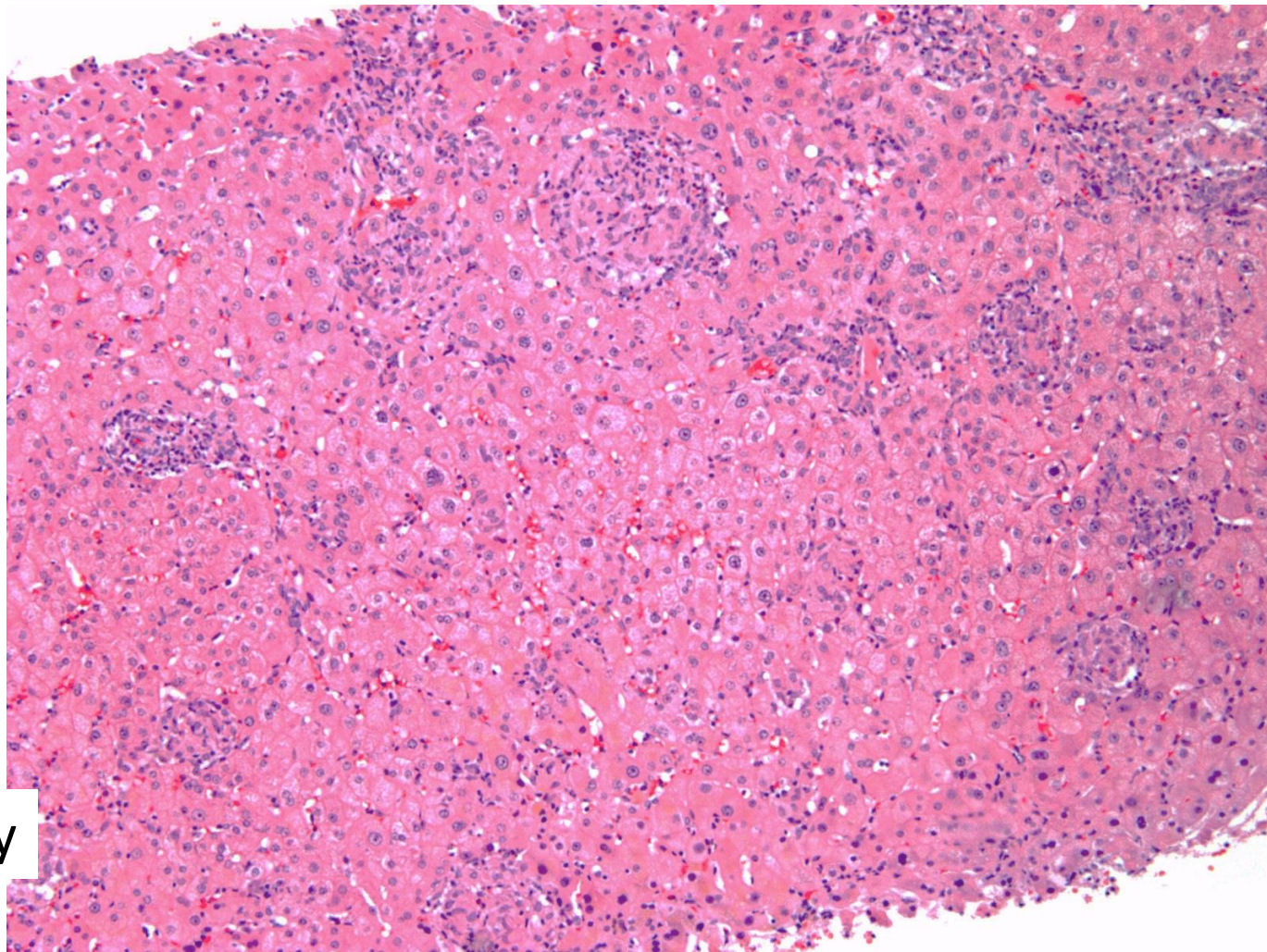


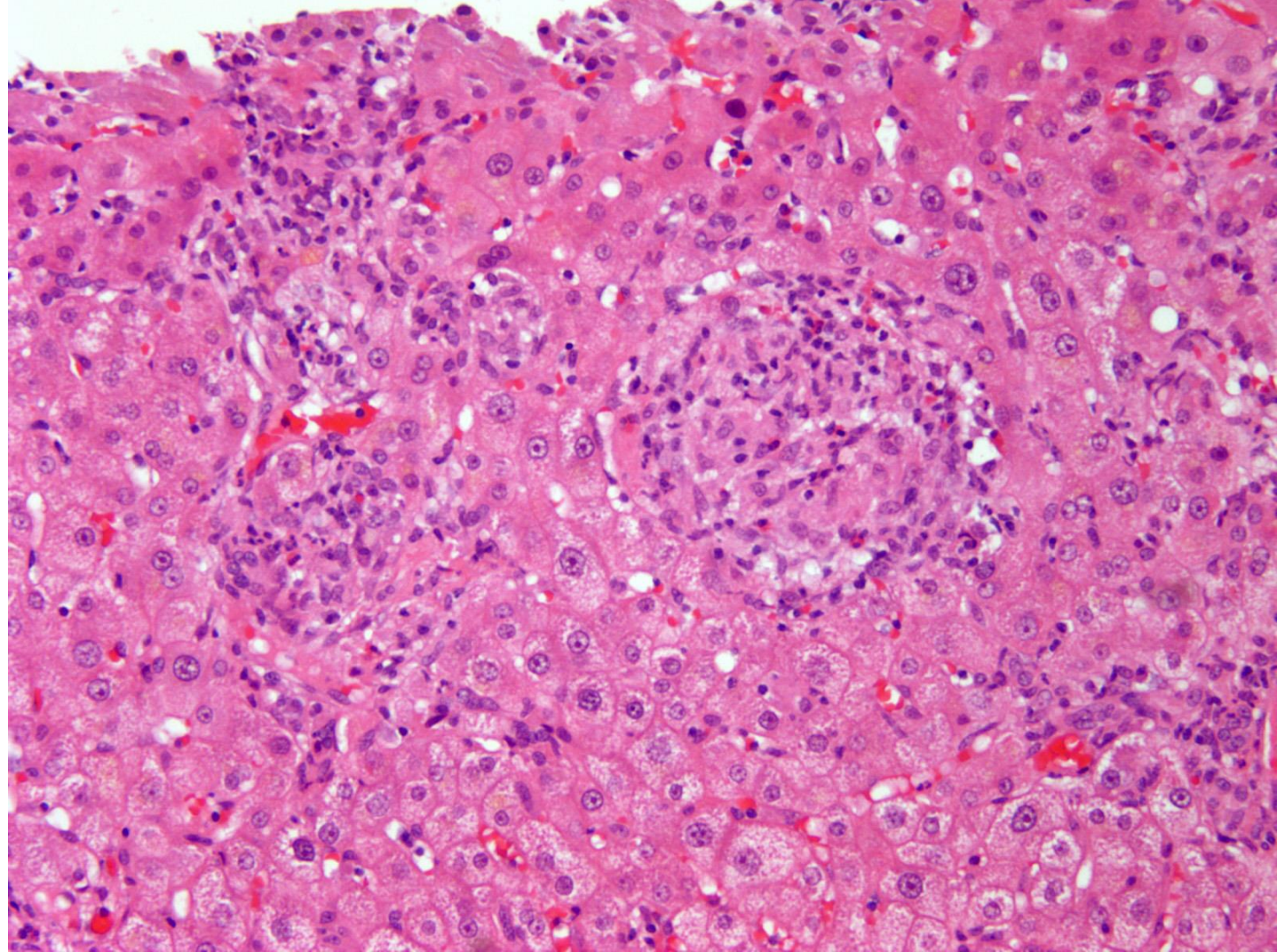


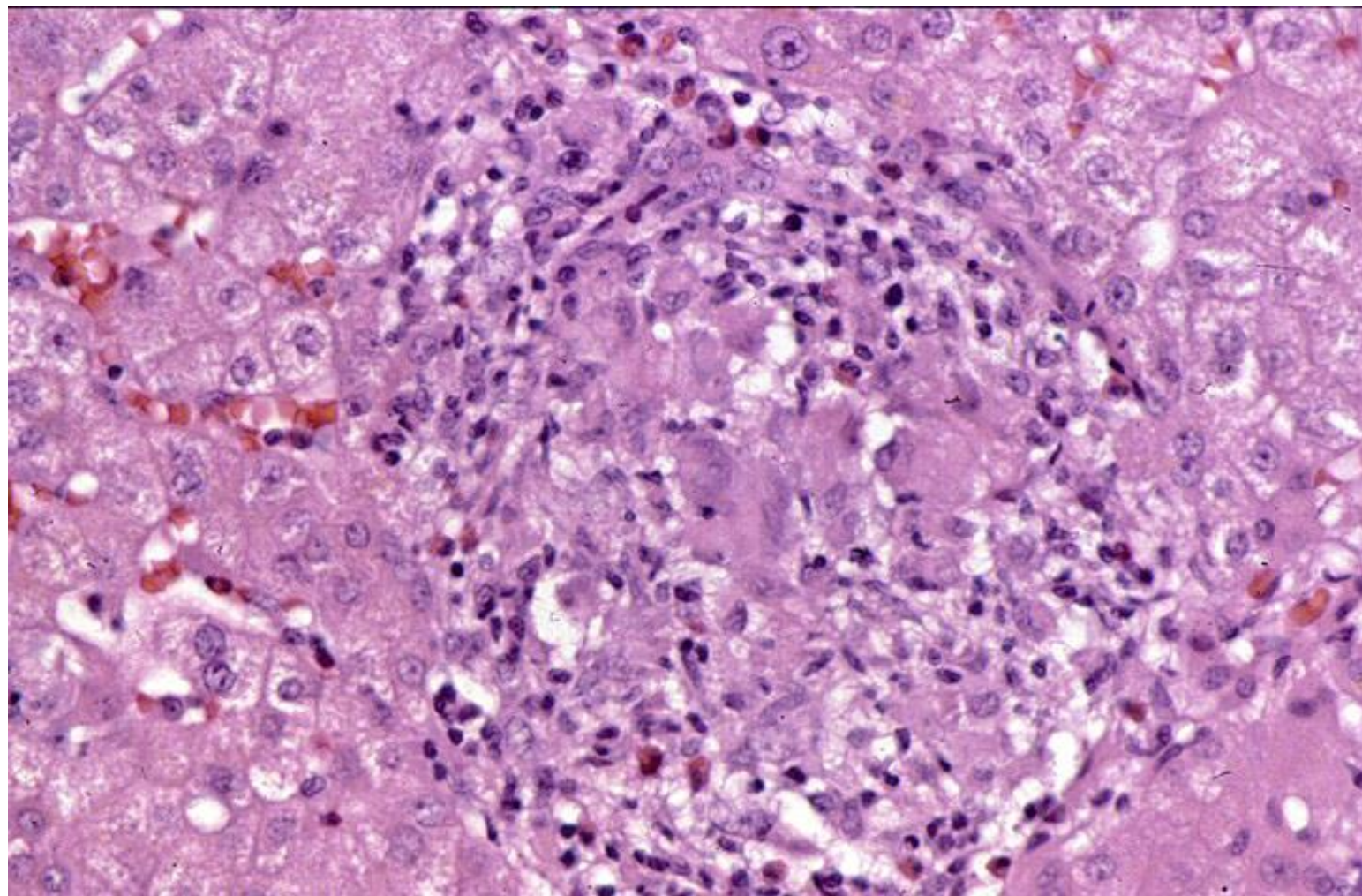
Leprosy

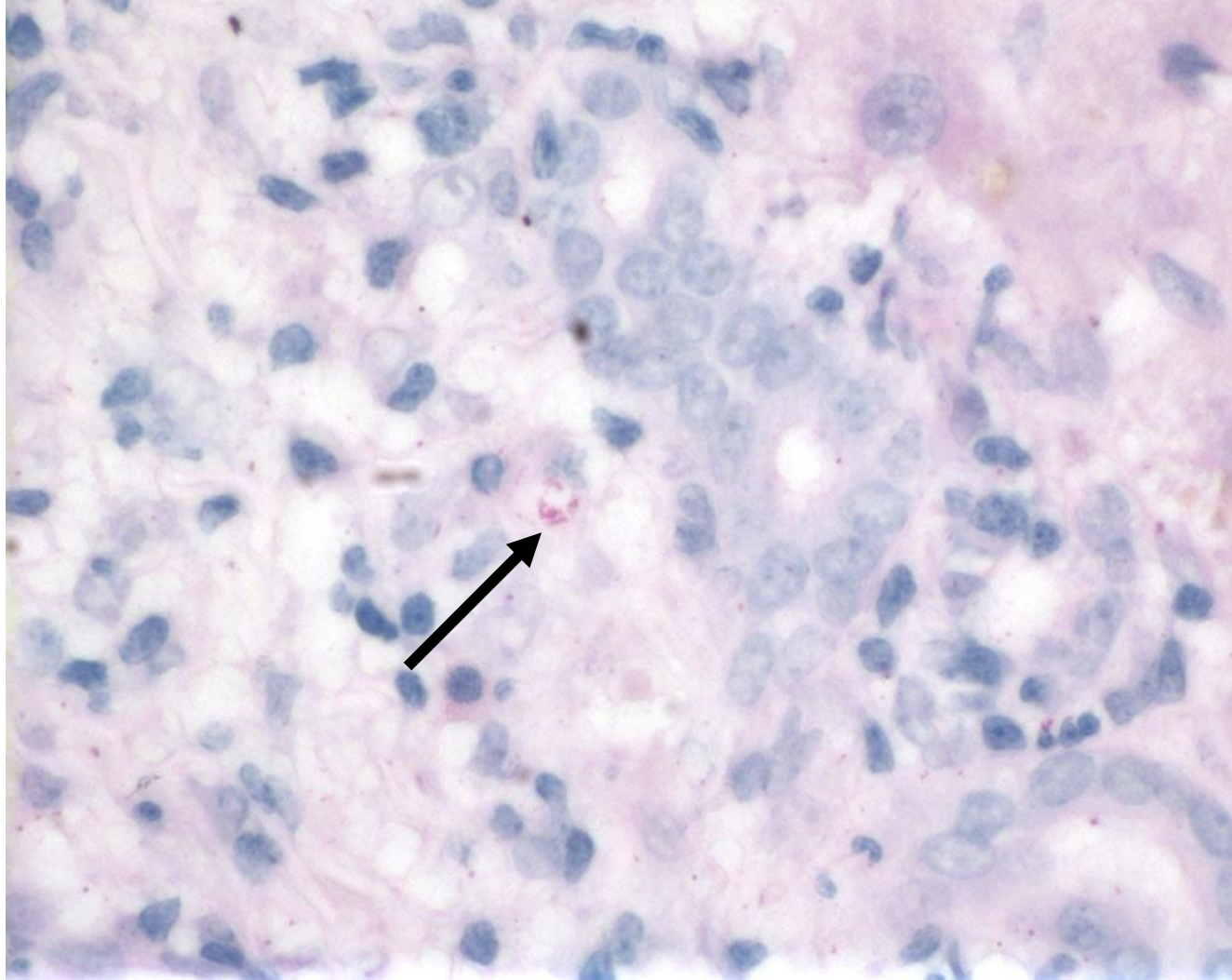
- Lepromatous
 - Foamy macrophage infiltrate; many organisms
 - Liver involved 60-90% of the time
- Tuberculoid
 - Noncaseating epithelioid granulomas; few organisms
 - Liver involved 20% of the time
- Often liver involvement is subclinical
- Liver may harbor bacilli even when skin is clear
- Diagnosis: special stains, molecular, culture

Leprosy



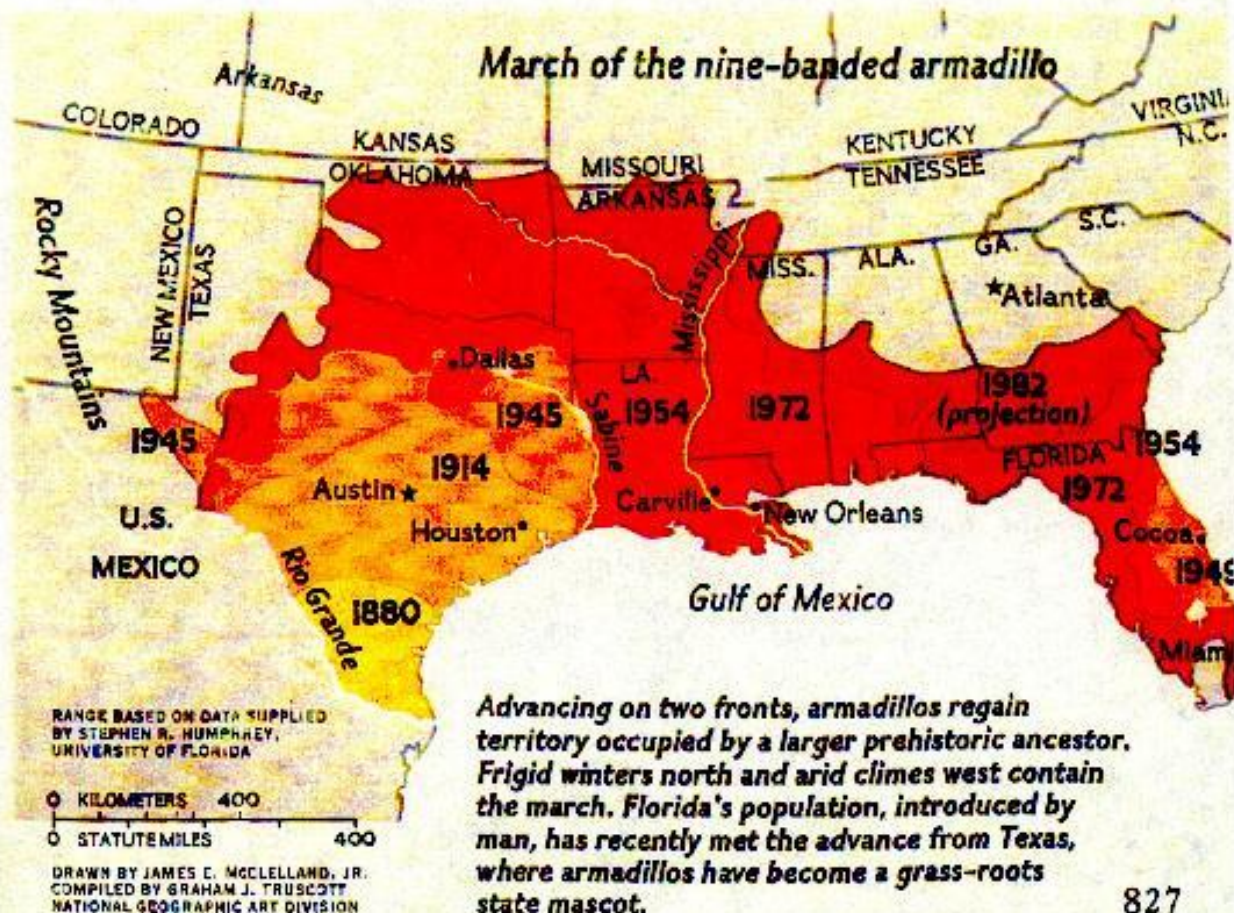






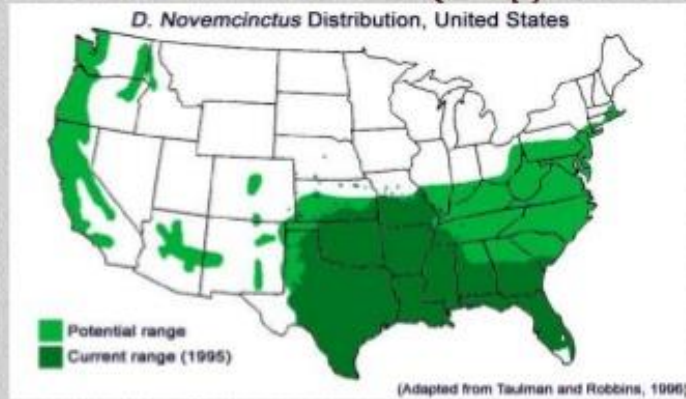


March of the nine-banded armadillo



Advancing on two fronts, armadillos regain territory occupied by a larger prehistoric ancestor. Frigid winters north and arid climes west contain the march. Florida's population, introduced by man, has recently met the advance from Texas, where armadillos have become a grass-roots state mascot.

Nine-Banded Armadillo (Migration Patterns)



- The Nine-Banded Armadillo originated in South America
 - First sighting in North America - (1840) Rio Grande Valley of Texas
 - Migrated from Texas to bordering states as far as Florida and to southern parts of Illinois and Indiana (2013 data)
 - Barrier to migration – Colder climates below 22°C
- (Google. n.d. Map. Available from: <https://www.google.com/search?q=Nine-Banded+armadillo+territories&ie=utf-8&oe=utf-8&q=t&rls=org.mozilla:en-US:official&client=firefox-a&channel=fflb#channel=fflb&q=Nine-Banded+armadillo+territories&rls=org.mozilla:en-US:official&spell=1>)

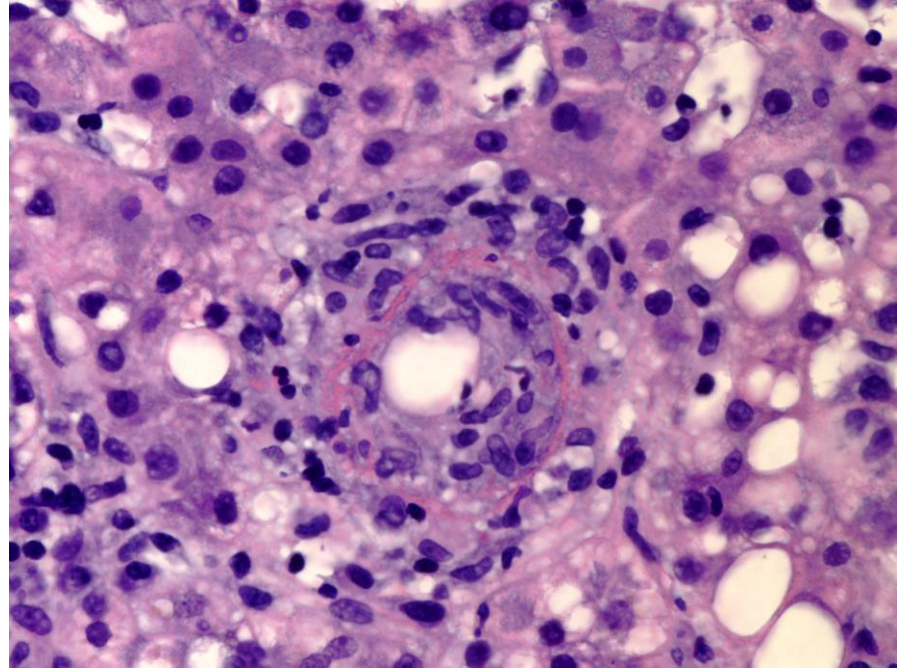


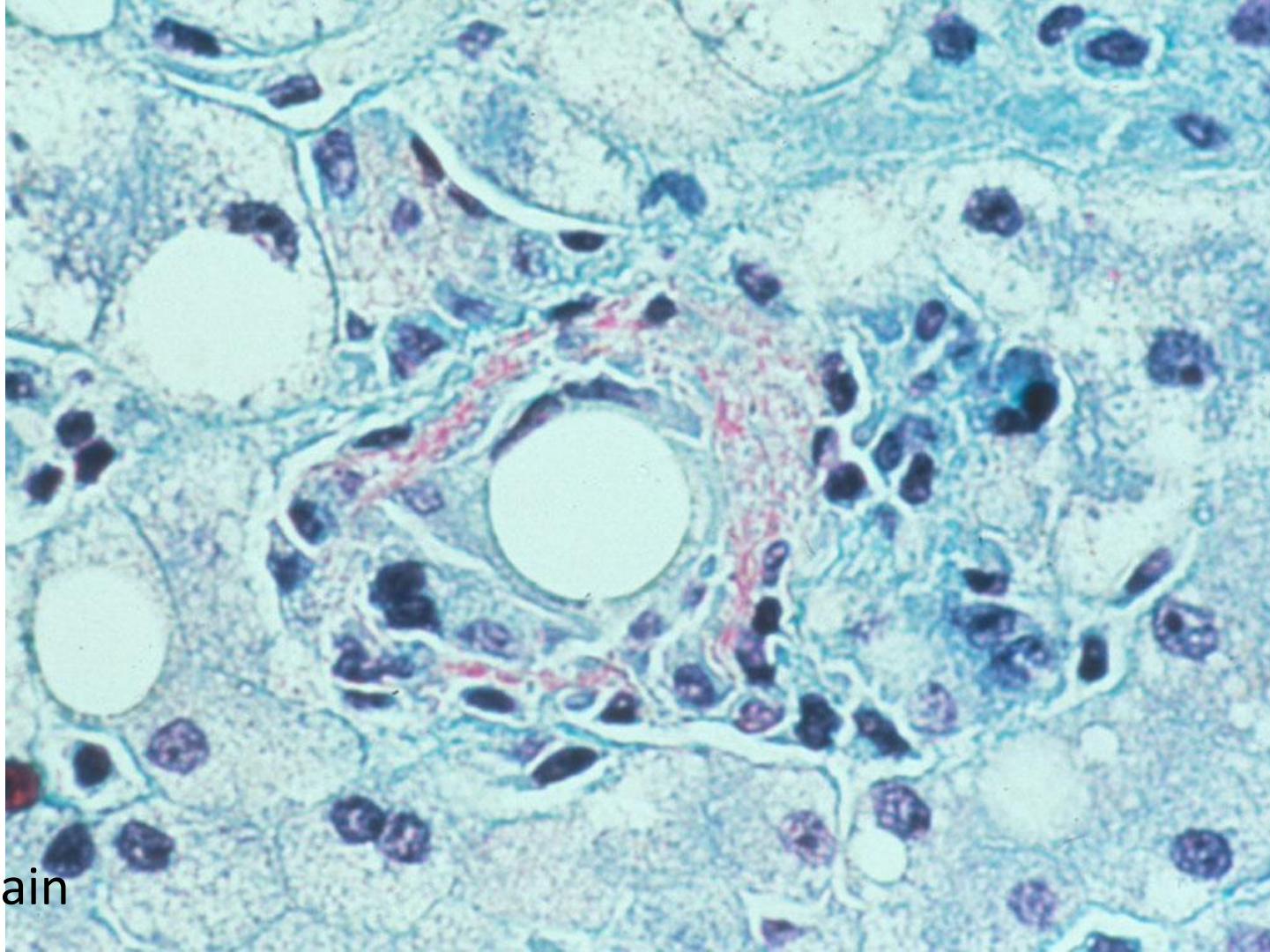
**For Your Safety
&
Due to The Carnivorous**

**We Will Not Be
Able to Open
The Pool This Season.**

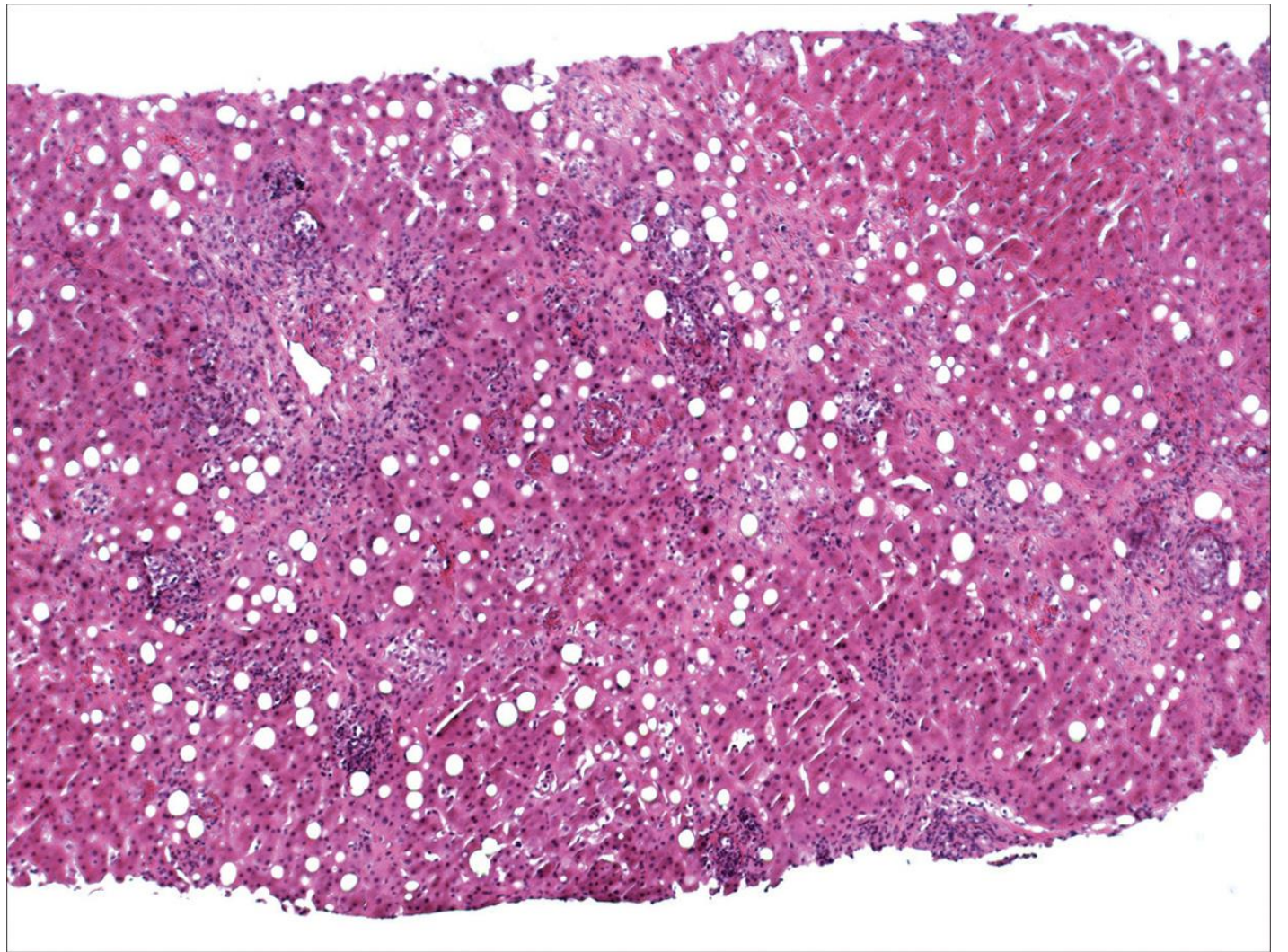
Morphological Classification of Granulomas

- Fibrin ring granuloma
 - Fairly specific to liver
 - Epithelioid granuloma composed of lipid vacuole surrounded by fibrin ring
 - DDX:
 - Infection
 - Drug reactions
 - Hodgkin disease





Fibrin Stain

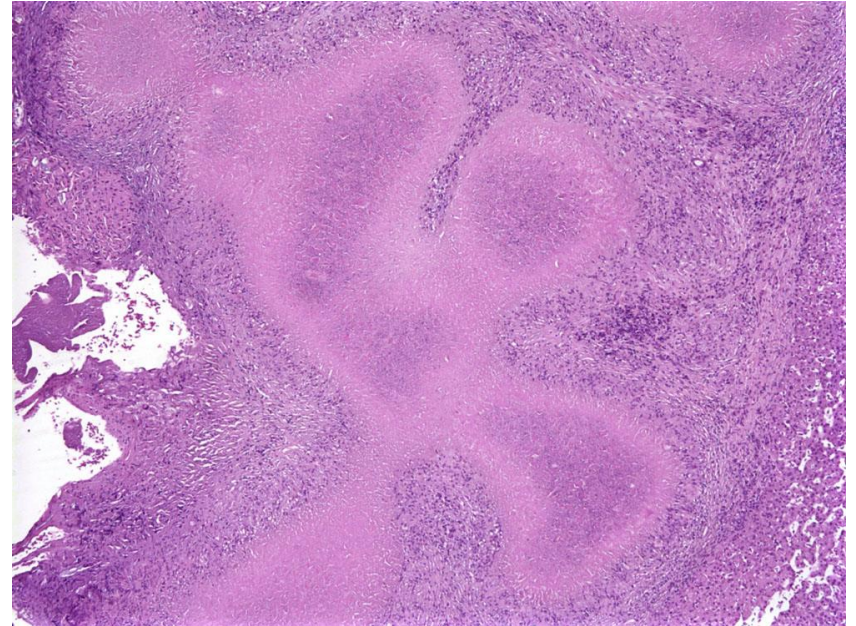


Q fever

Courtesy Dr. Dhanpat Jain

Morphological Classification of Granulomas

- Stellate abscess with granulomatous inflammation
 - Central abscess, often irregular
 - Surrounding granulomatous inflammation

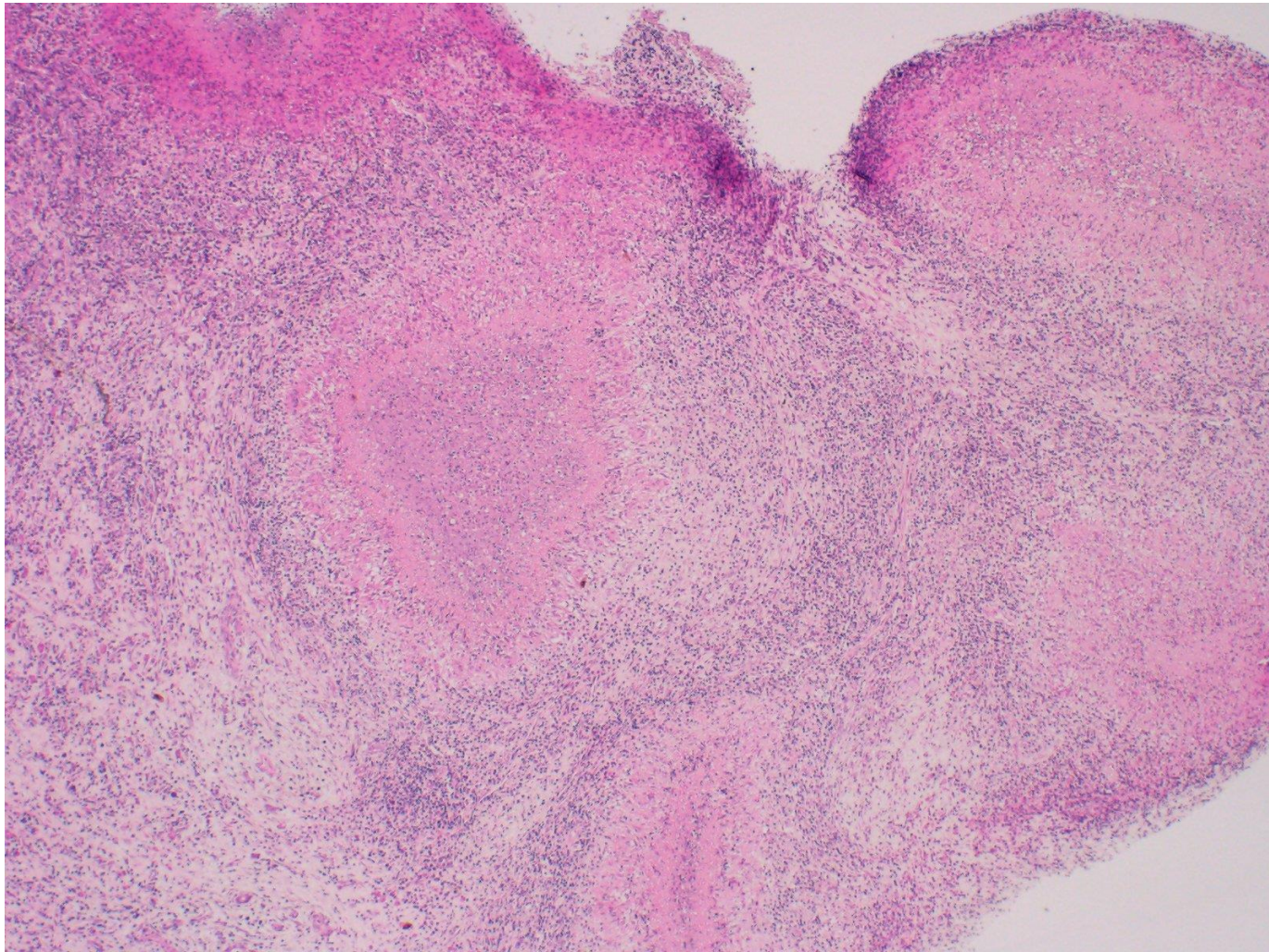


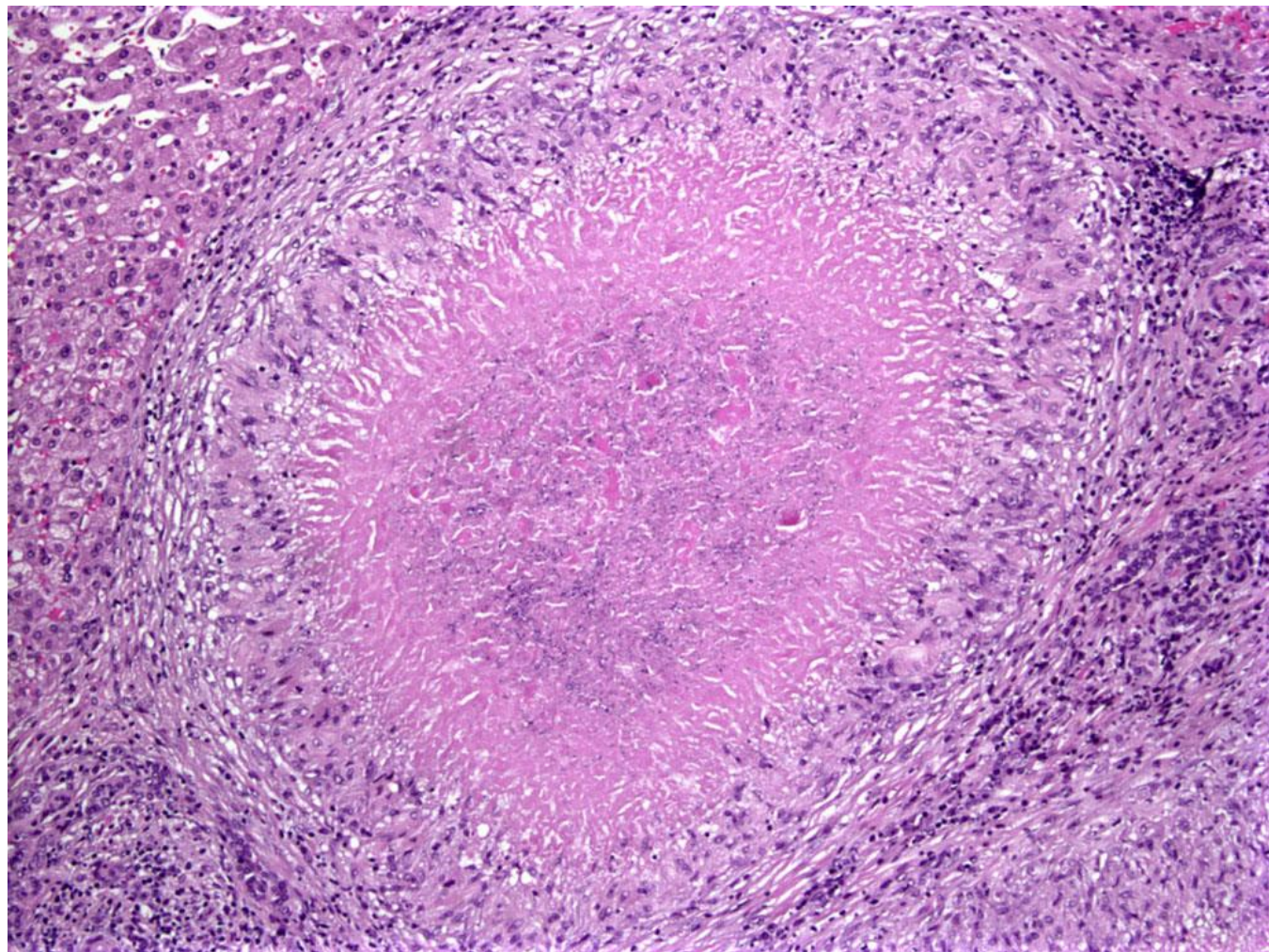
Cat Scratch Disease

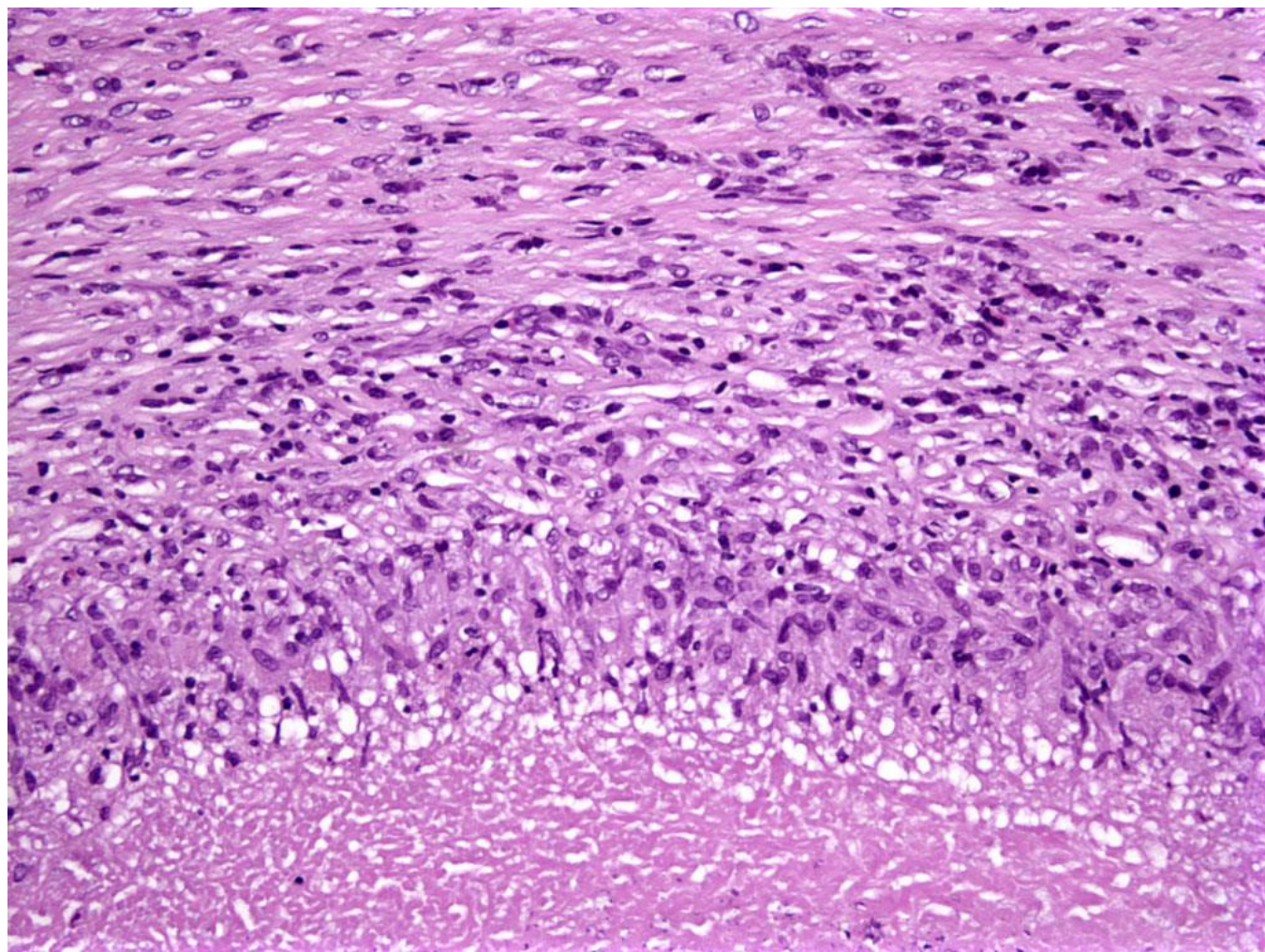
- Small percentage of patients have disseminated/visceral disease
- Lack inoculation site
- Usually not immunocompromised
- Diagnosis: PCR, serologies, special stains, immunohistochemistry, history

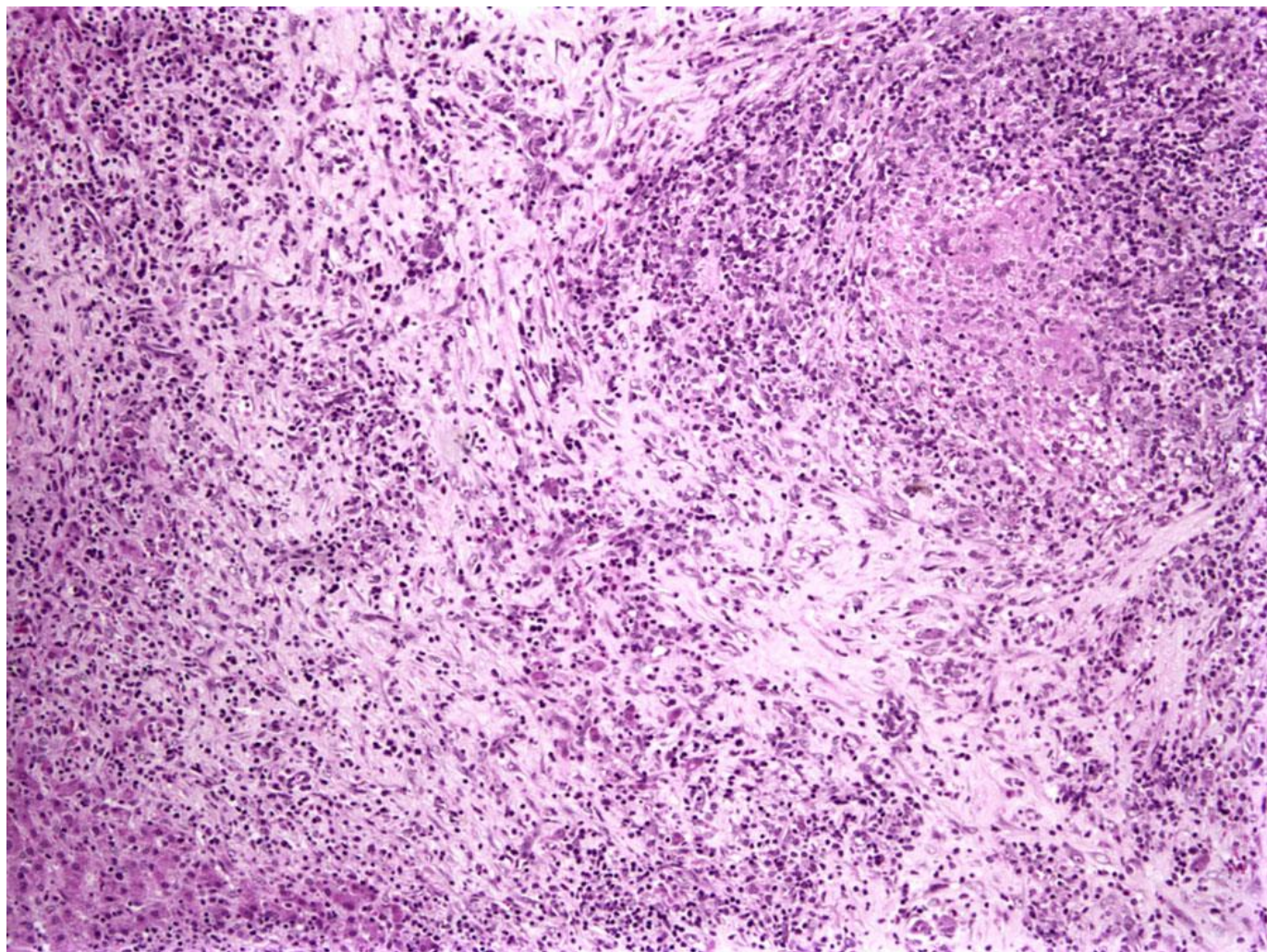


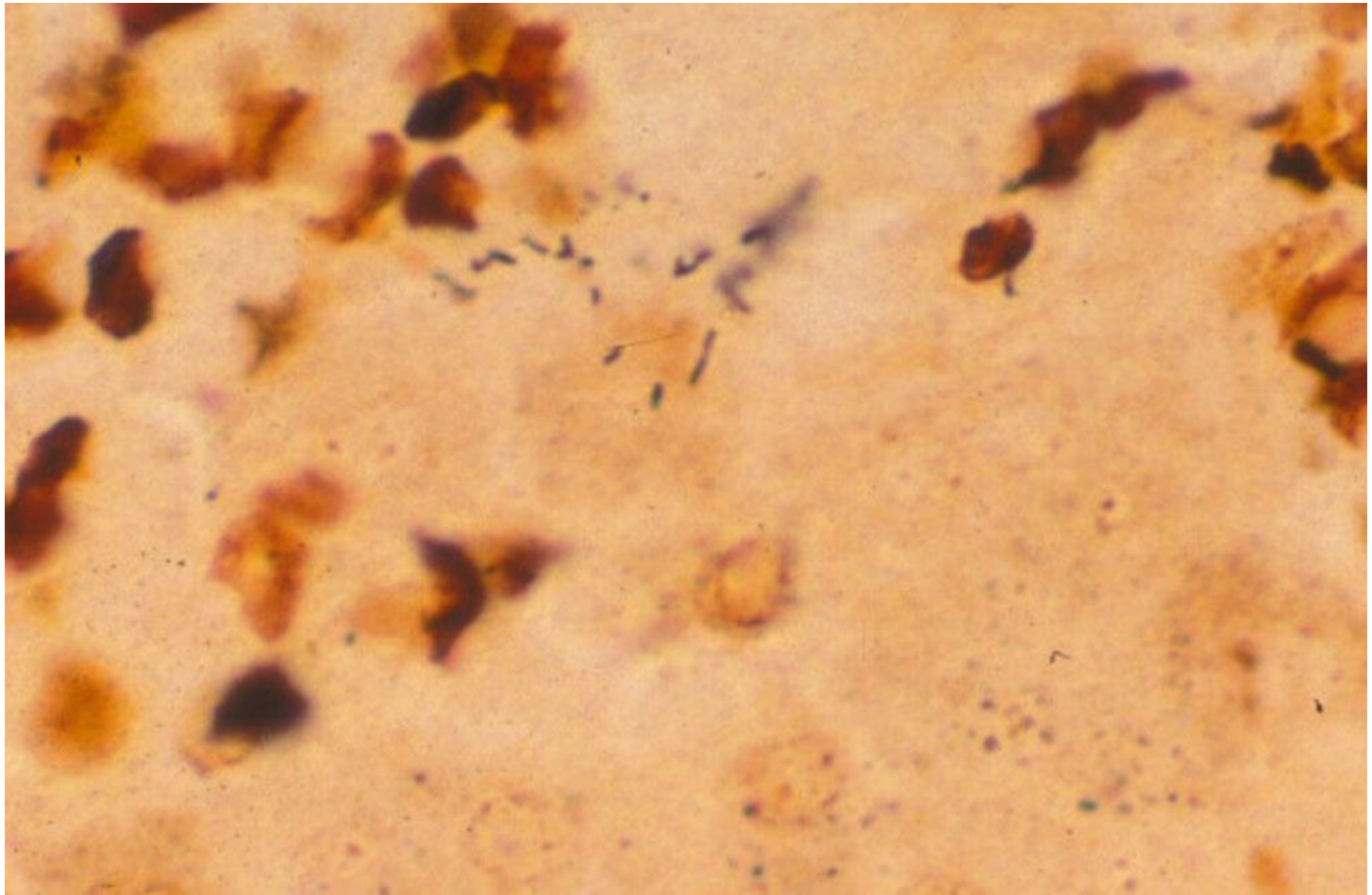




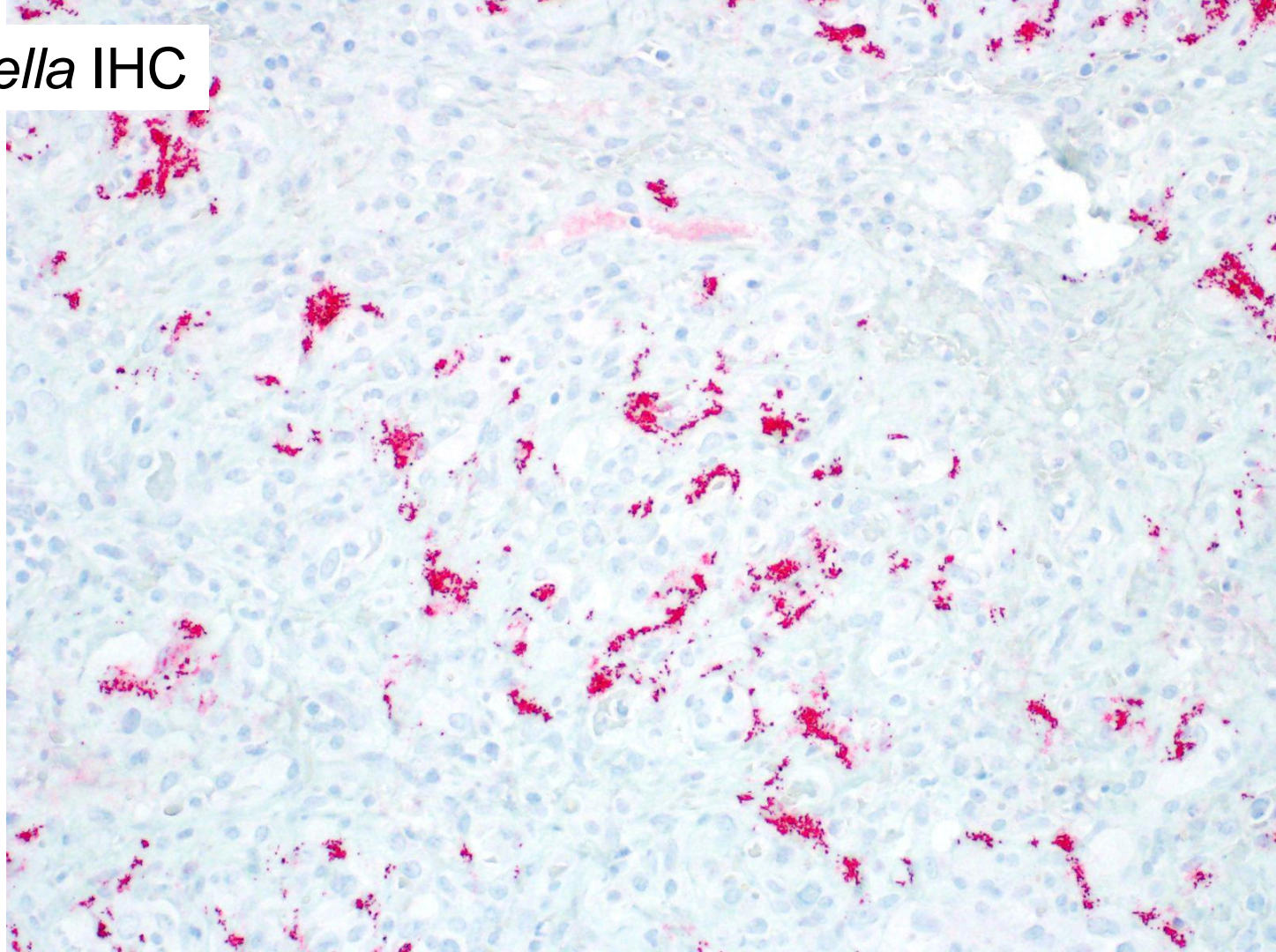


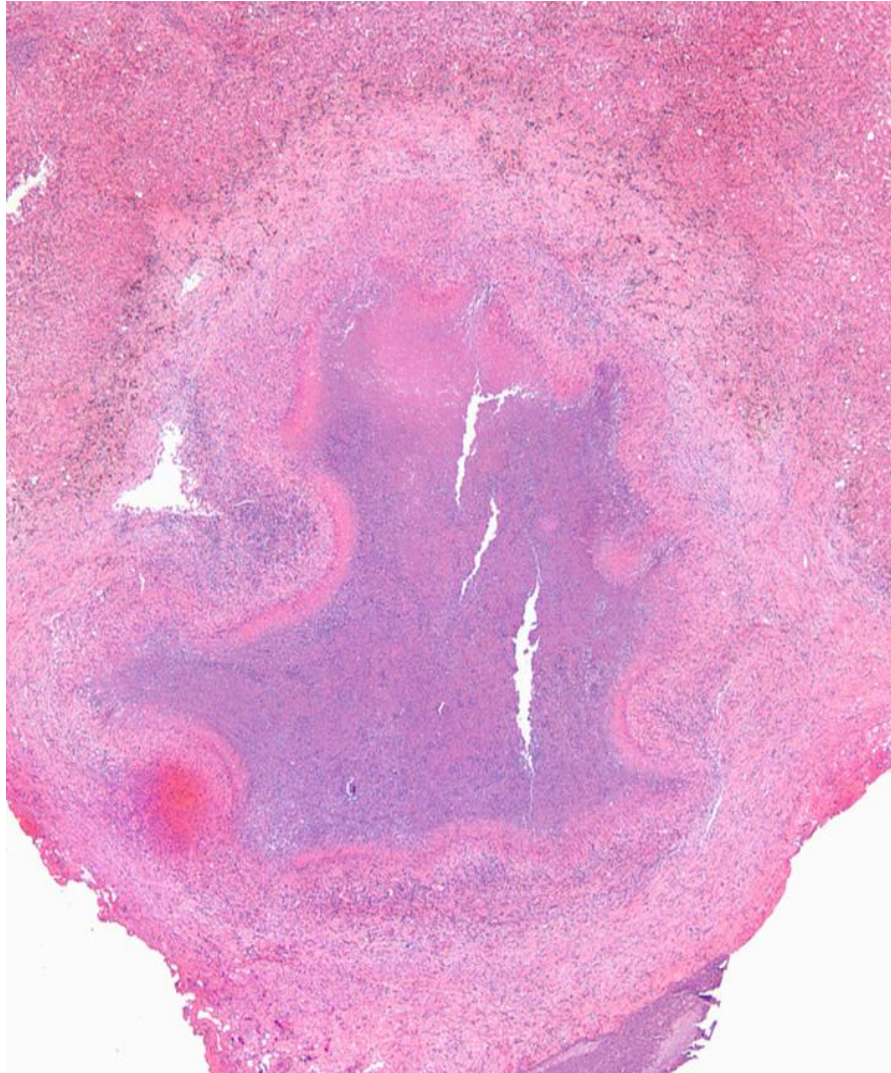




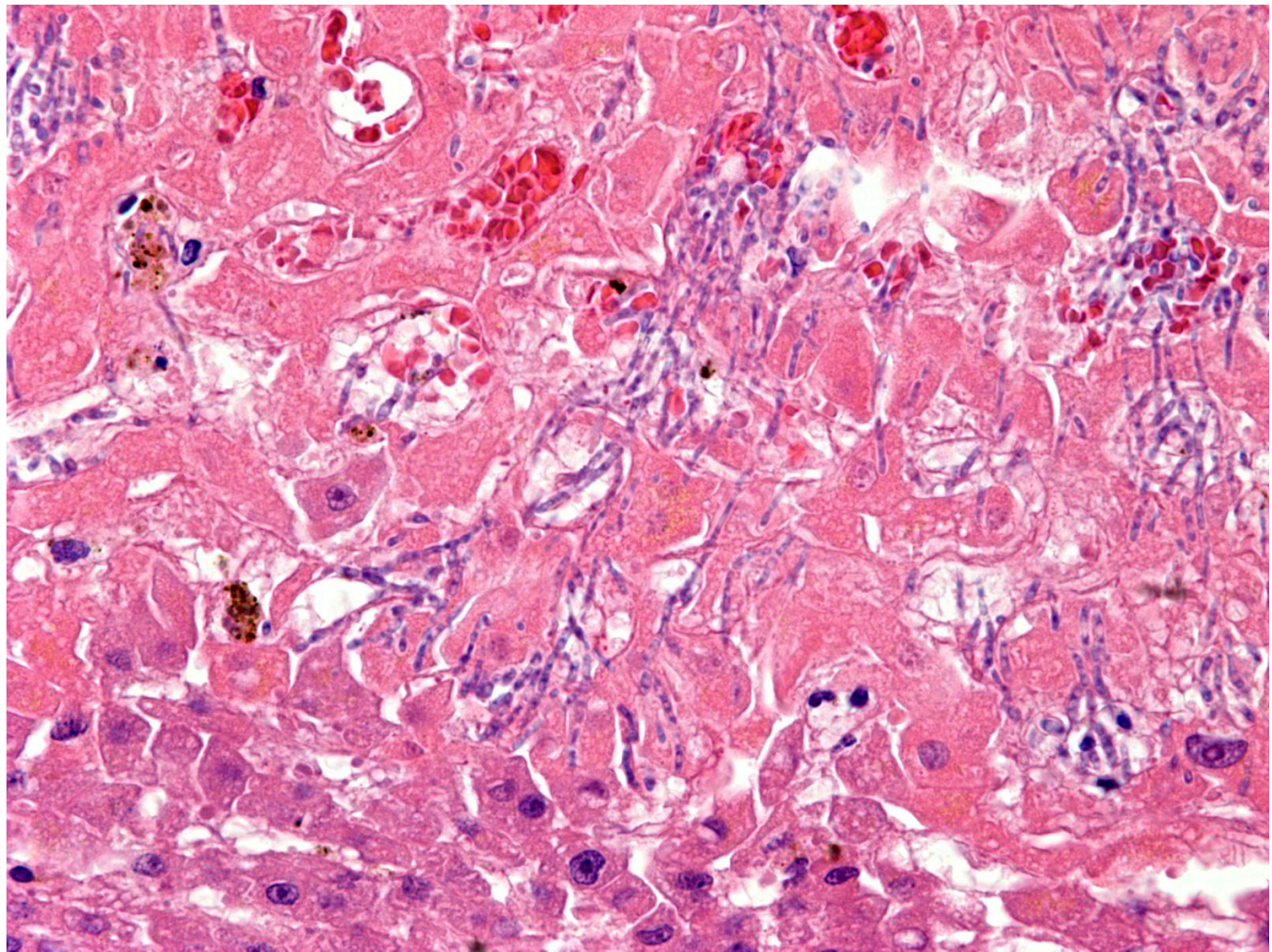


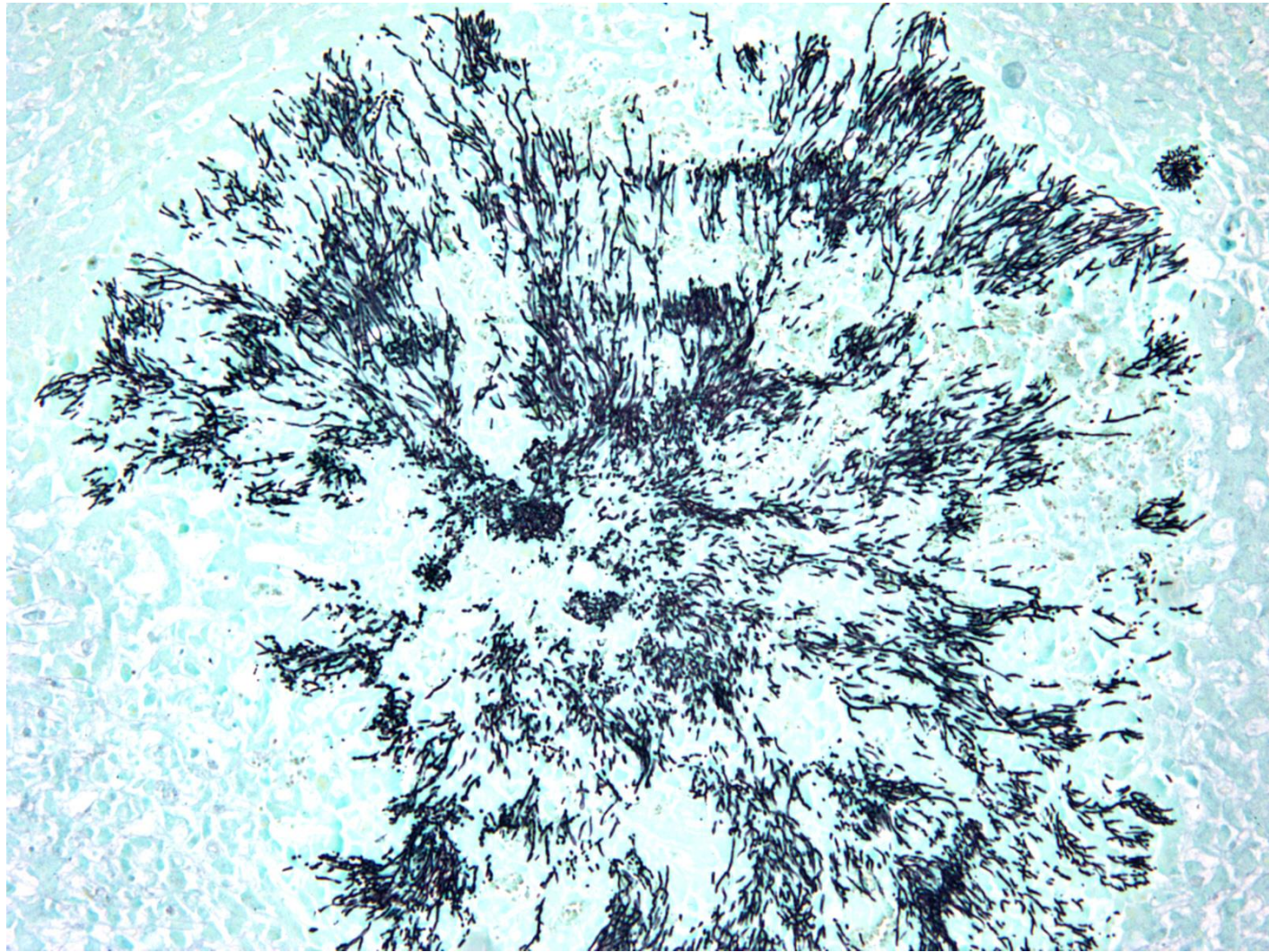
Bartonella IHC





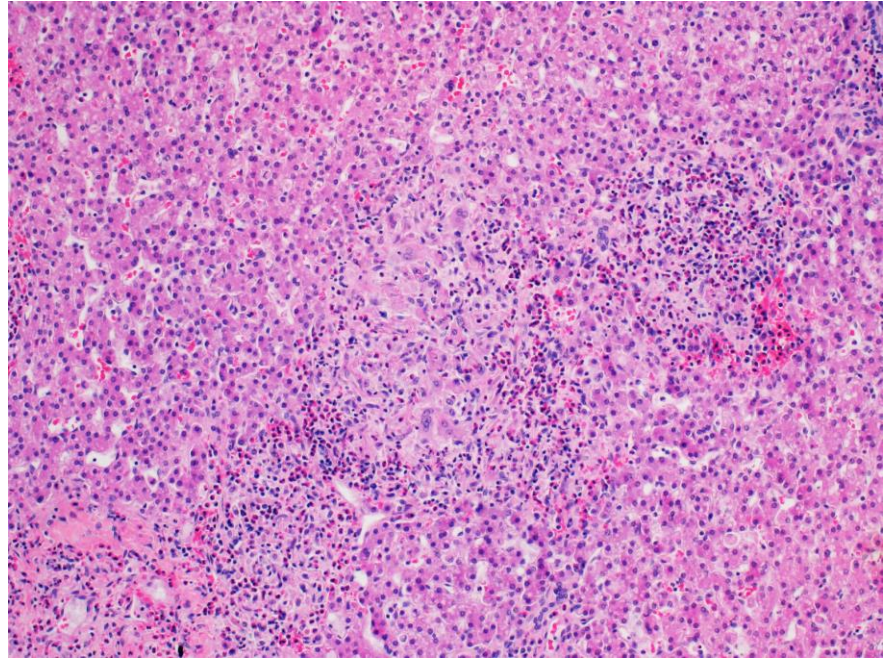
Candida abscess
Courtesy Dr. Lisa Yerian





Morphological Classification of Granulomas

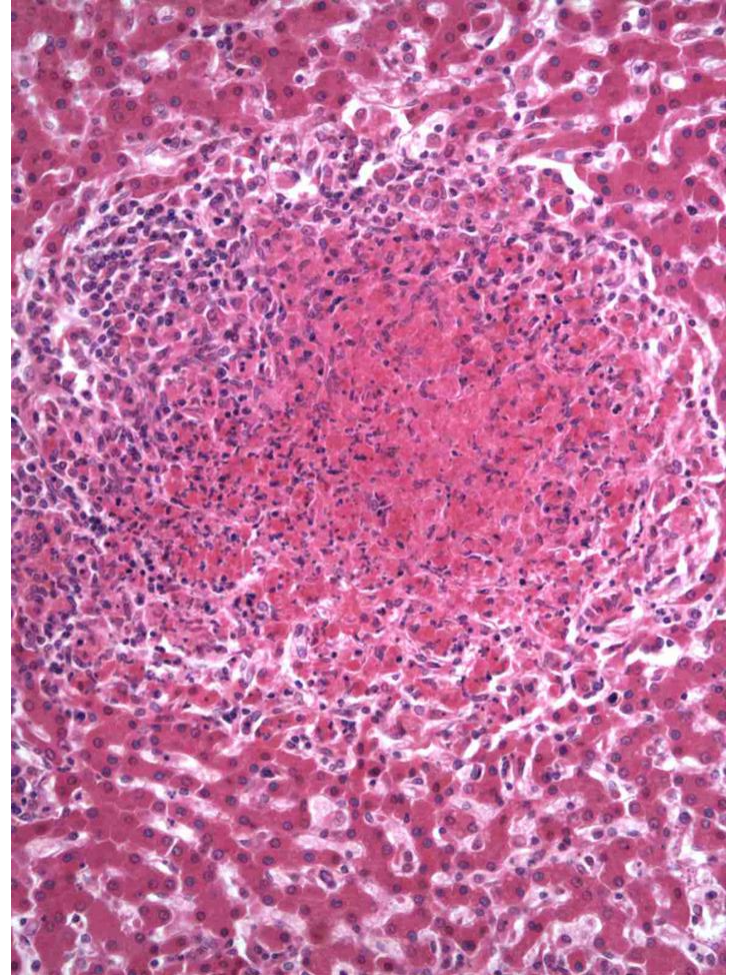
- Granulomatous inflammation
 - Less well delineated, indistinct edges
 - Often admixed with other inflammatory cells, including neutrophils

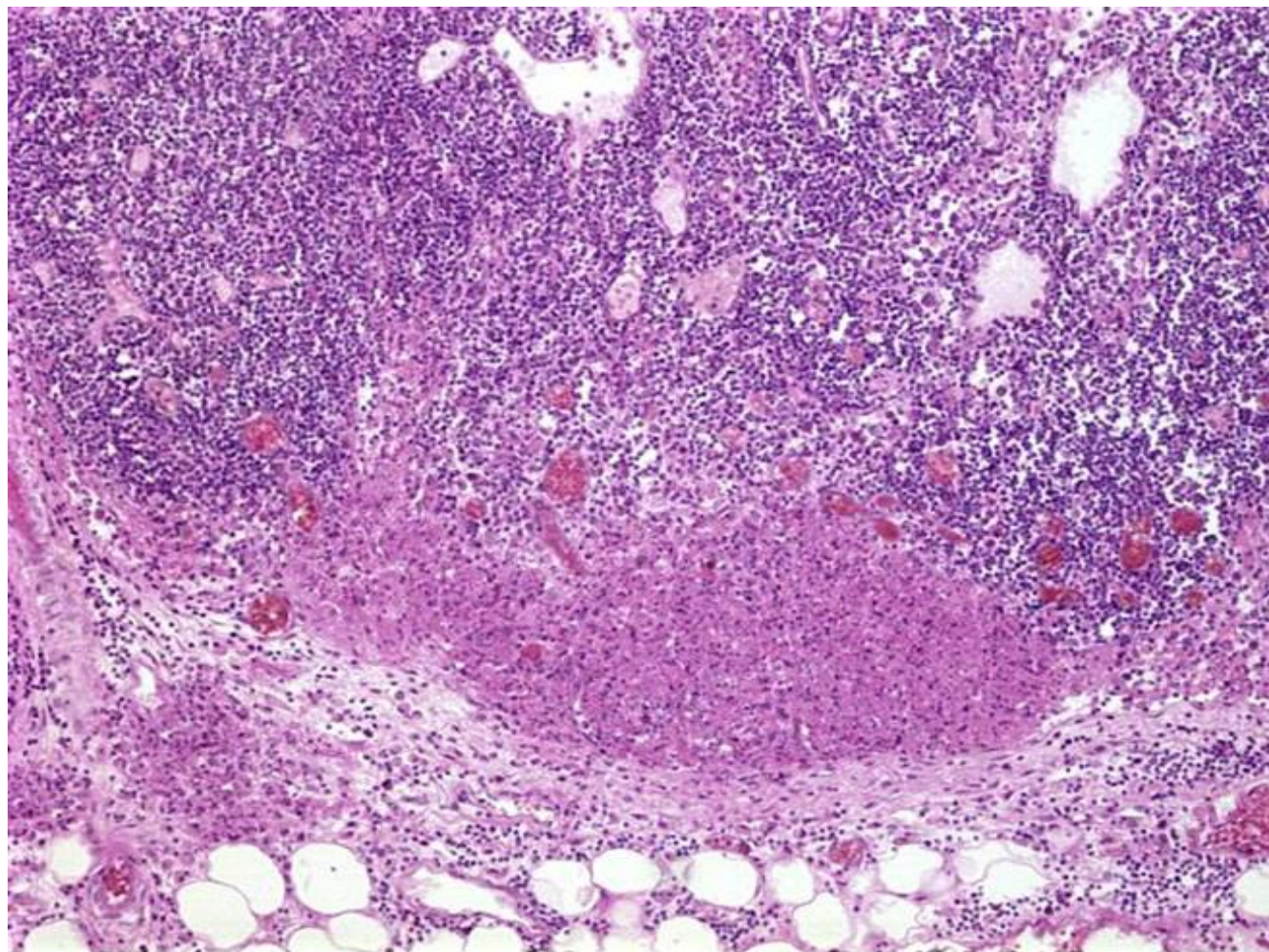


Ascaris

Tularemia

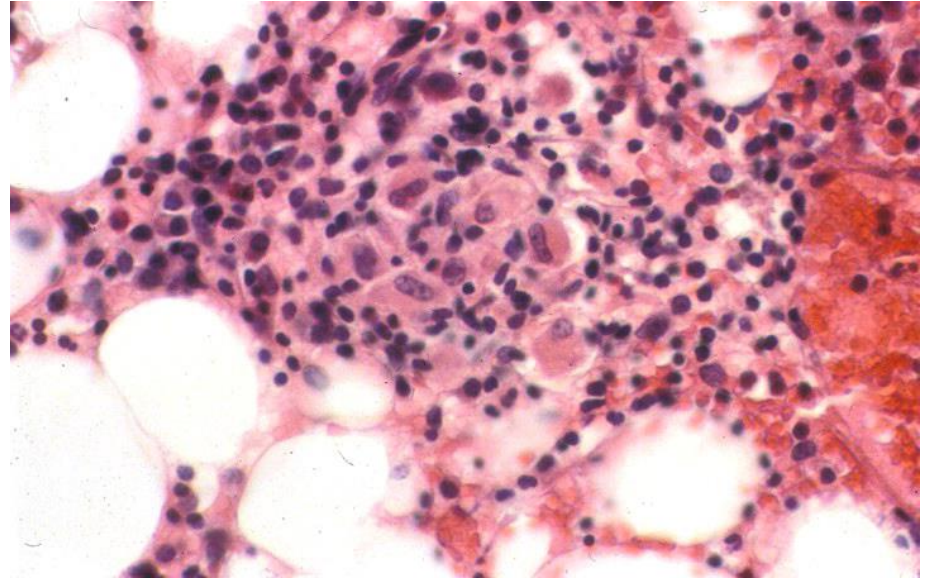
- Transmitted through contact with rodents/rabbits
- Patients often systemically ill, +/- hepatomegaly and elevated transaminases
- Diagnosis: serologies, molecular, culture; special stains not helpful





Brucellosis

- Exposure to infected farm animals, contaminated food or dairy
- Fever, chills, headache, arthralgia
 - Liver involved in about half of cases
- Diagnosis: history, serologies; special stains and culture not helpful



FIGS: A DIAGRAM.



Fig 1.



Fig 2.



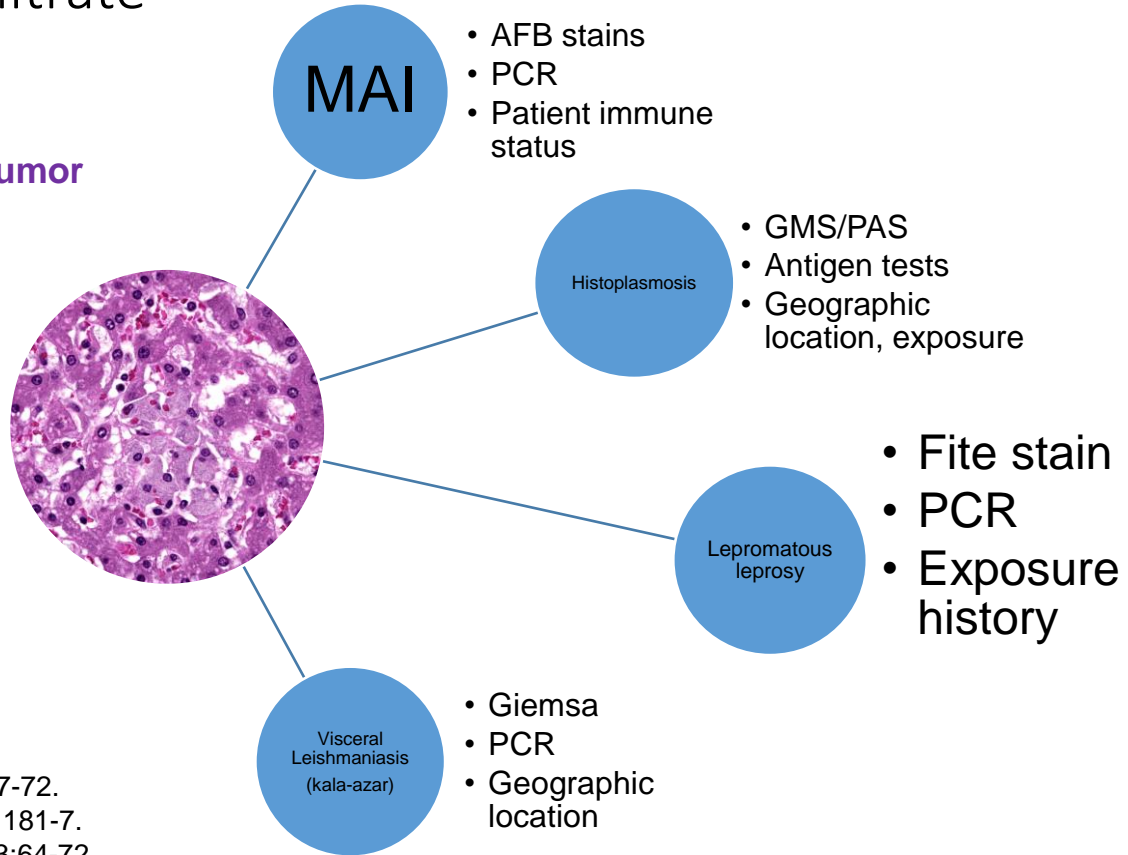
Fig 3.



Fig 4.

Foamy histiocyte infiltrate

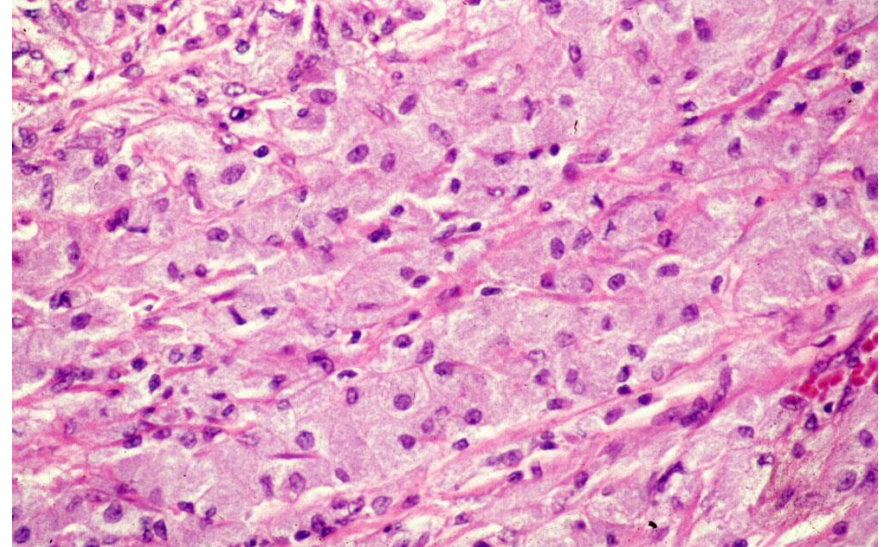
DDx:
IgG4 inflammatory pseudotumor
Rosai-Dorfmann disease



Farhi DC *et al.* Am J Clin Pathol 1886;85:67-72.
Umlas J *et al.* Am J Surg Pathol 1991; 15:1181-7.
Lamps LW *et al.* Am J Clin Pathol 2000;113:64-72.
Zen Y *et al.* Mod Pathol 2007;20:884-94.
Alruwaili ZI *et al.* Am J Surg Pathol 2019;43:1644-52.

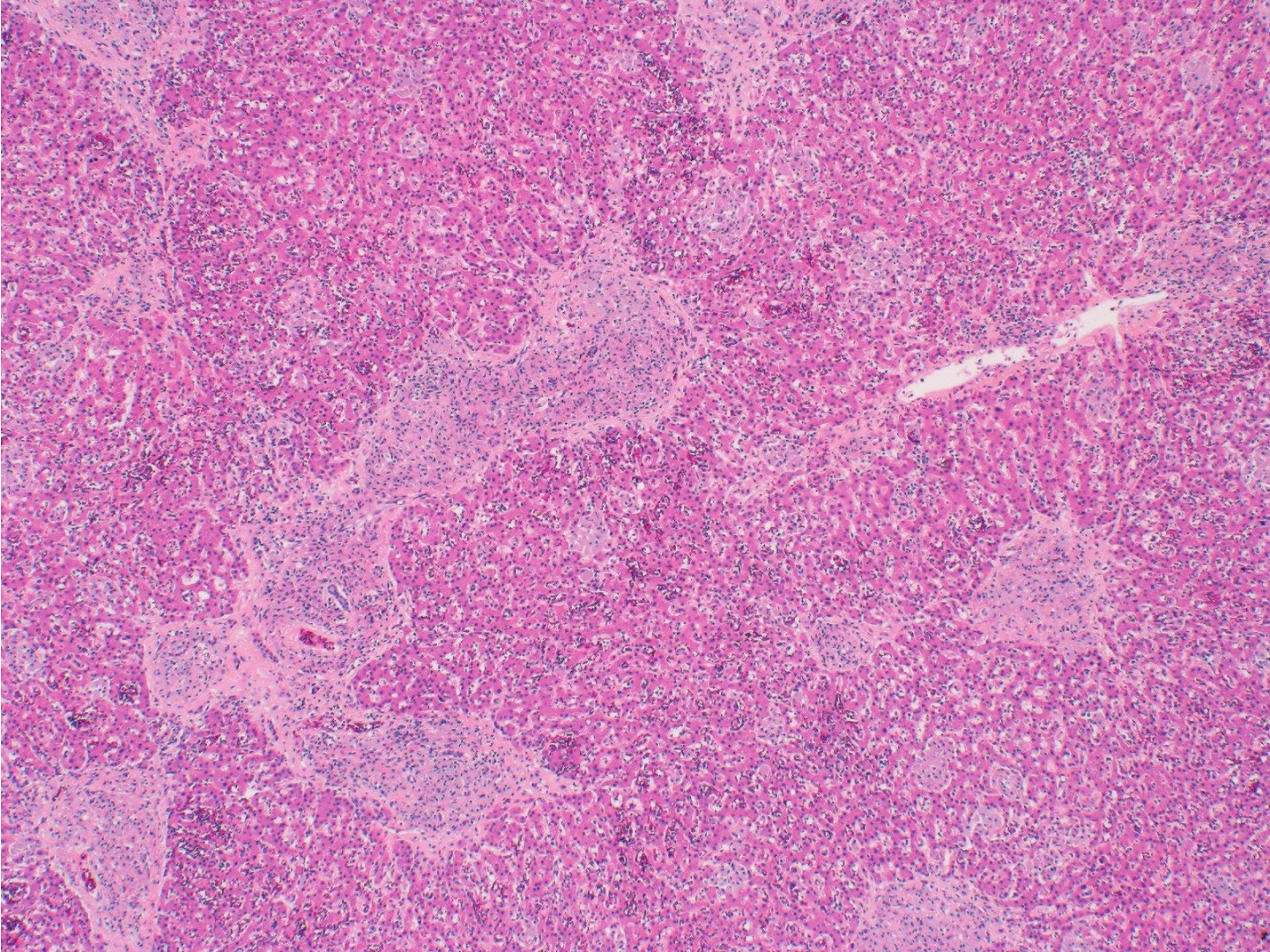
Morphological Classification of Granulomas

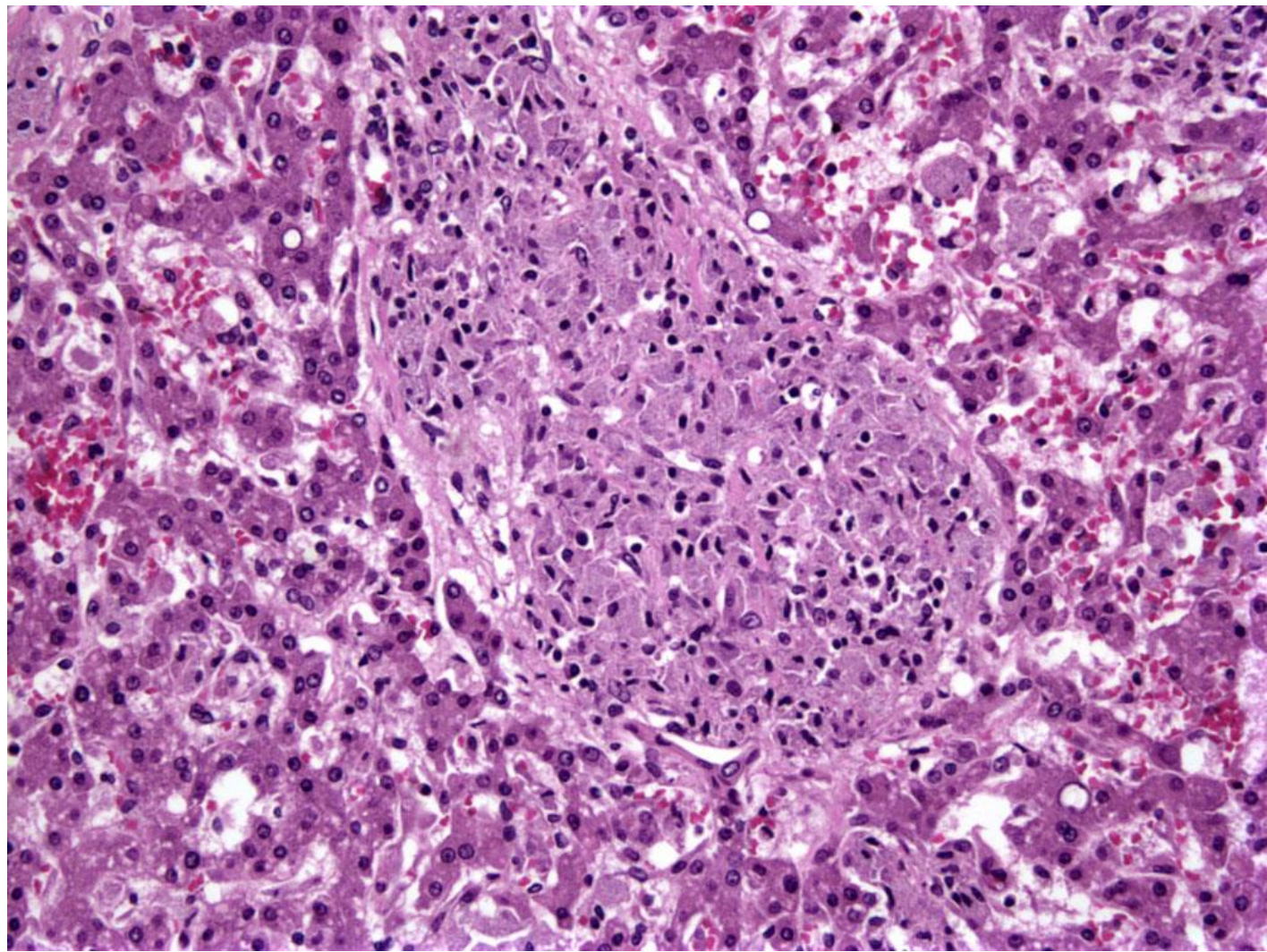
- Foamy macrophage aggregates
 - Usually immunocompromised patients
 - Other inflammatory cells variably present

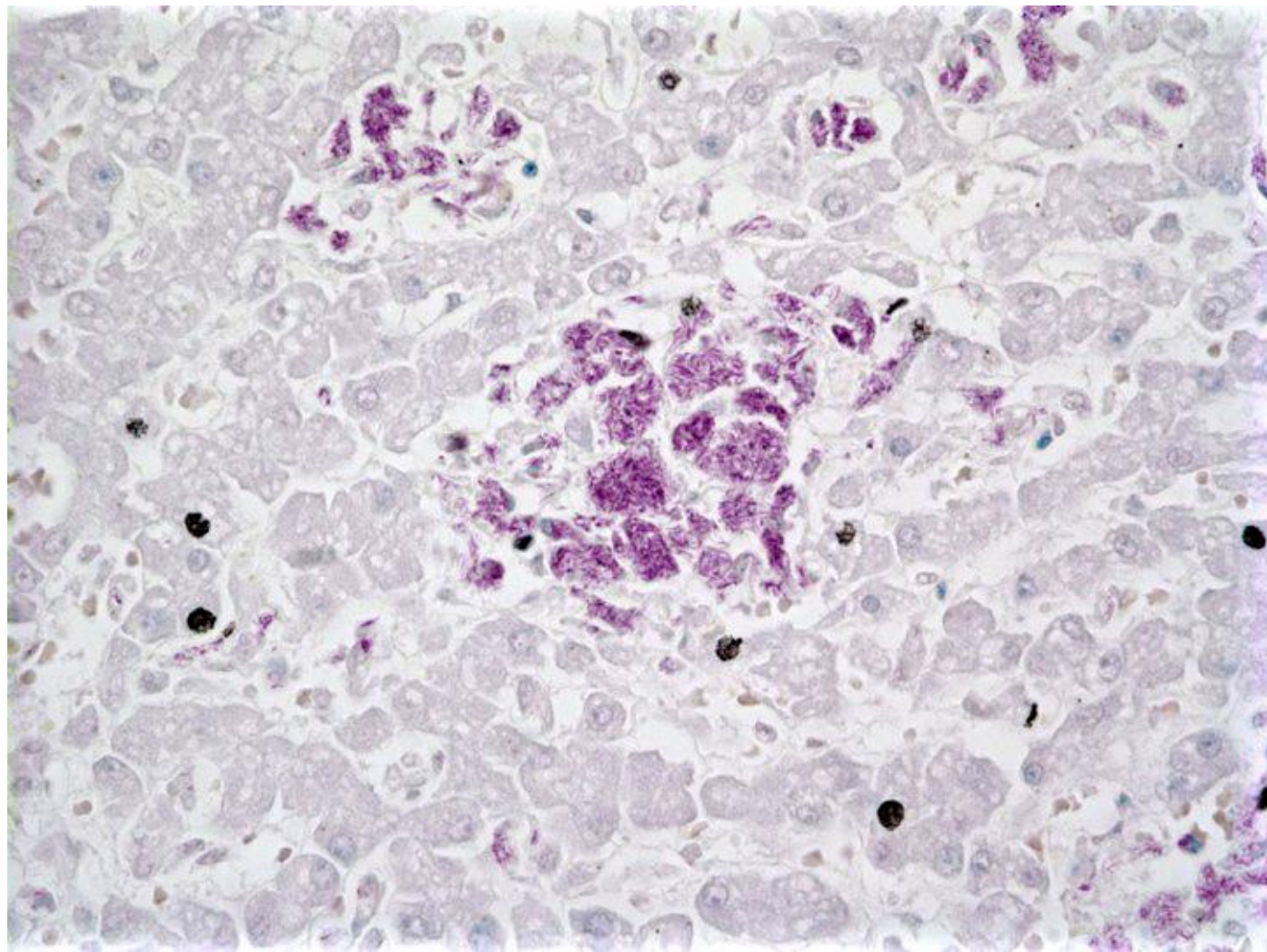


MAI

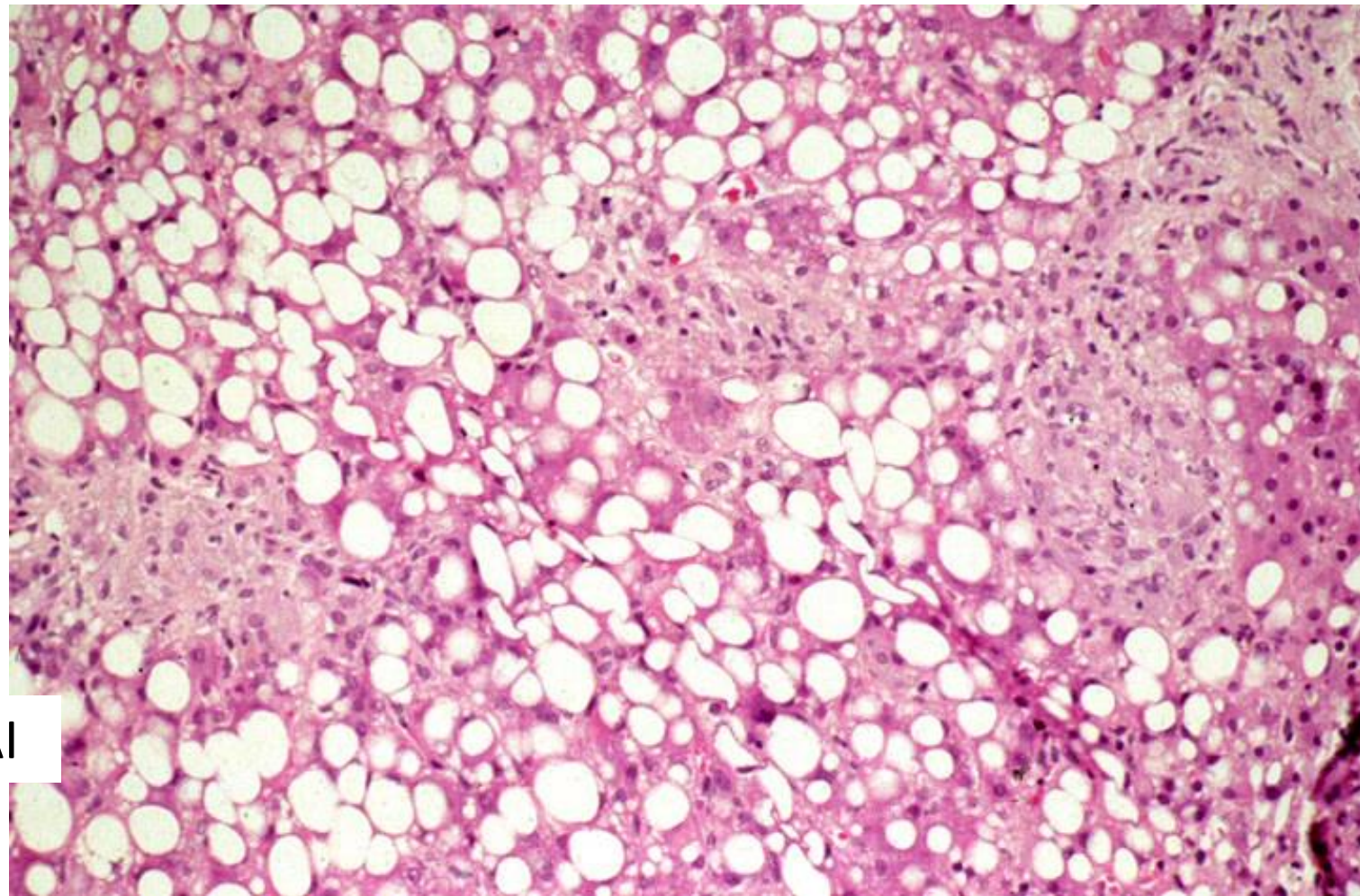
- Most common in immunocompromised patients
- Increasing in patients without AIDS
 - Chronic pulmonary disease, immunosuppressive medications and comorbid diseases
 - 25% of patients in one large study had no known risk factors
- Variable lesions depending on site and immune status of host:
 - Discrete granulomas
 - Foamy macrophage infiltrate
 - Fibrin ring granulomas
 - Spindle cell nodule
- Diagnosis: special stains, molecular, culture

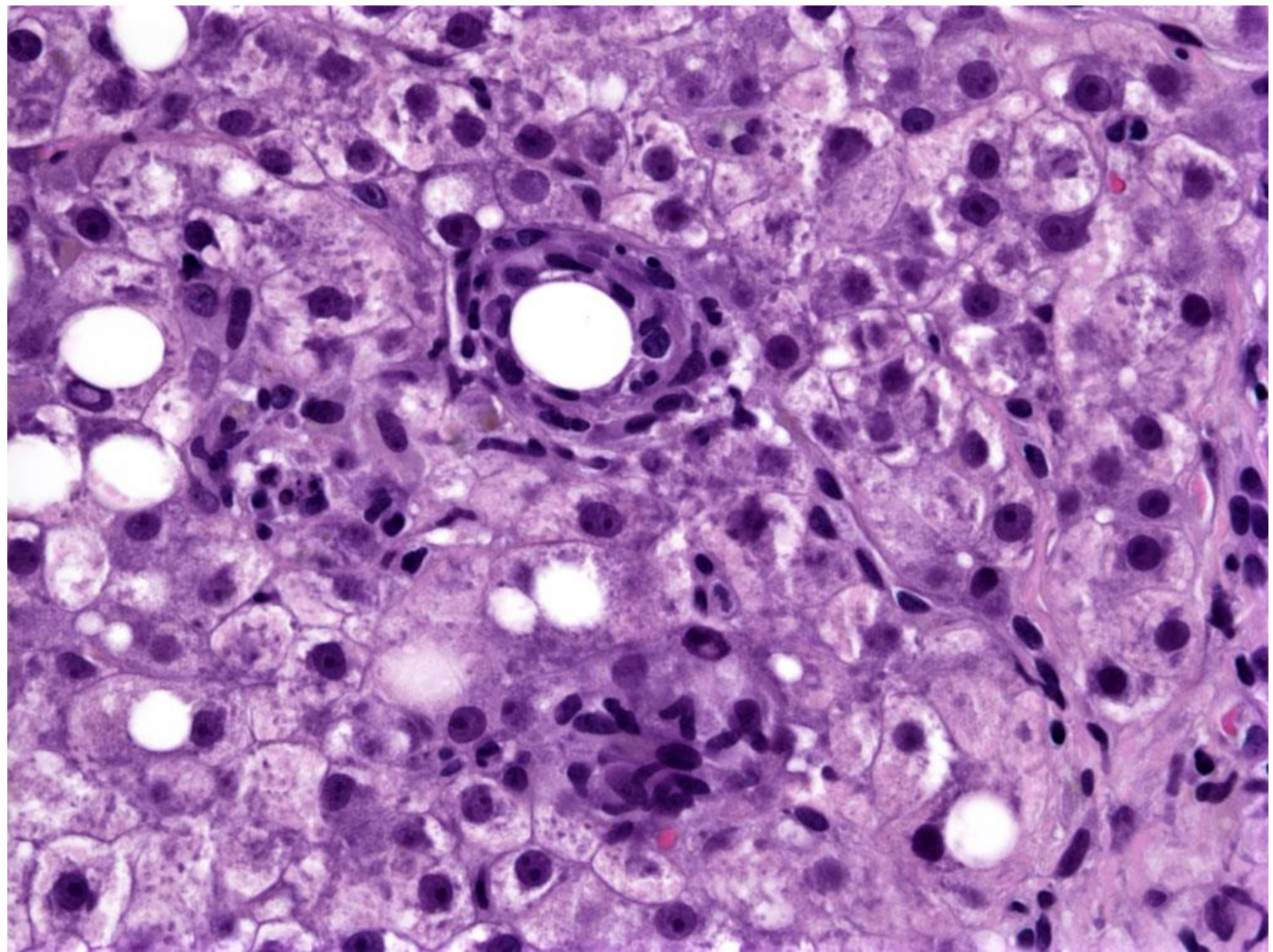


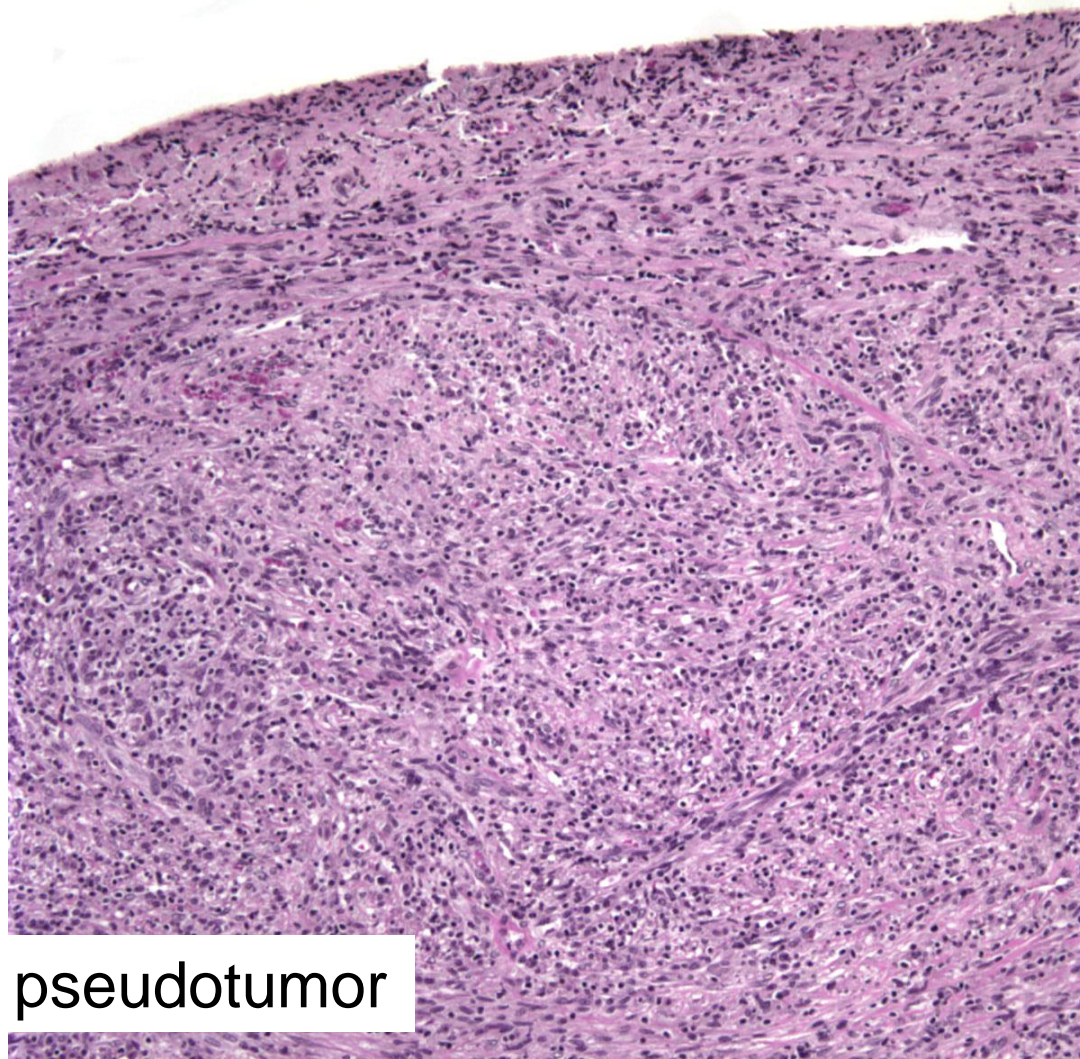




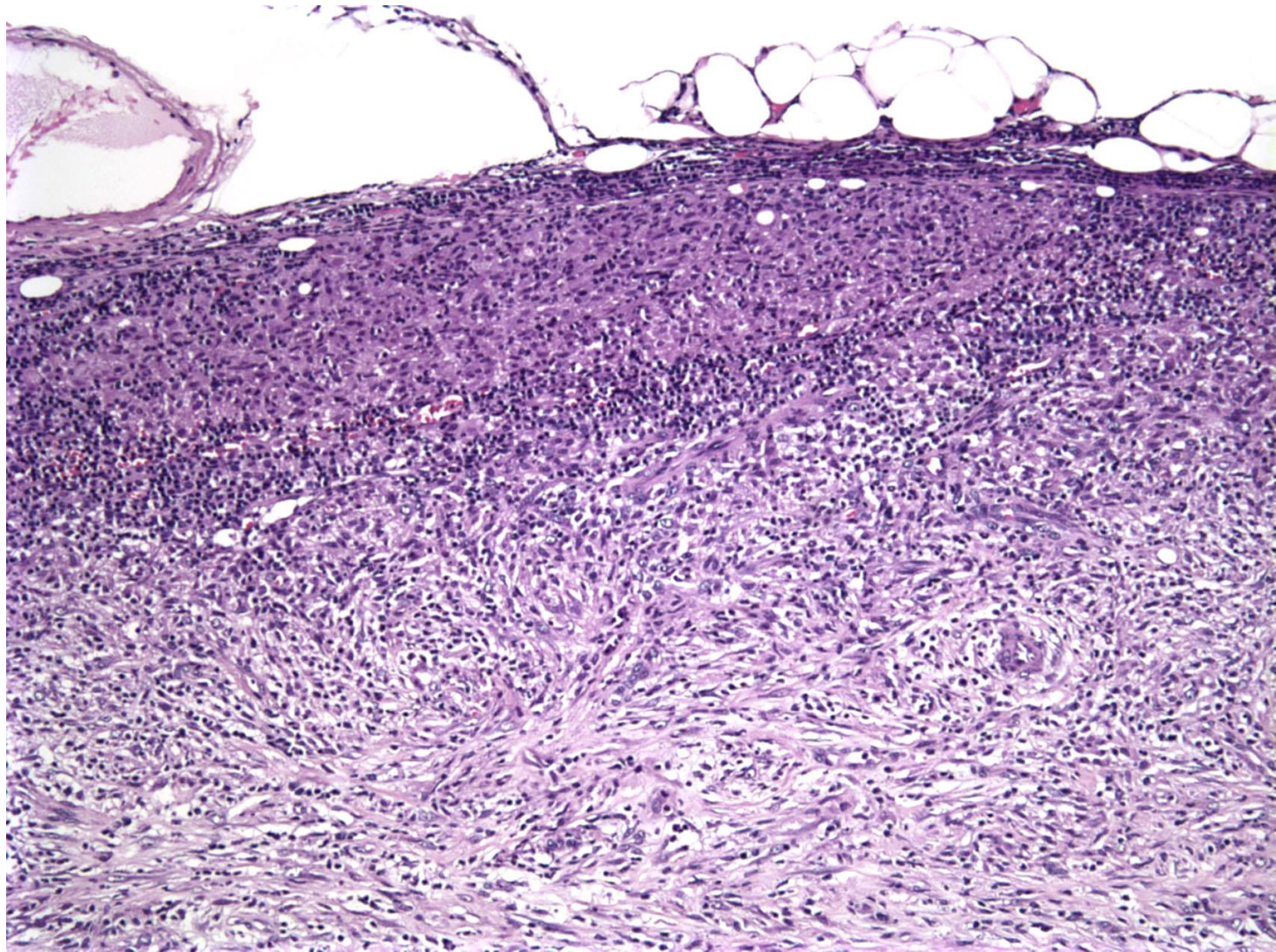
MAI

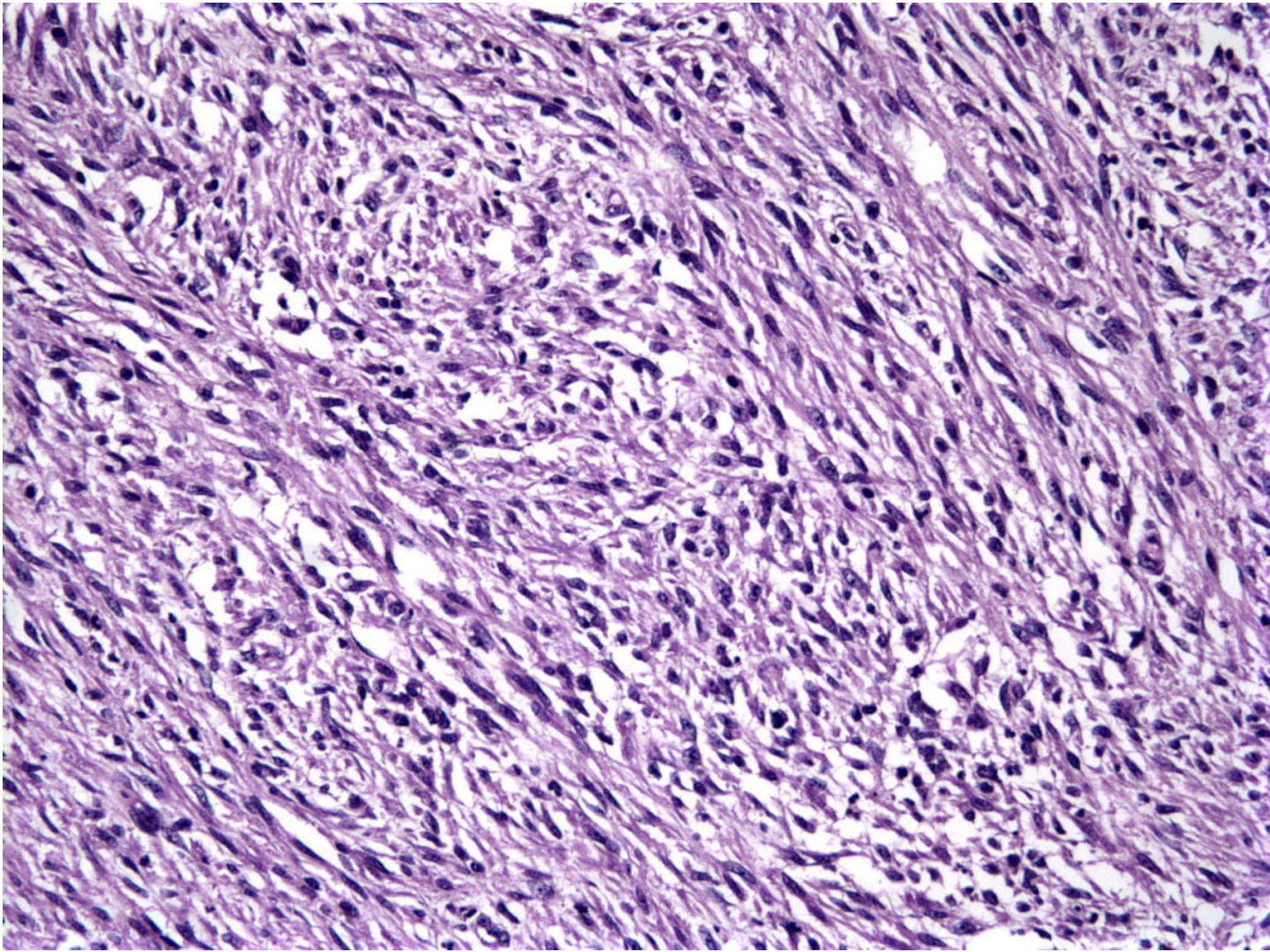


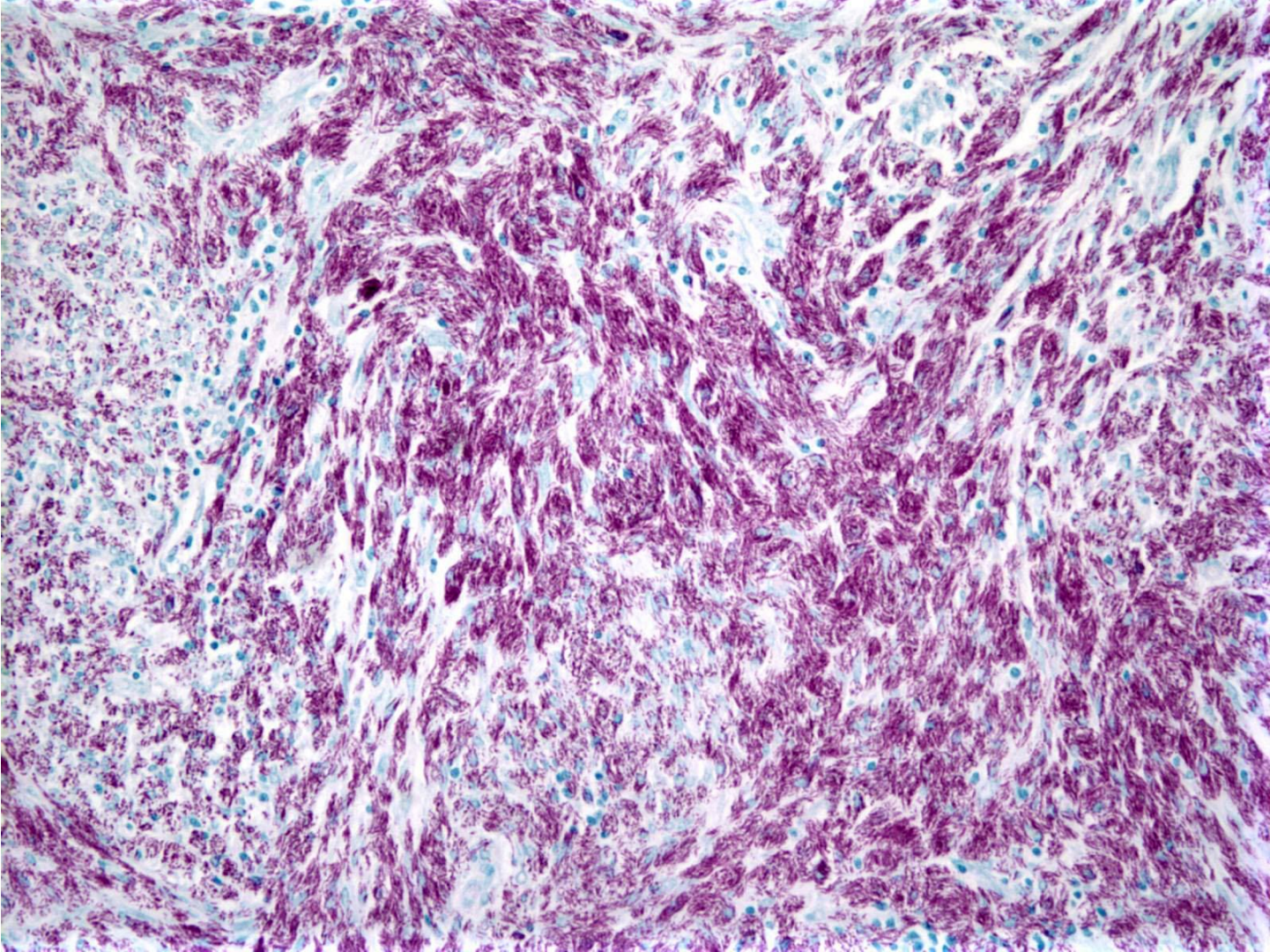


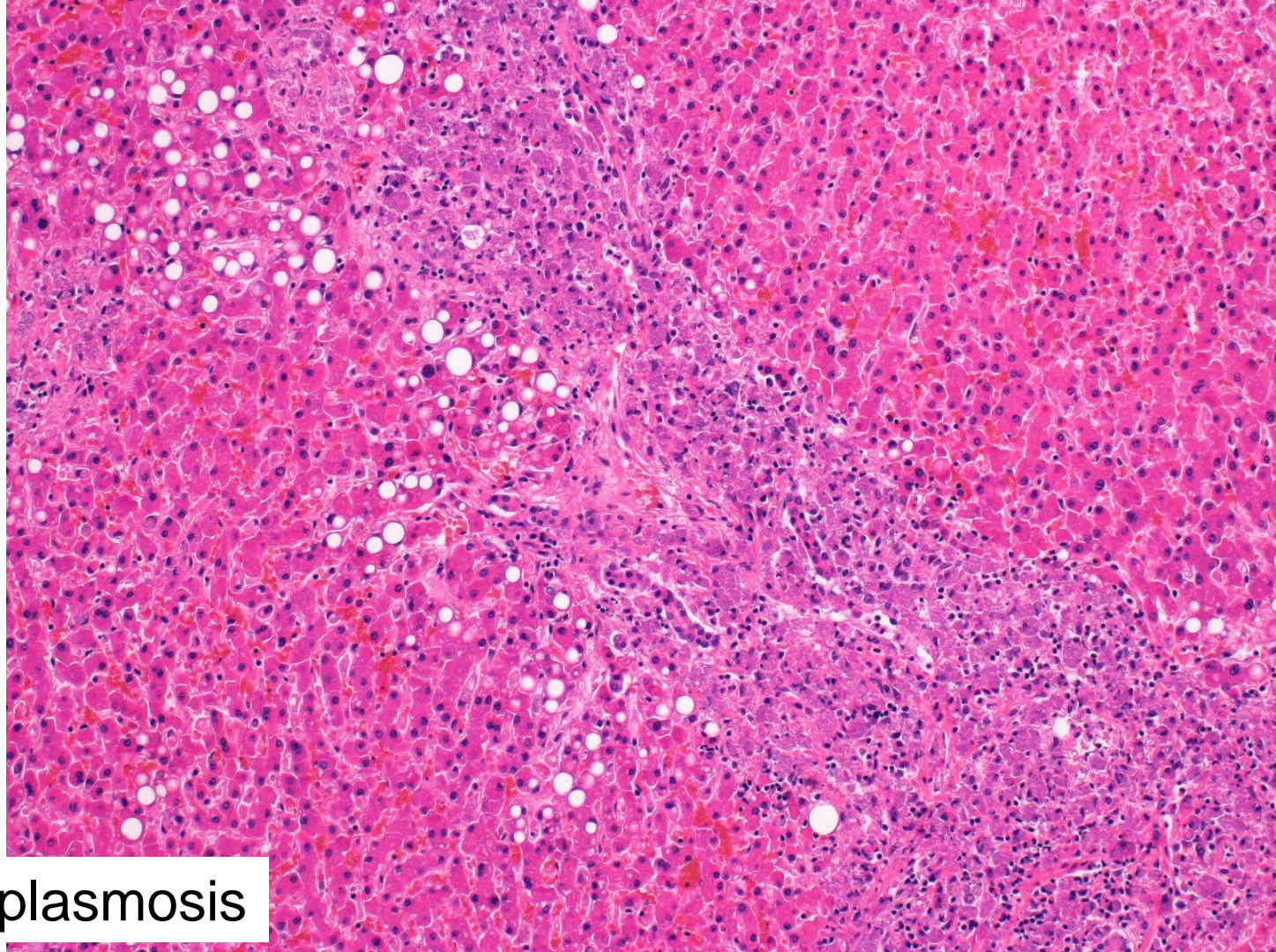


Spindle cell pseudotumor

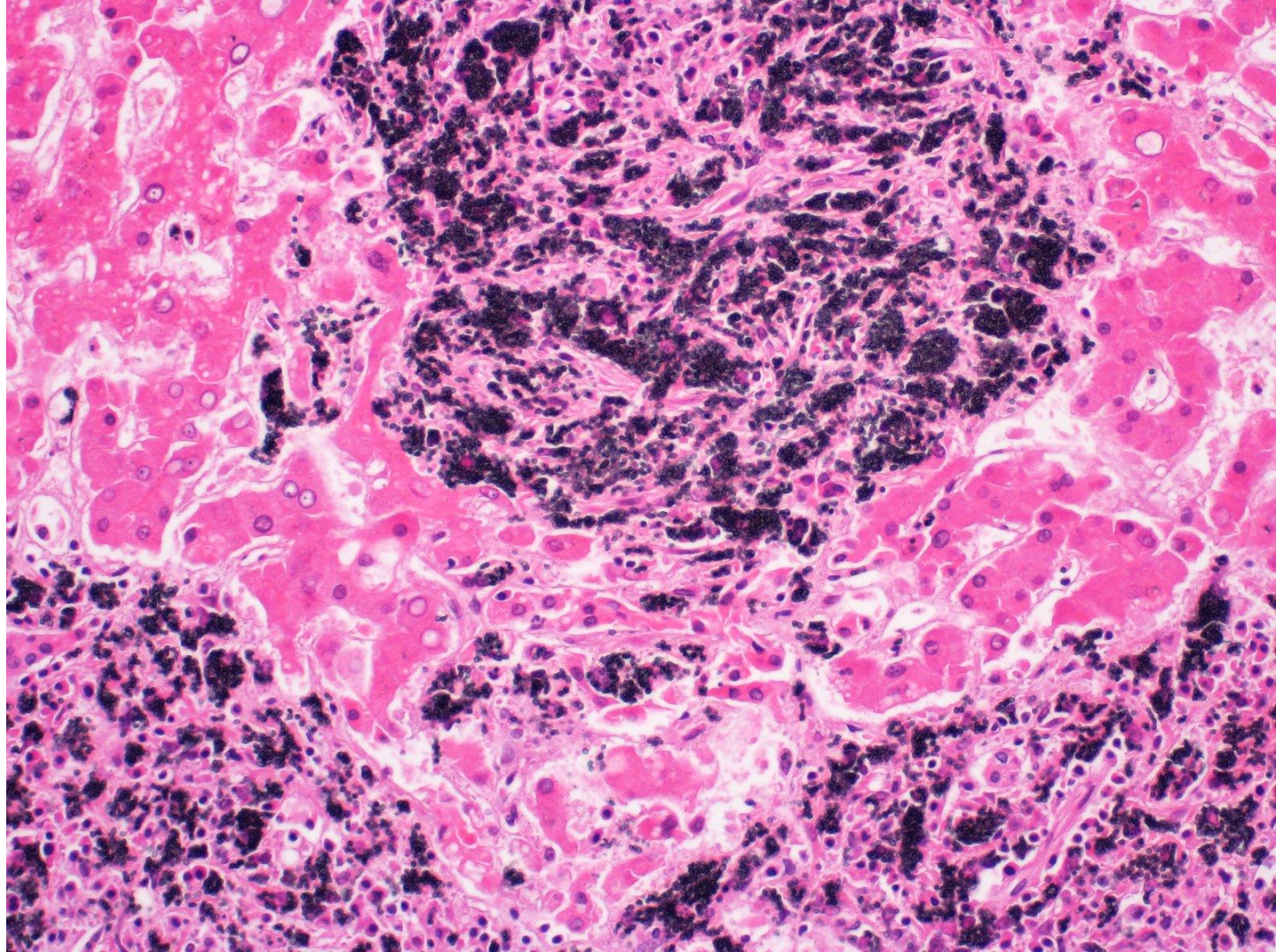


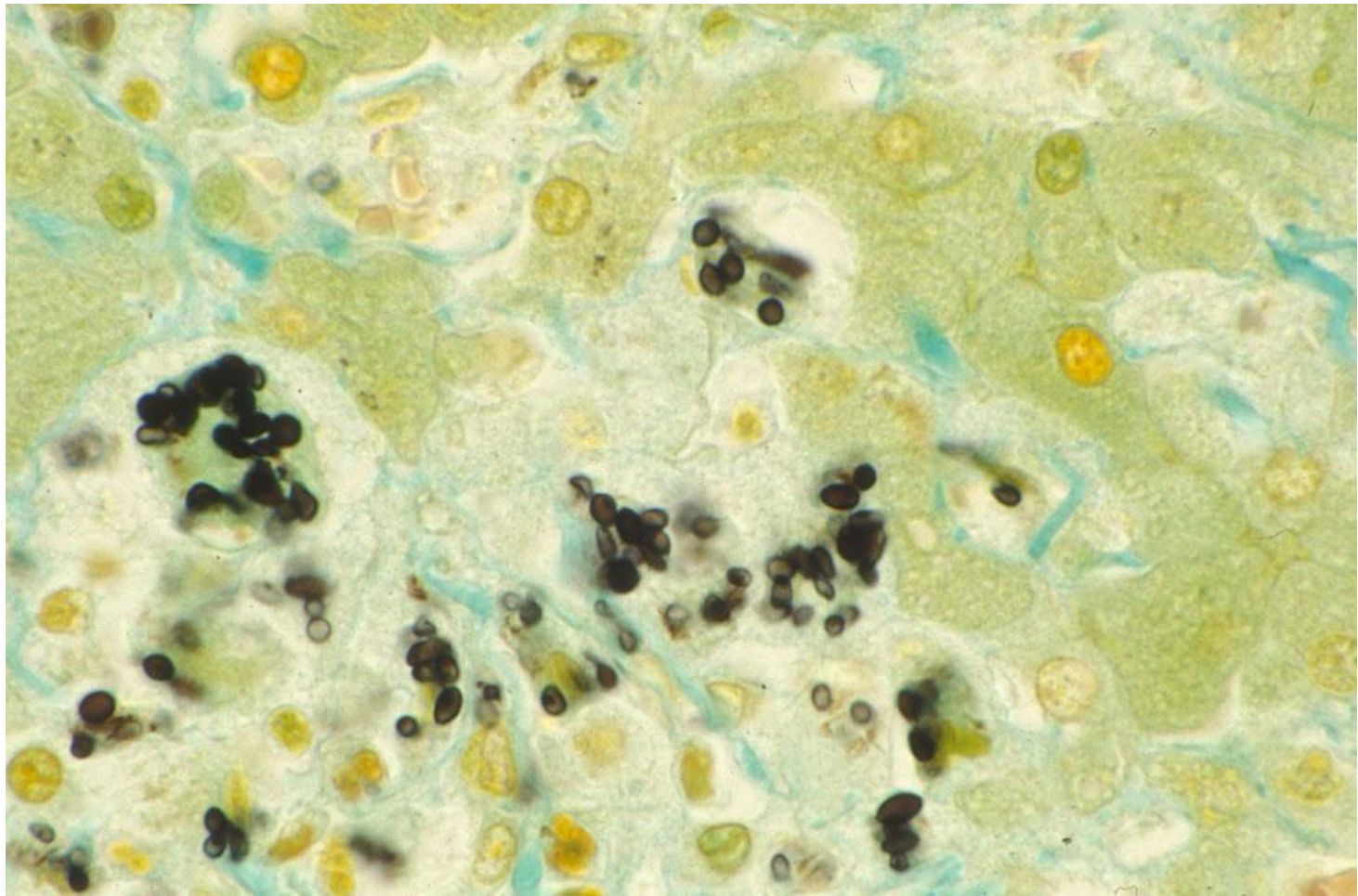


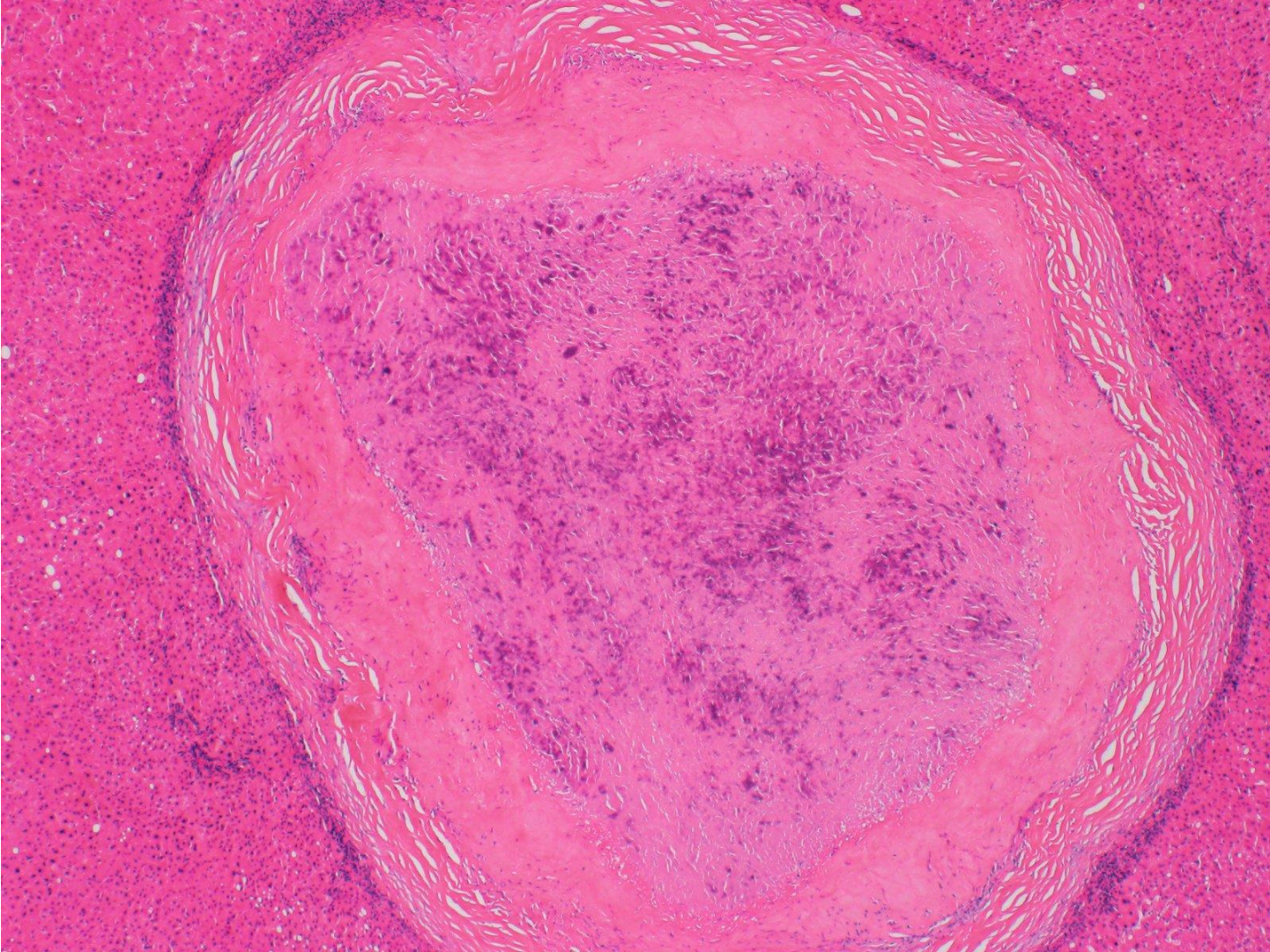


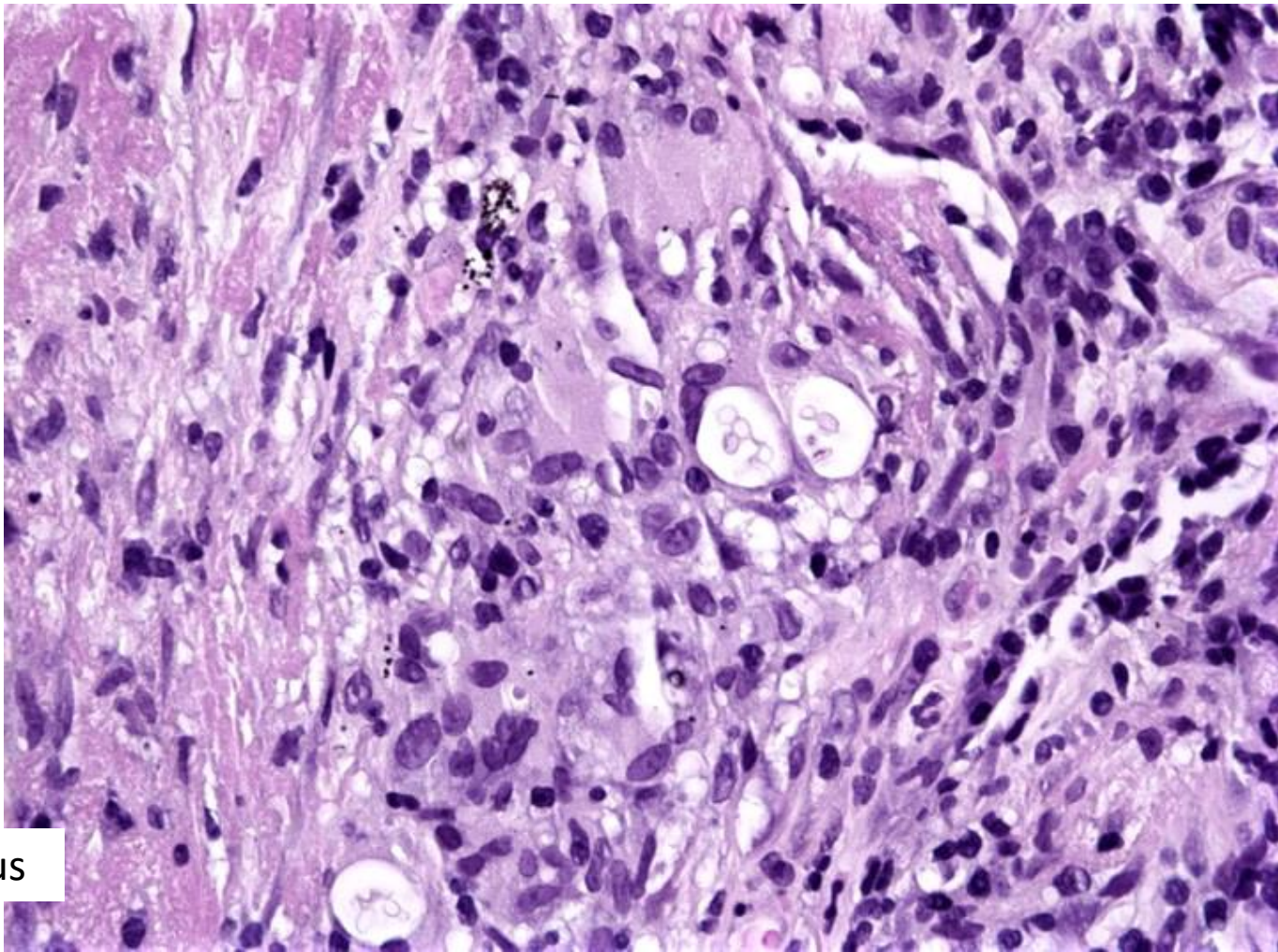


Histoplasmosis

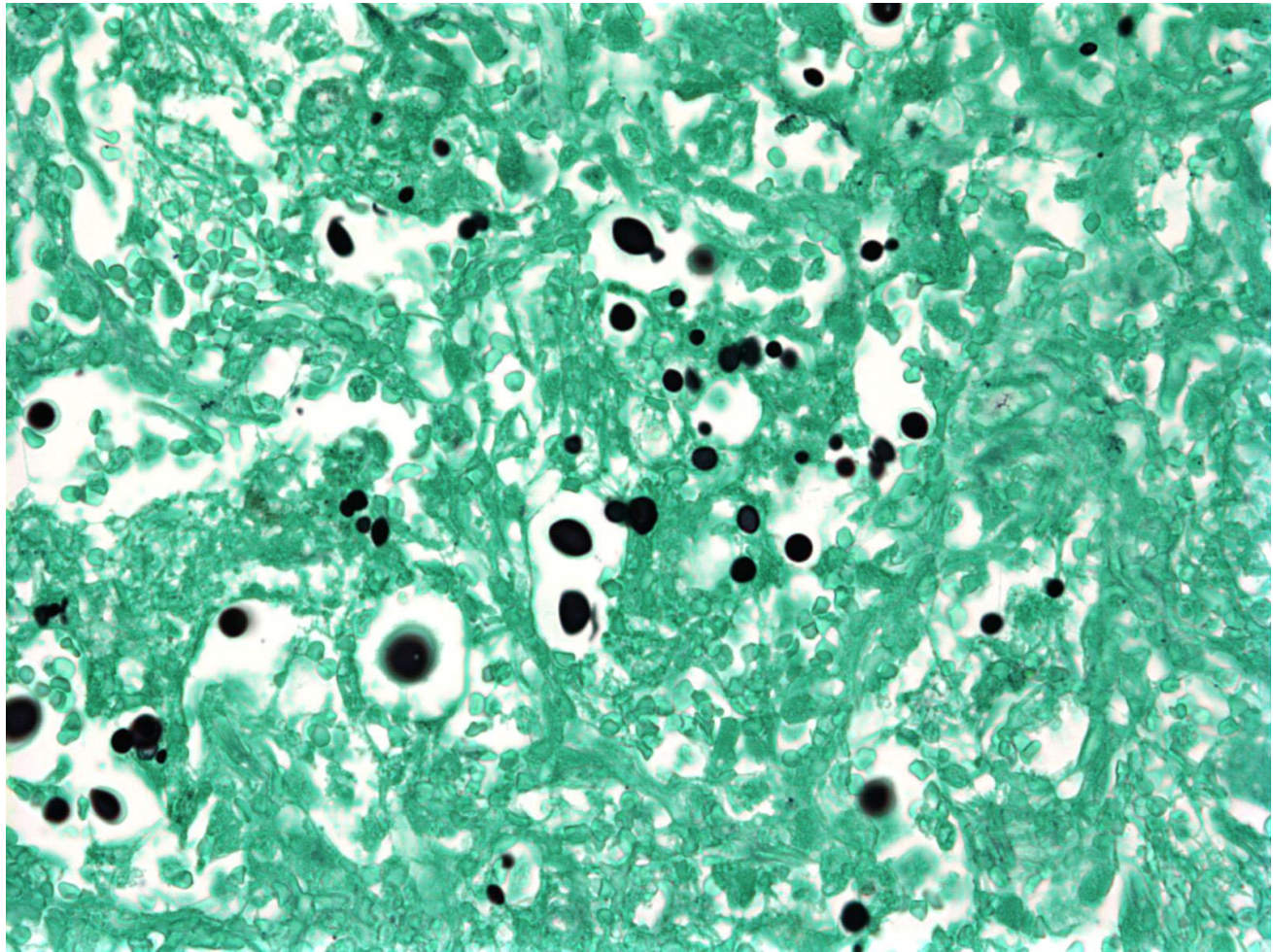


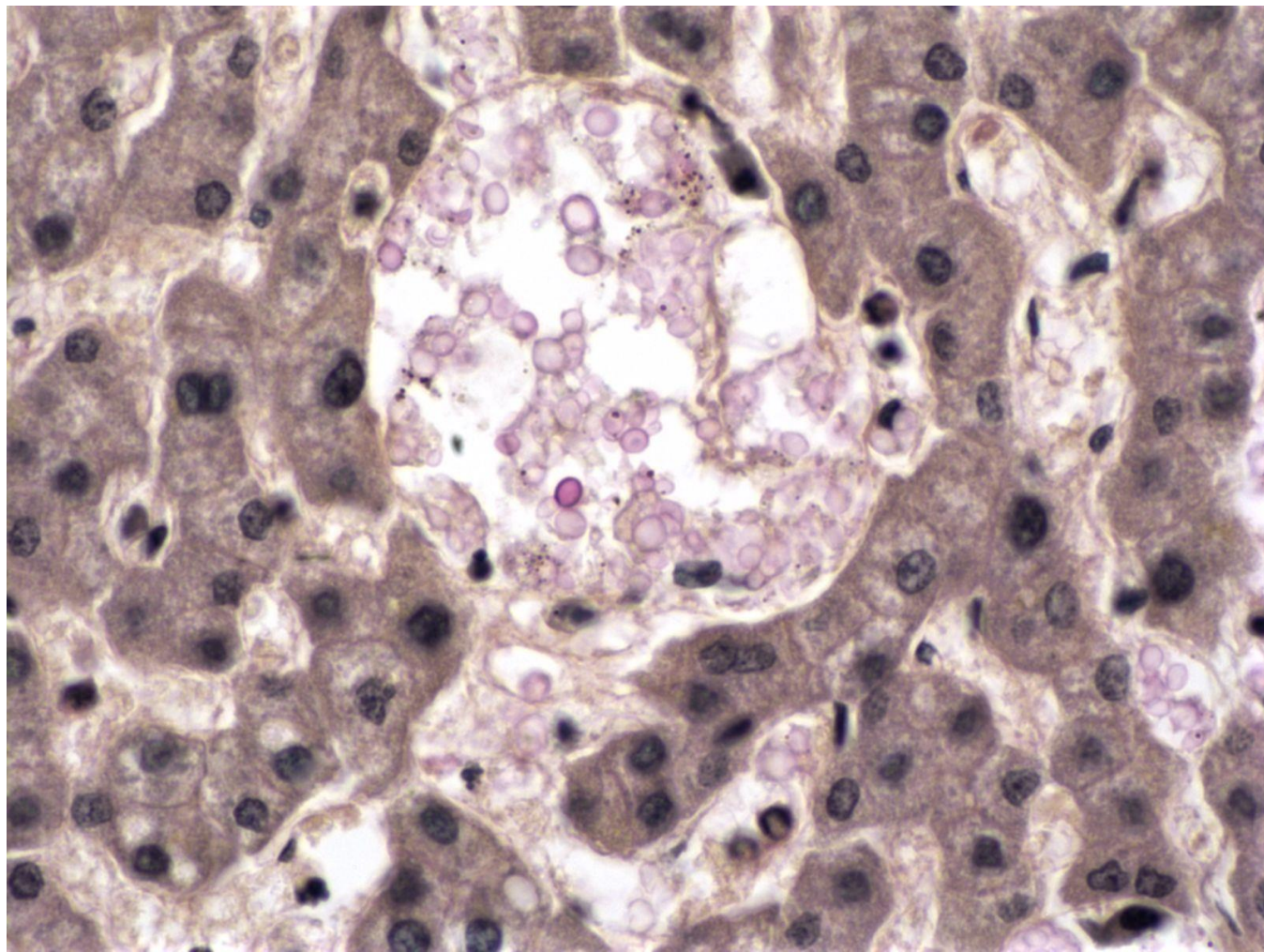




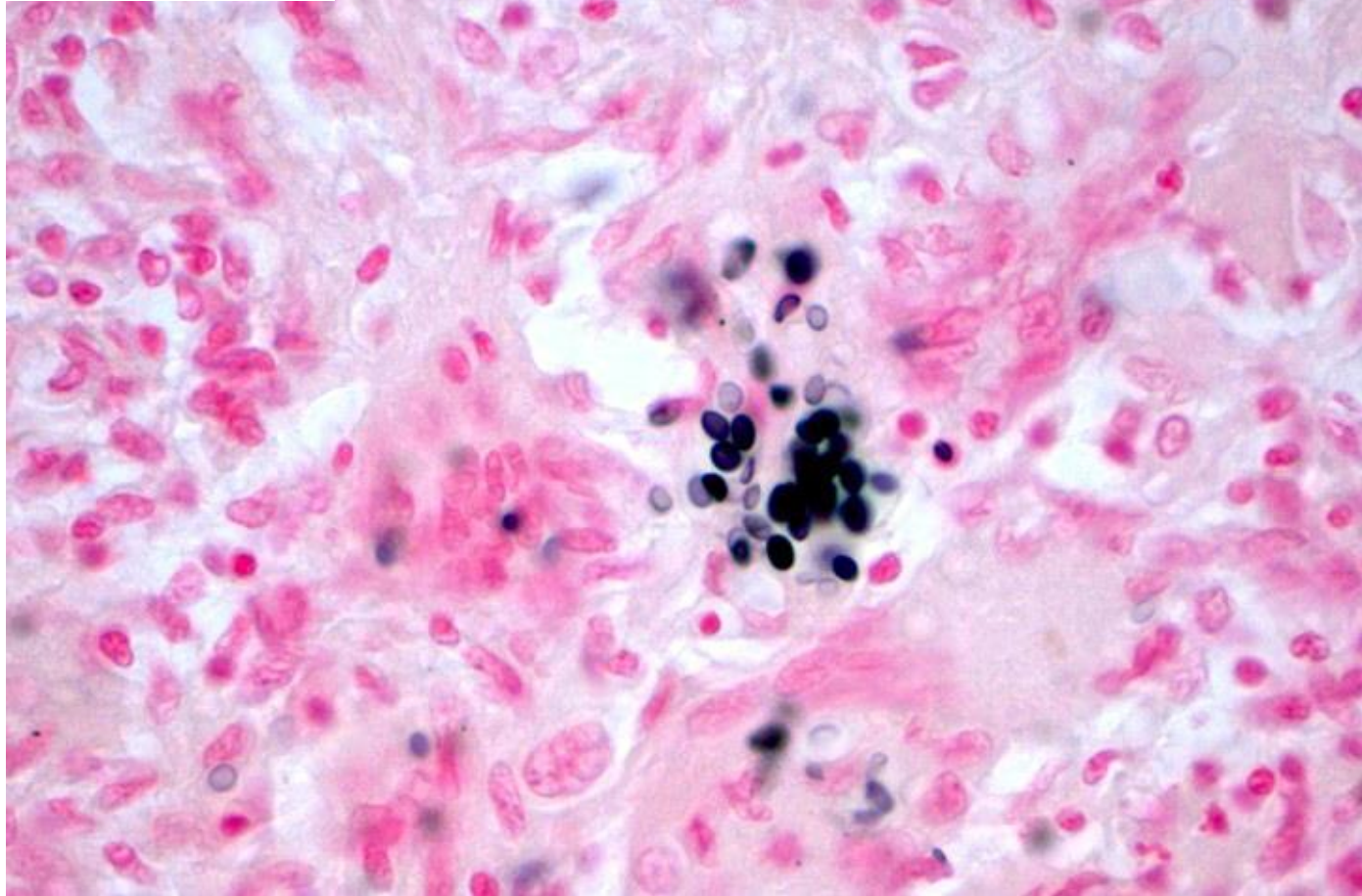


Cryptococcus



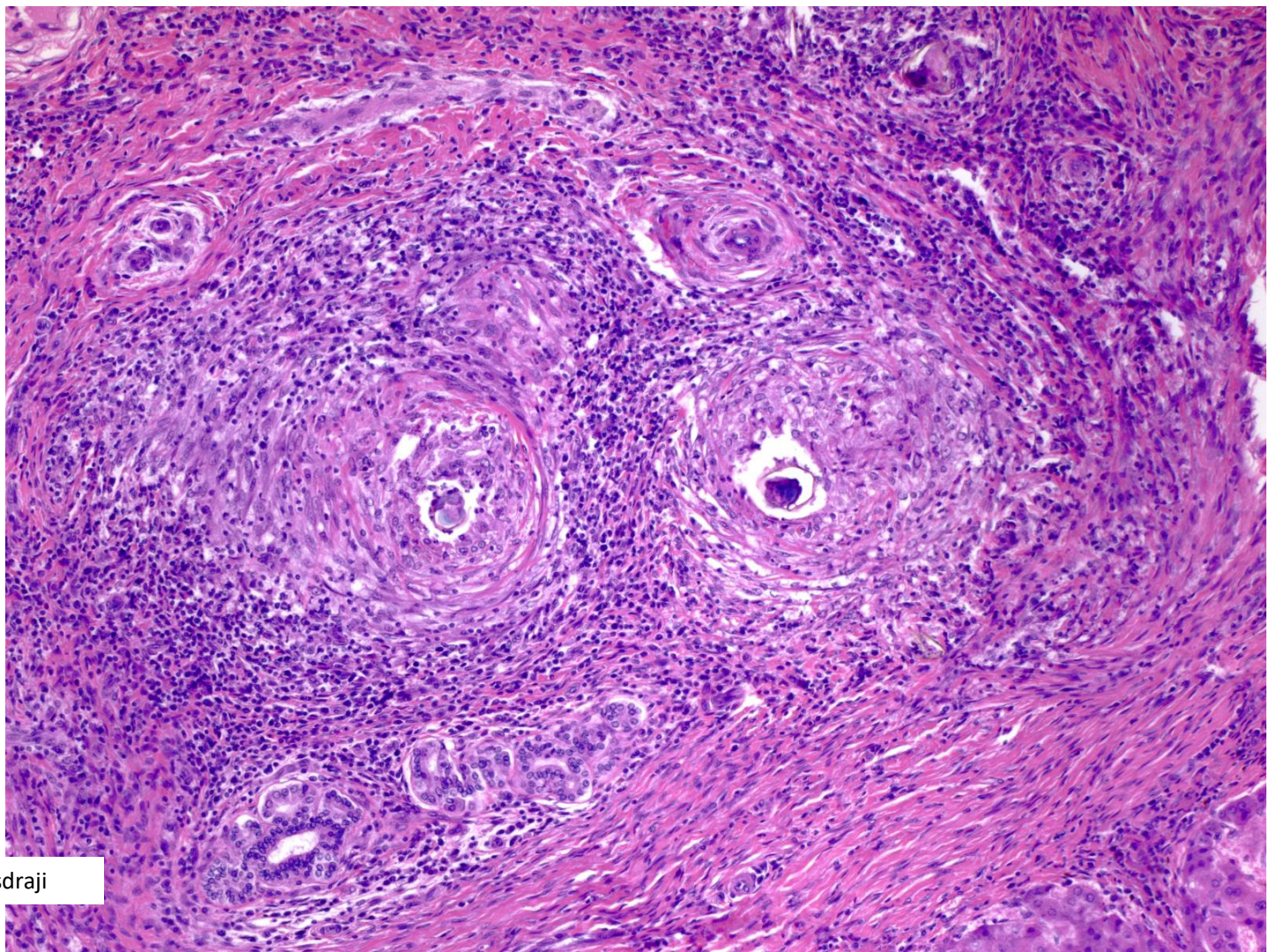


Fontana-Masson

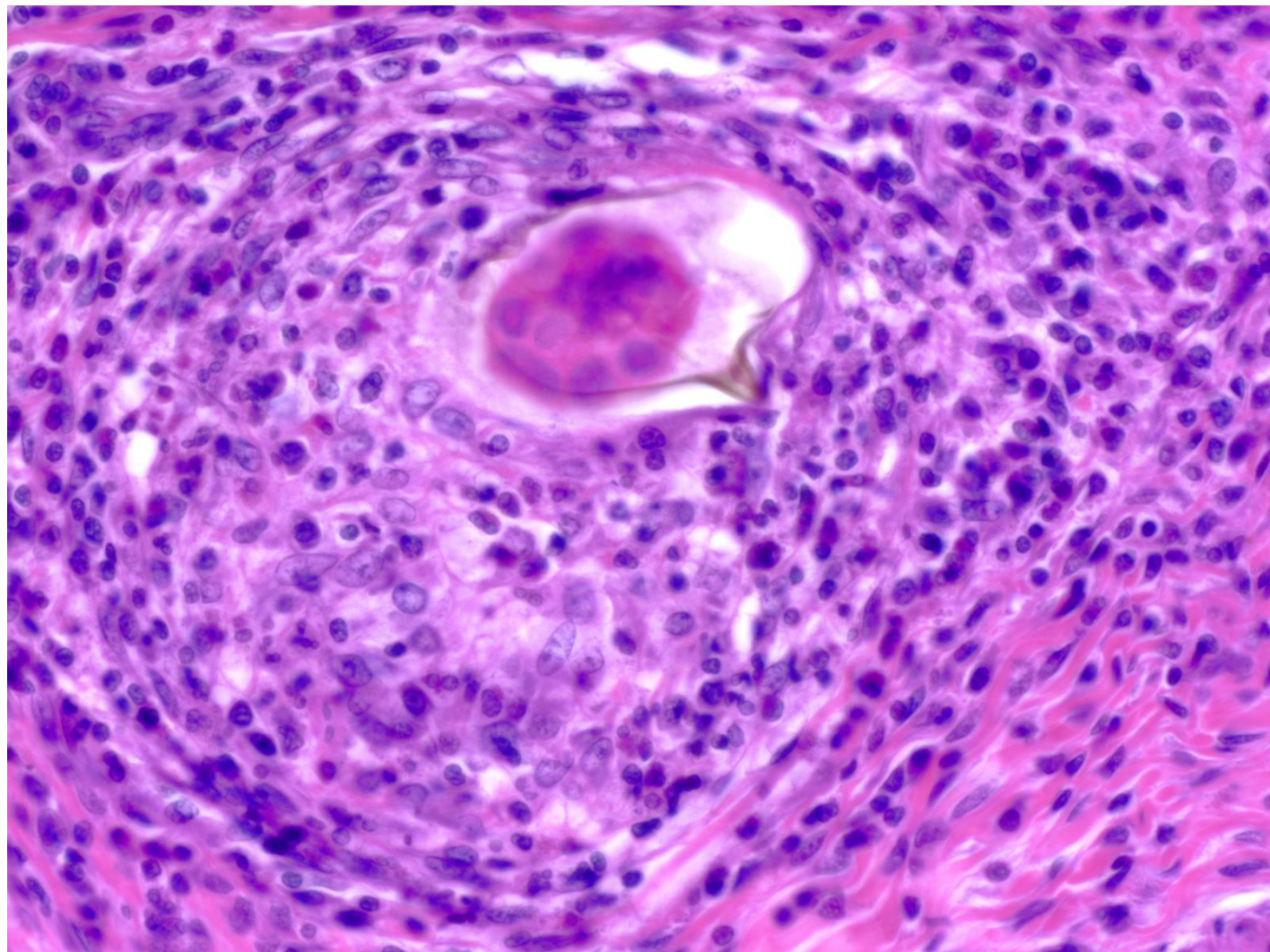


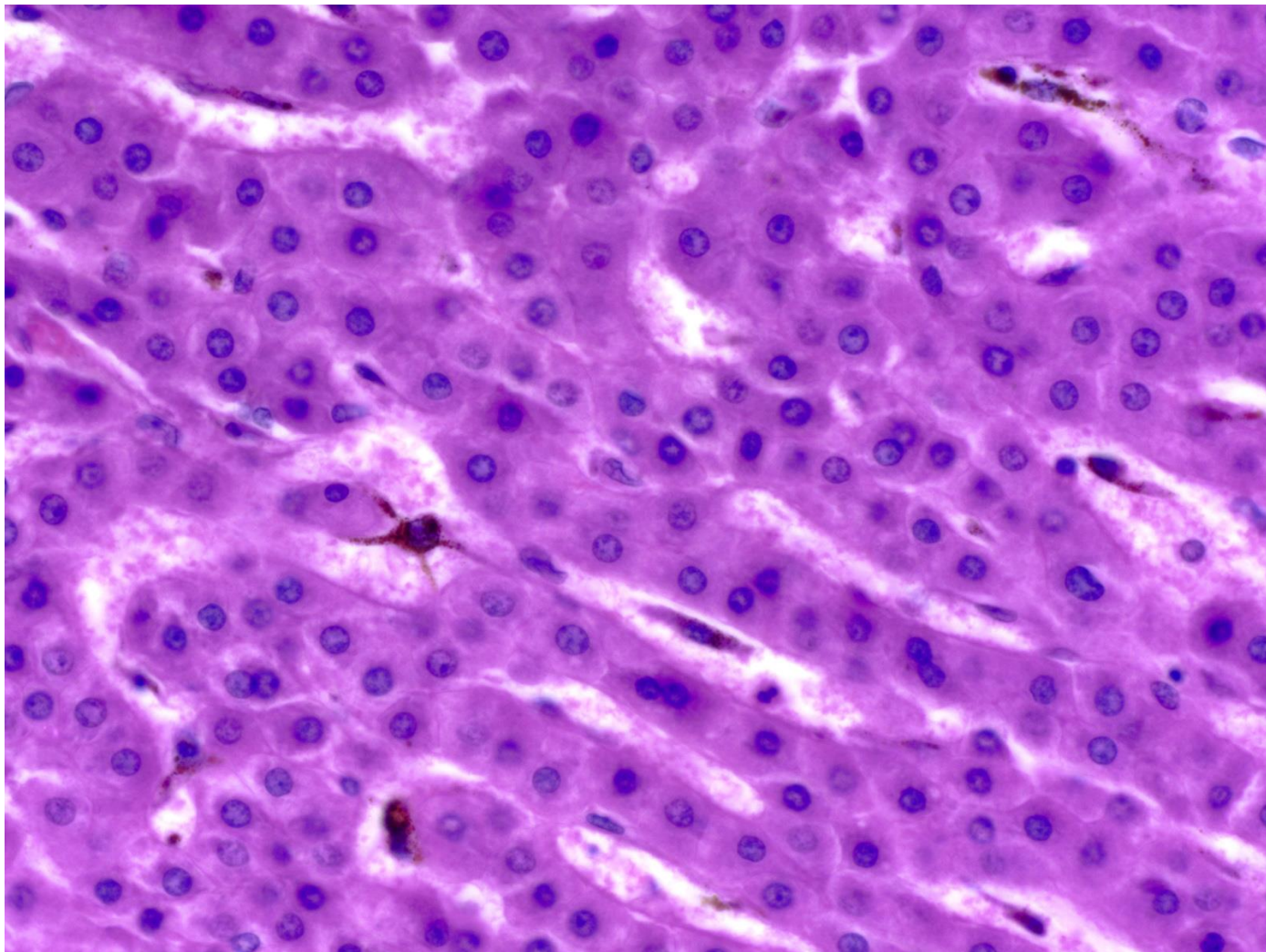
Schistosomiasis

- Most common worldwide cause of portal hypertension
- Granulomatous reaction is usually to the eggs; eggs harder to find as disease progresses
- Diagnosis: finding eggs in urine, feces, or tissue (shells and spines variably acid-fast); serologies, molecular



Courtesy Dr. Joe Misdraji



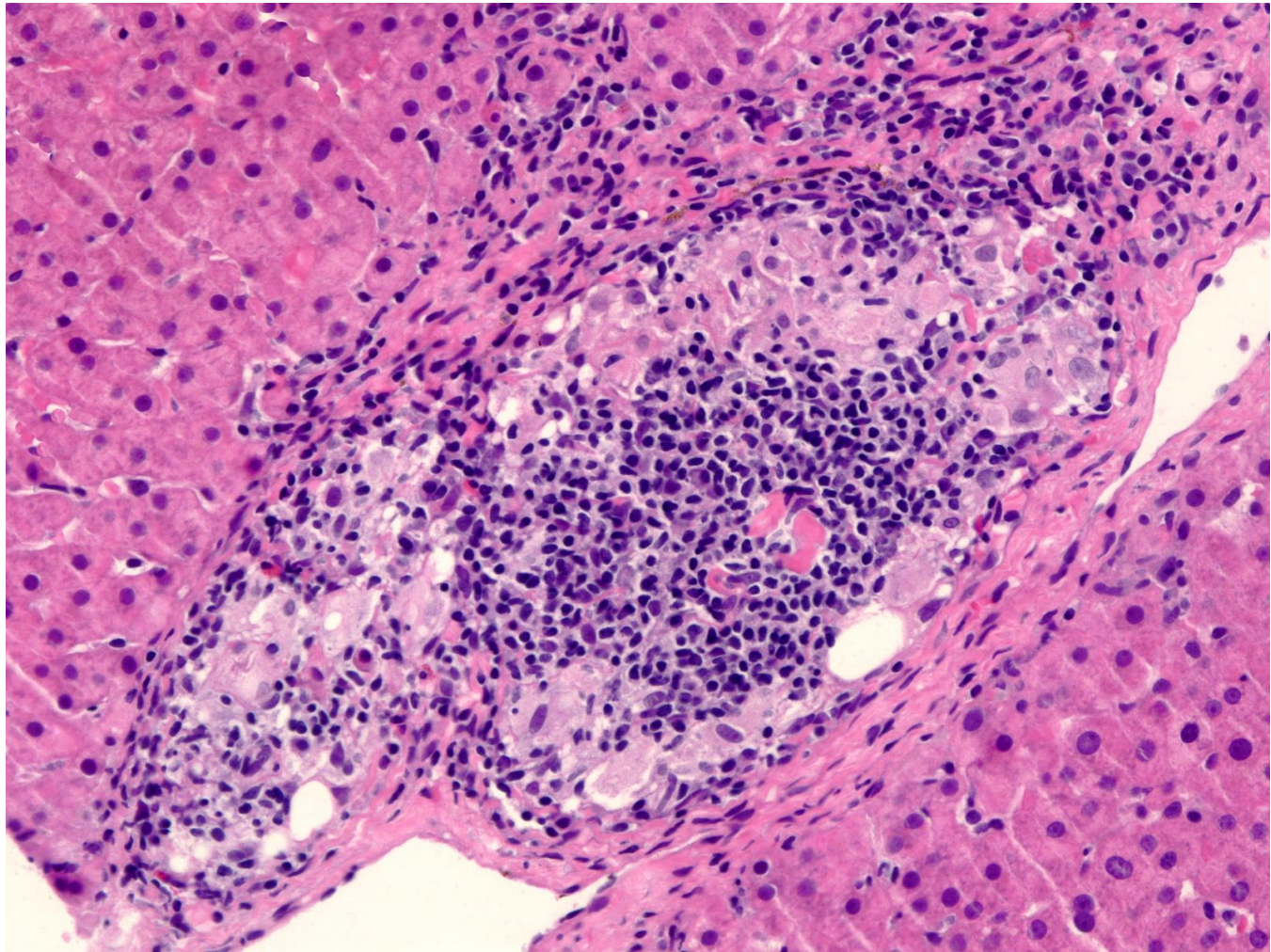




Viral Infections

- Both epithelioid and fibrin ring granulomas associated with EBV, CMV
- Also in a minority of HCV and HBV patients
- Must rule out other causes of hepatic granulomas, however

HCV



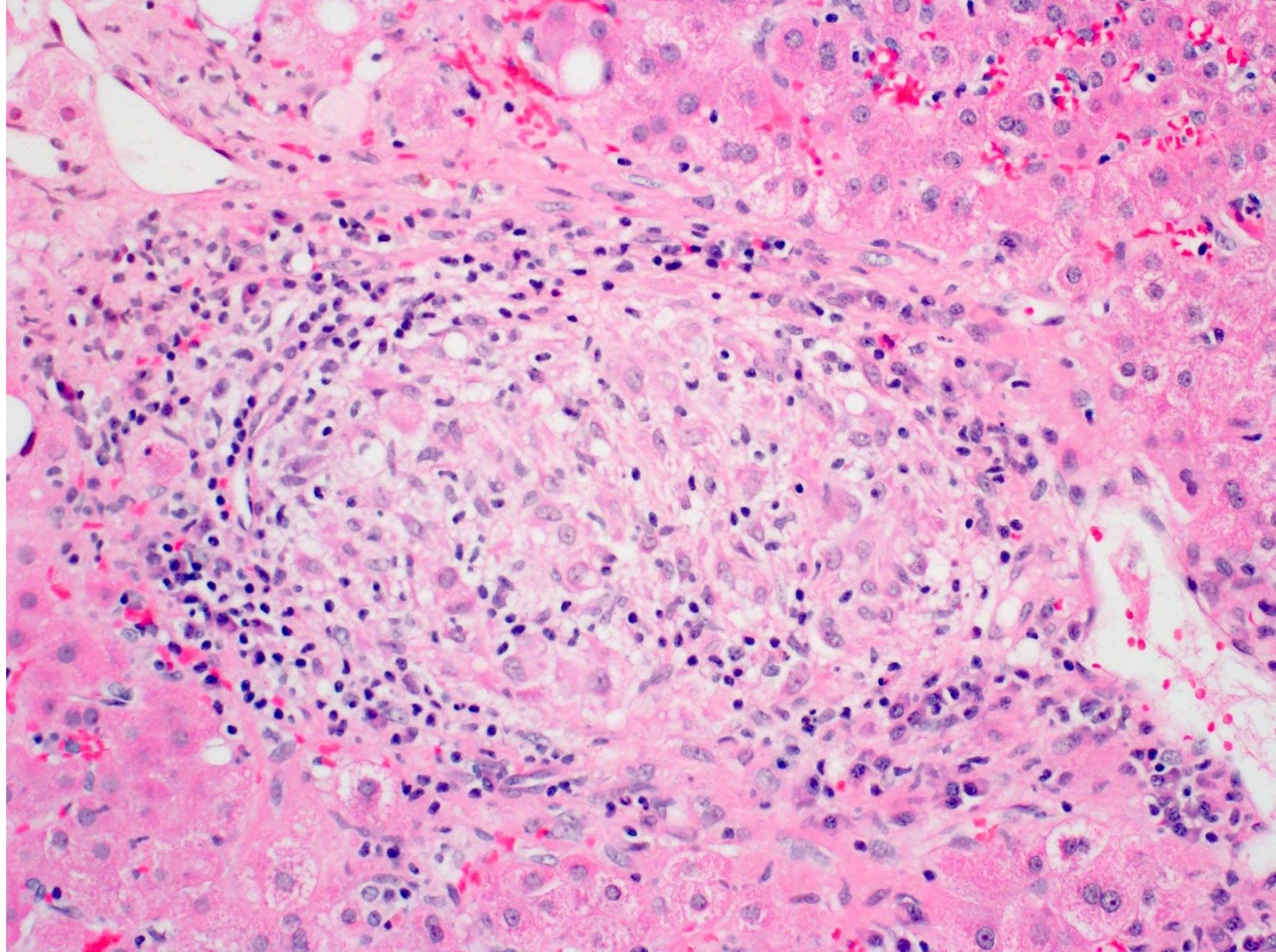


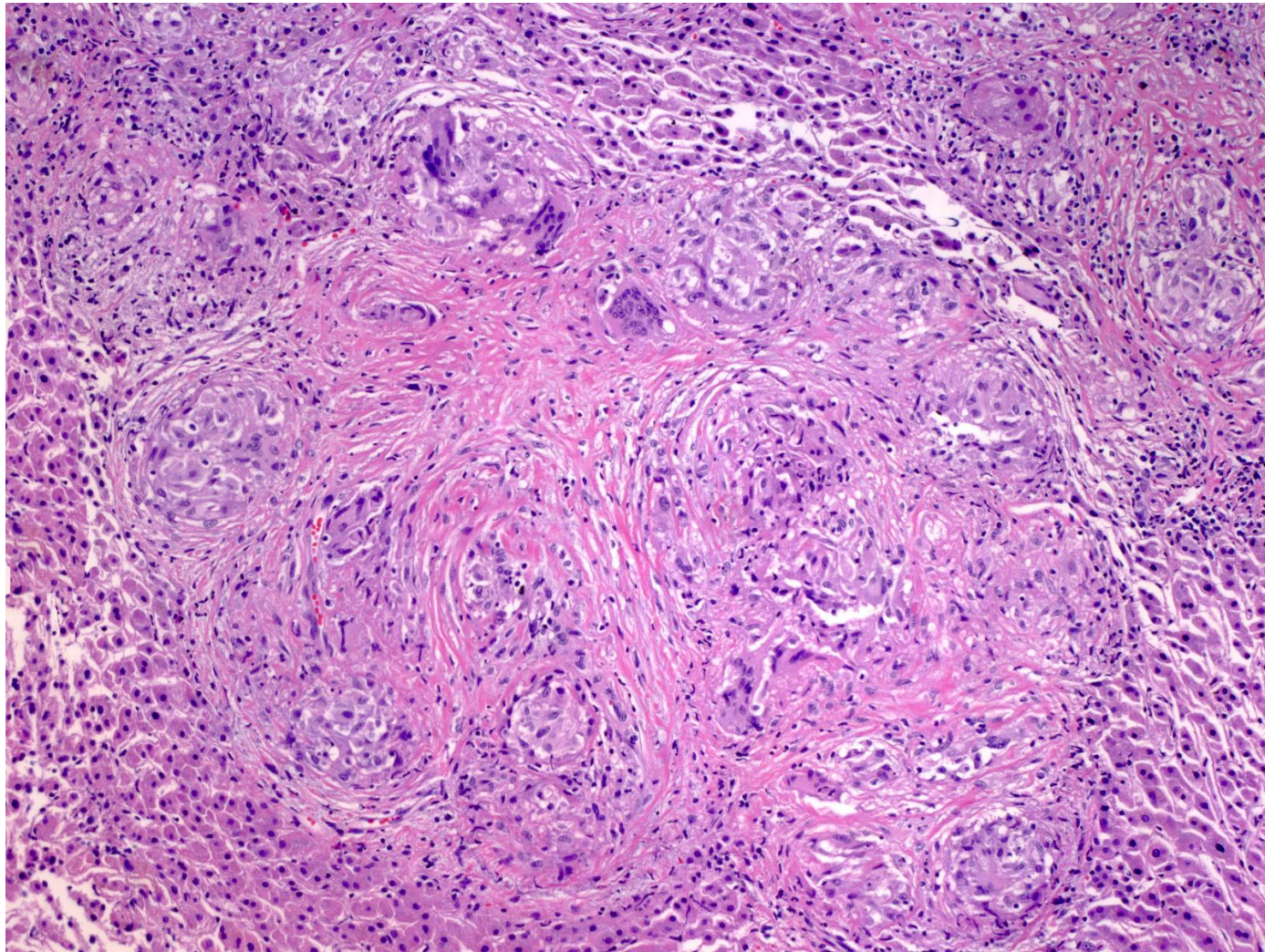
Important Non-infectious Causes of Liver Granulomas

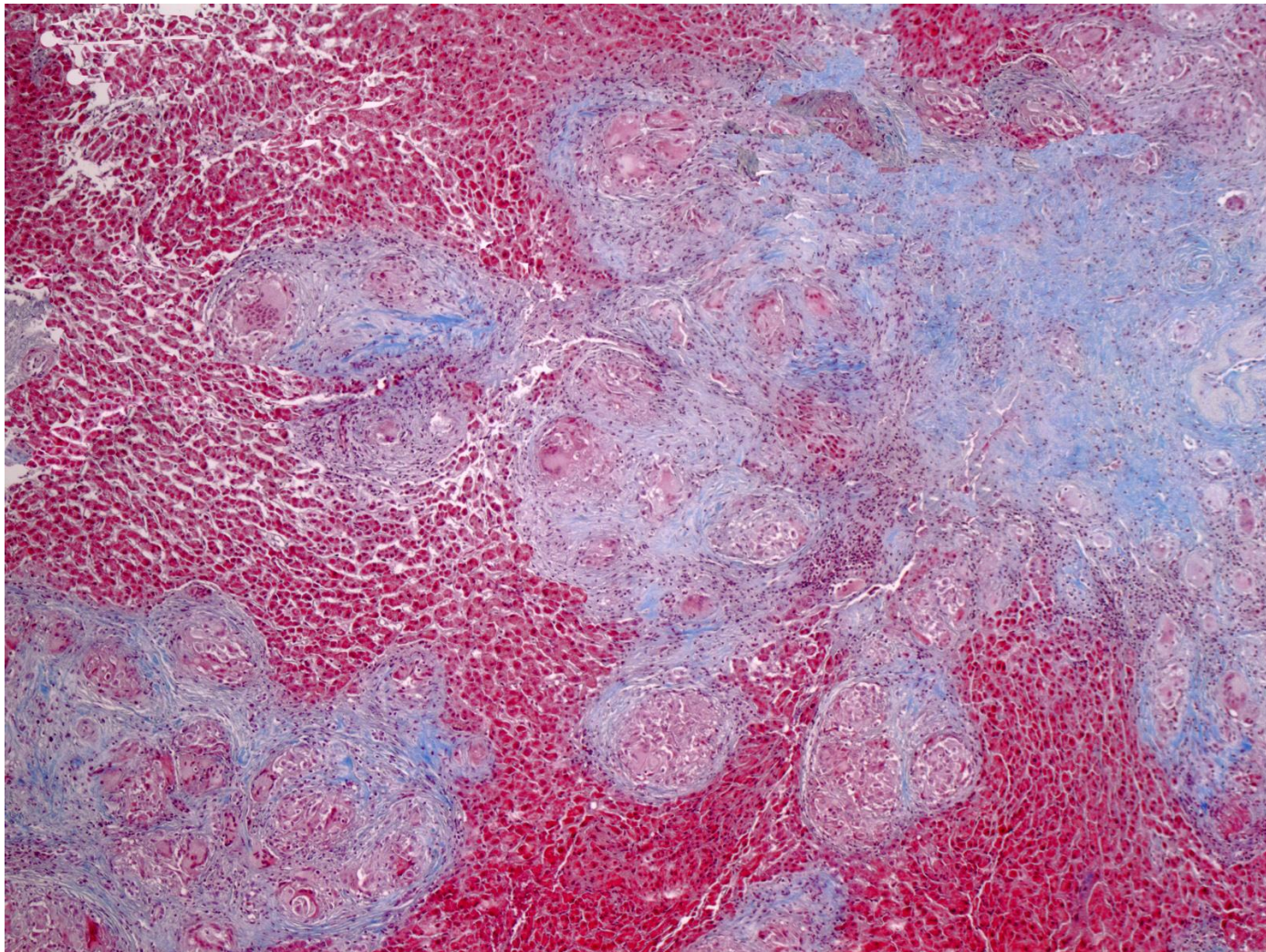
- Primary cholestatic disorders
- Chronic GI disease
- Vasculitides
- Adverse drug reaction
- Metal toxicity
- Foreign material
- Inherited disorders
- Reaction to neoplasms
- Sarcoidosis

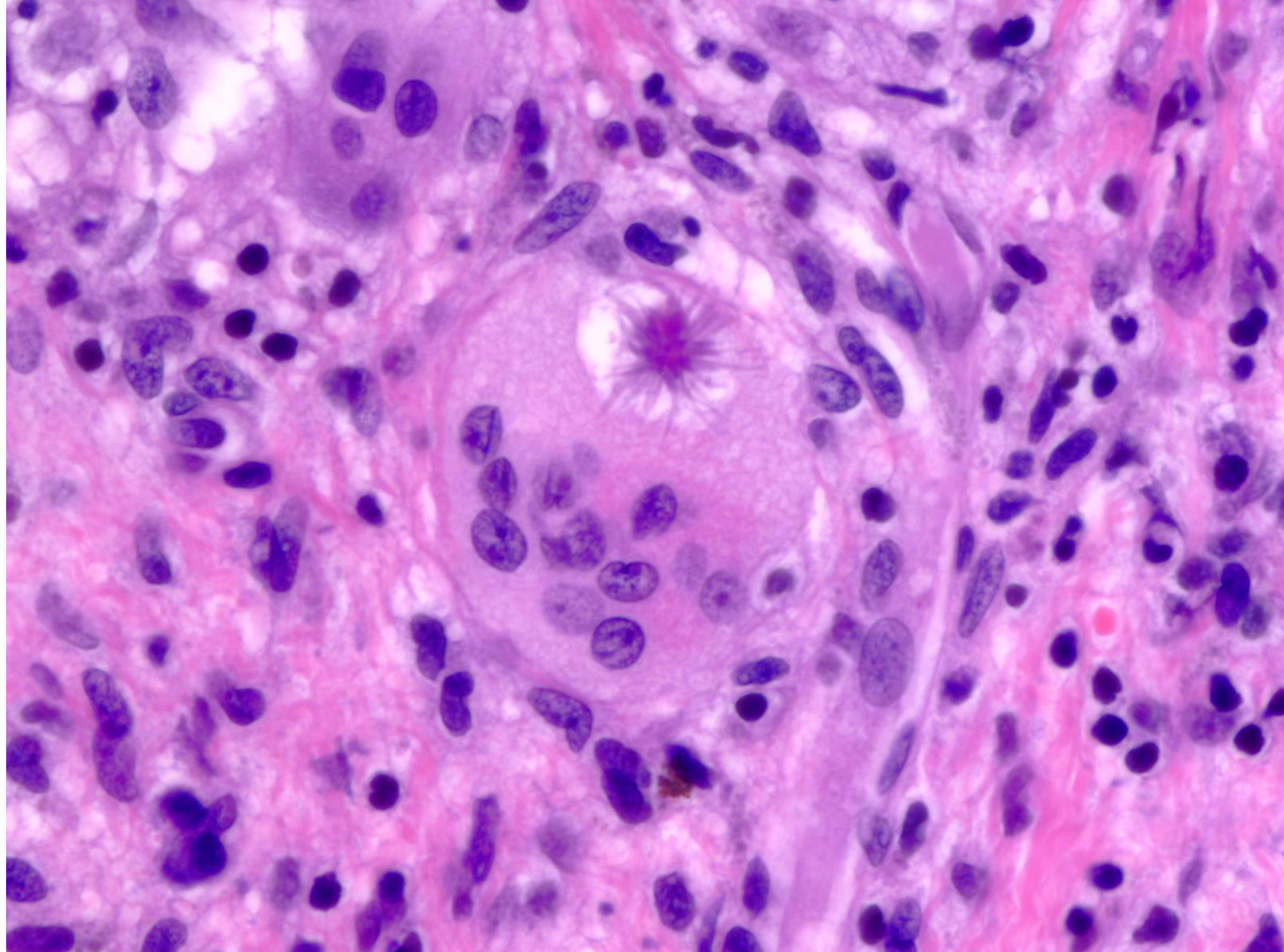
Sarcoidosis

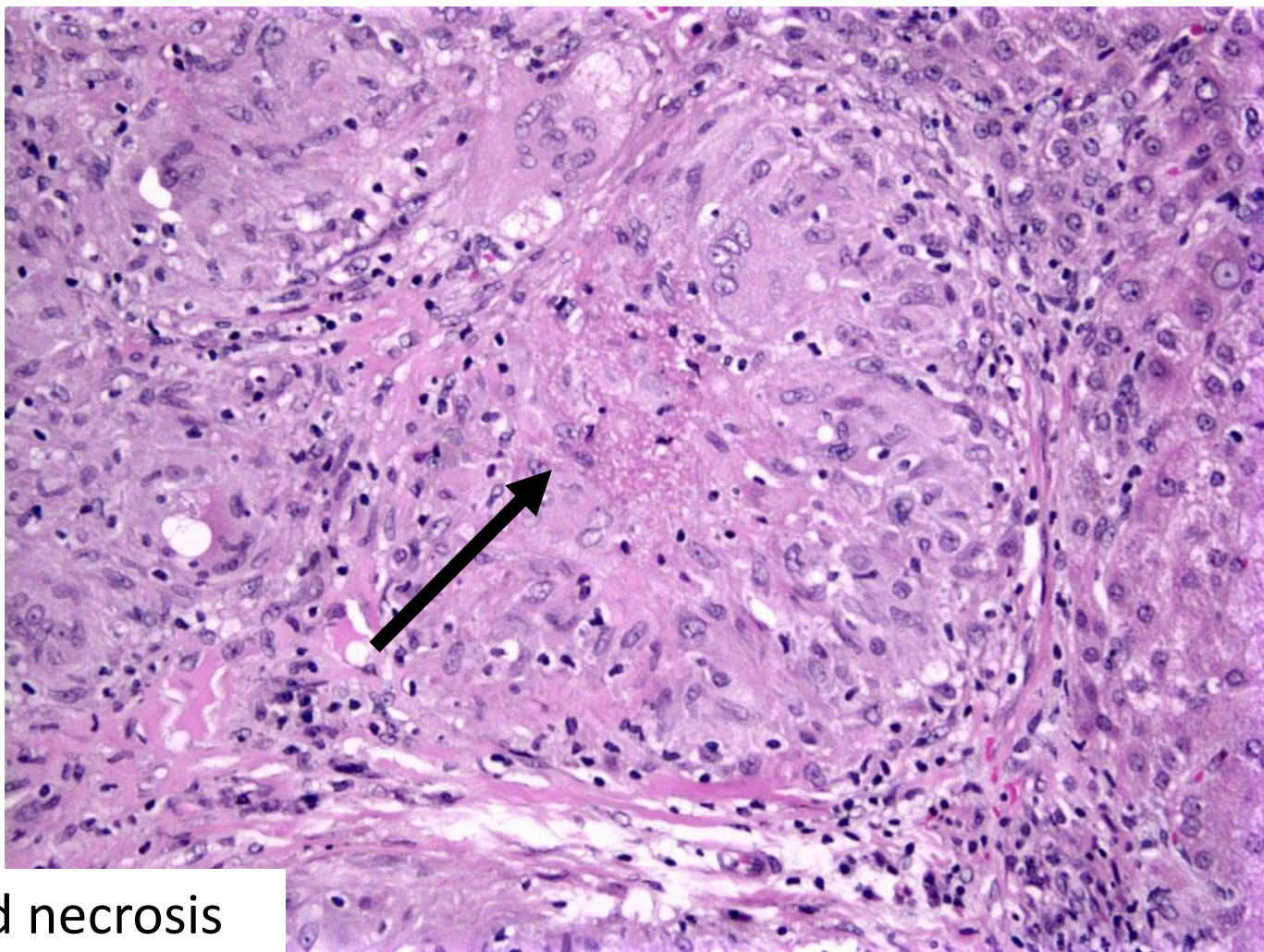
- Liver involved in majority of cases
 - Second only to lung, skin, and nodes
- May cause fibrosis, cirrhosis, and cholestatic liver disease
- Diagnosis: chest xray, serum ACE assay
 - Must rule out other causes of granulomas



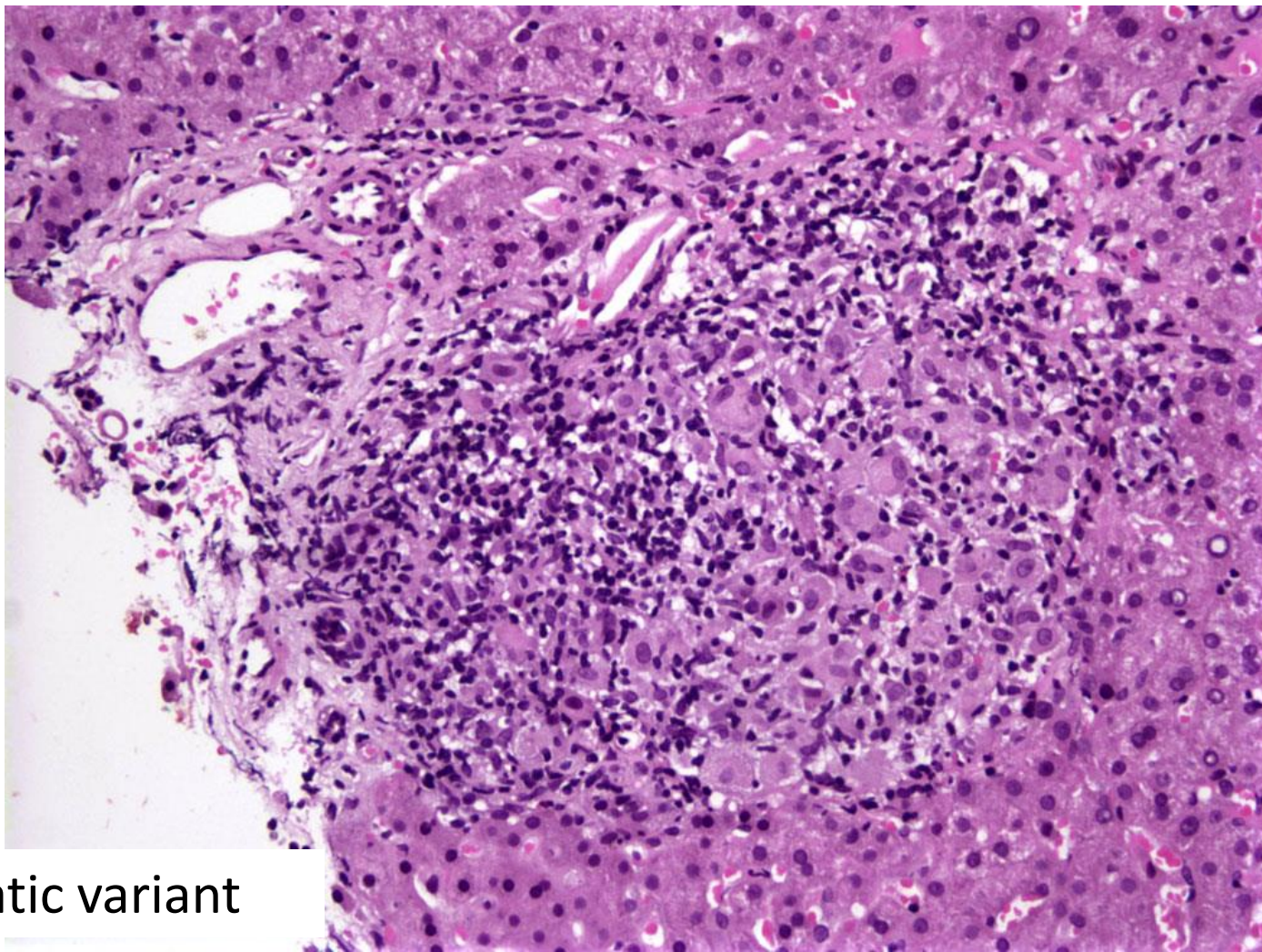




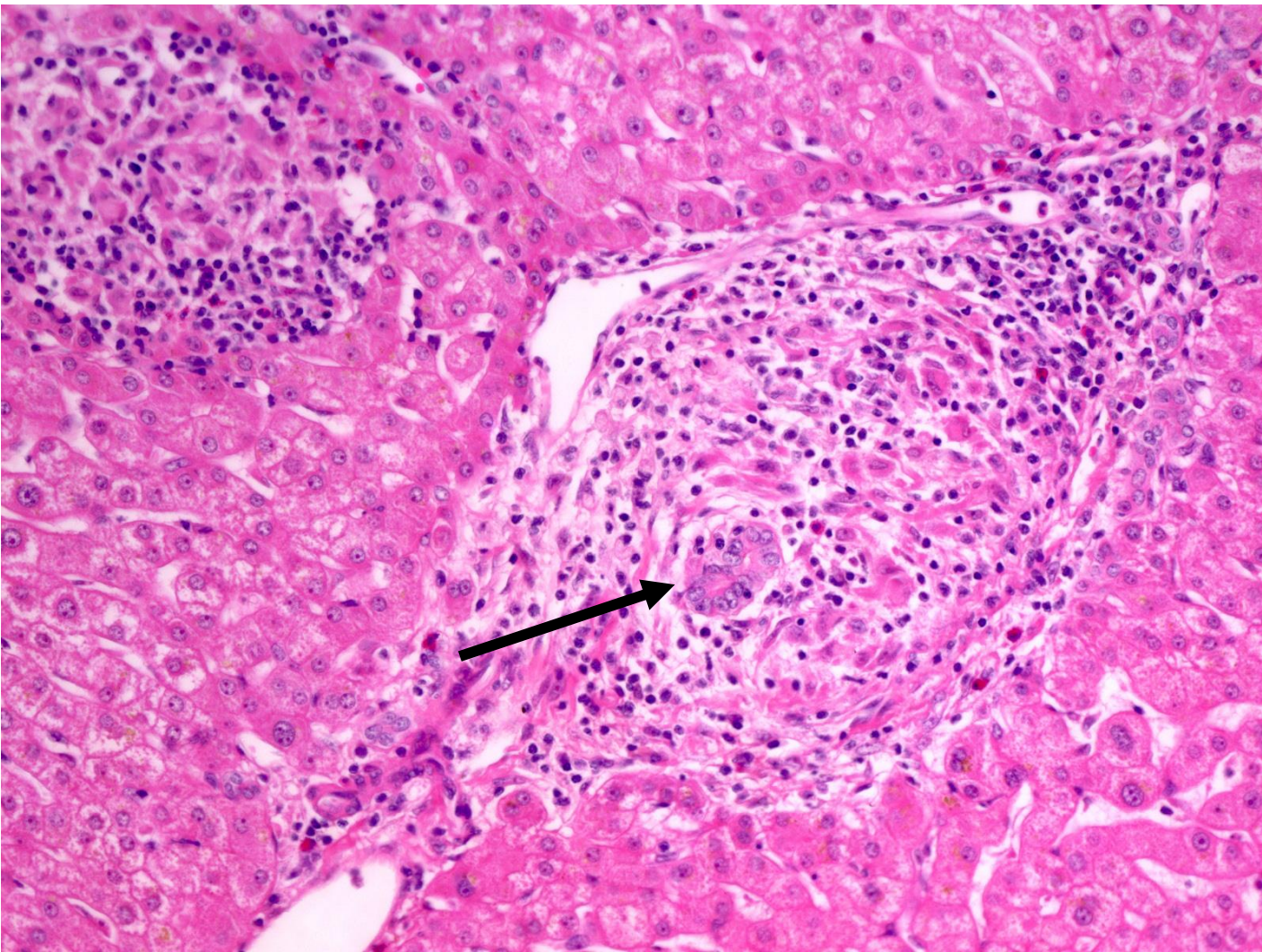




Fibrinoid necrosis



Cholestatic variant

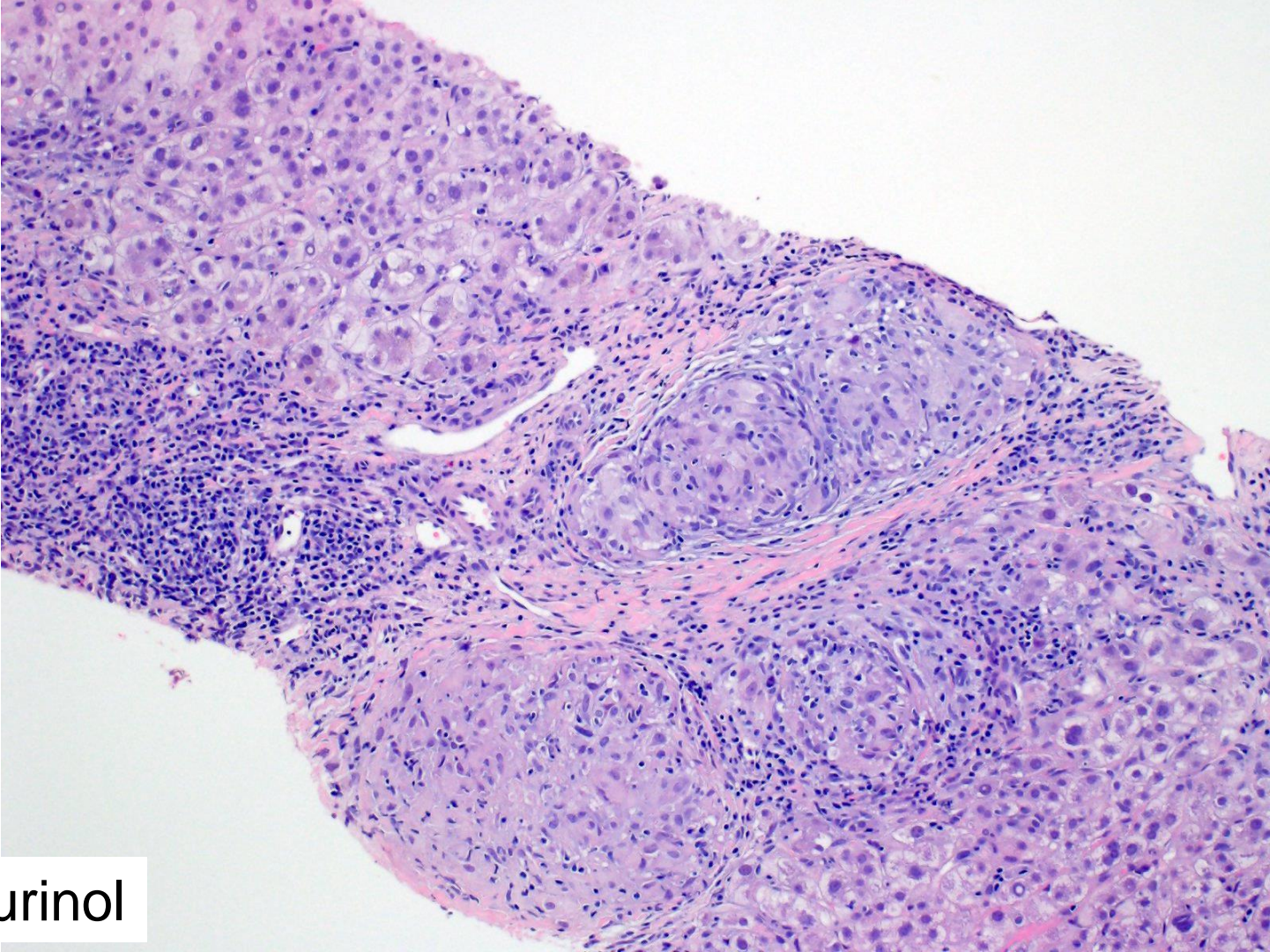


Adverse Drug Reaction

- Many different granuloma morphologies
 - Epithelioid
 - Necrosis is rare
 - Microgranulomas/granulomatous inflammation
- Associated hepatocyte, duct, or vascular injury
- Combination of granulomatous inflammation + hepatocellular damage very suggestive of DILI

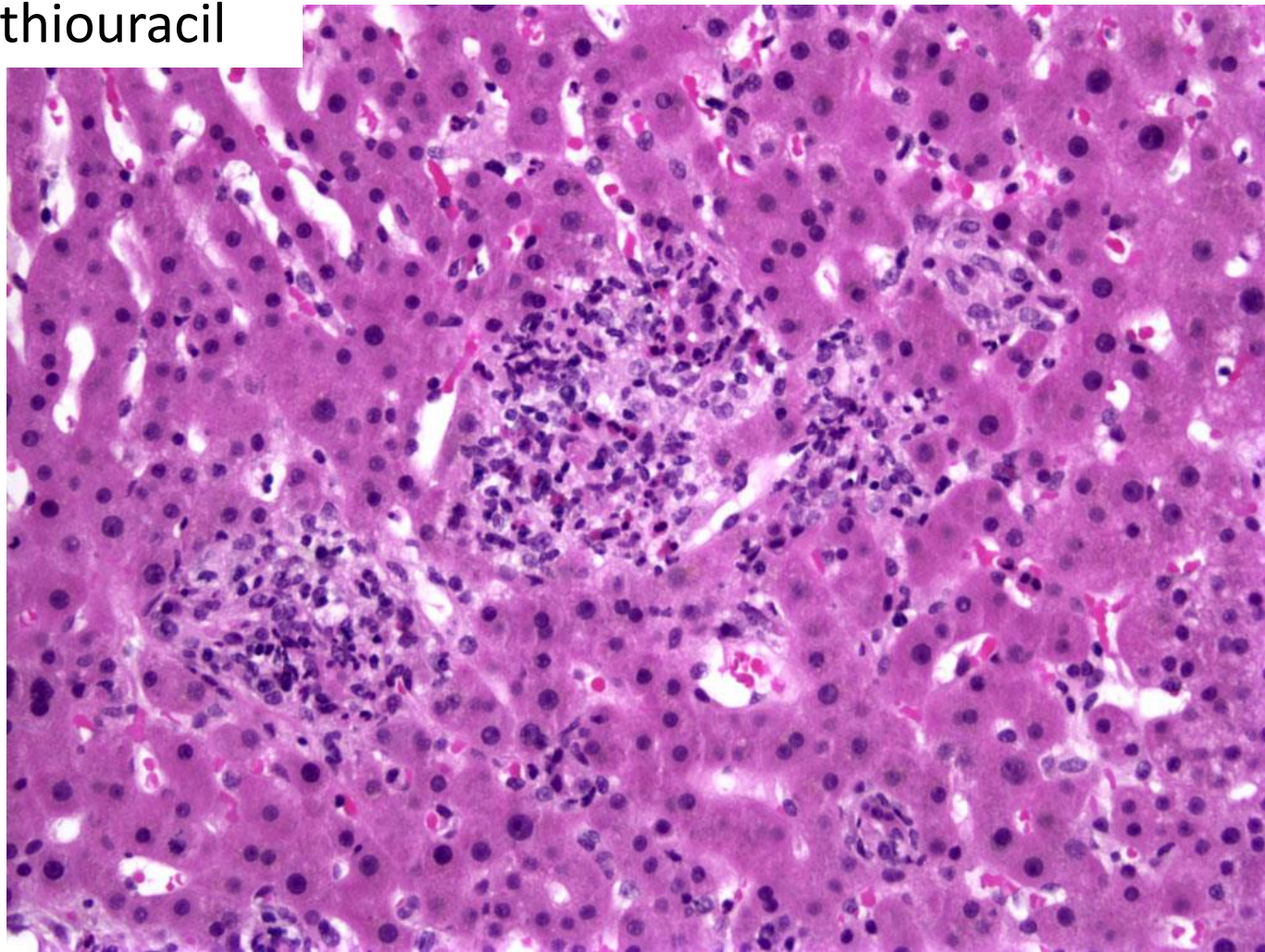
Common drugs likely to cause granulomatous drug reactions

- Allopurinol
- Amiodarone
- Cephalexin
- Diazepam
- Isoniazid
- Nitrofurantoin
- Penicillins
- Phenytoin
- Propylthiouracil
- Quinidine
- Sulfa drugs

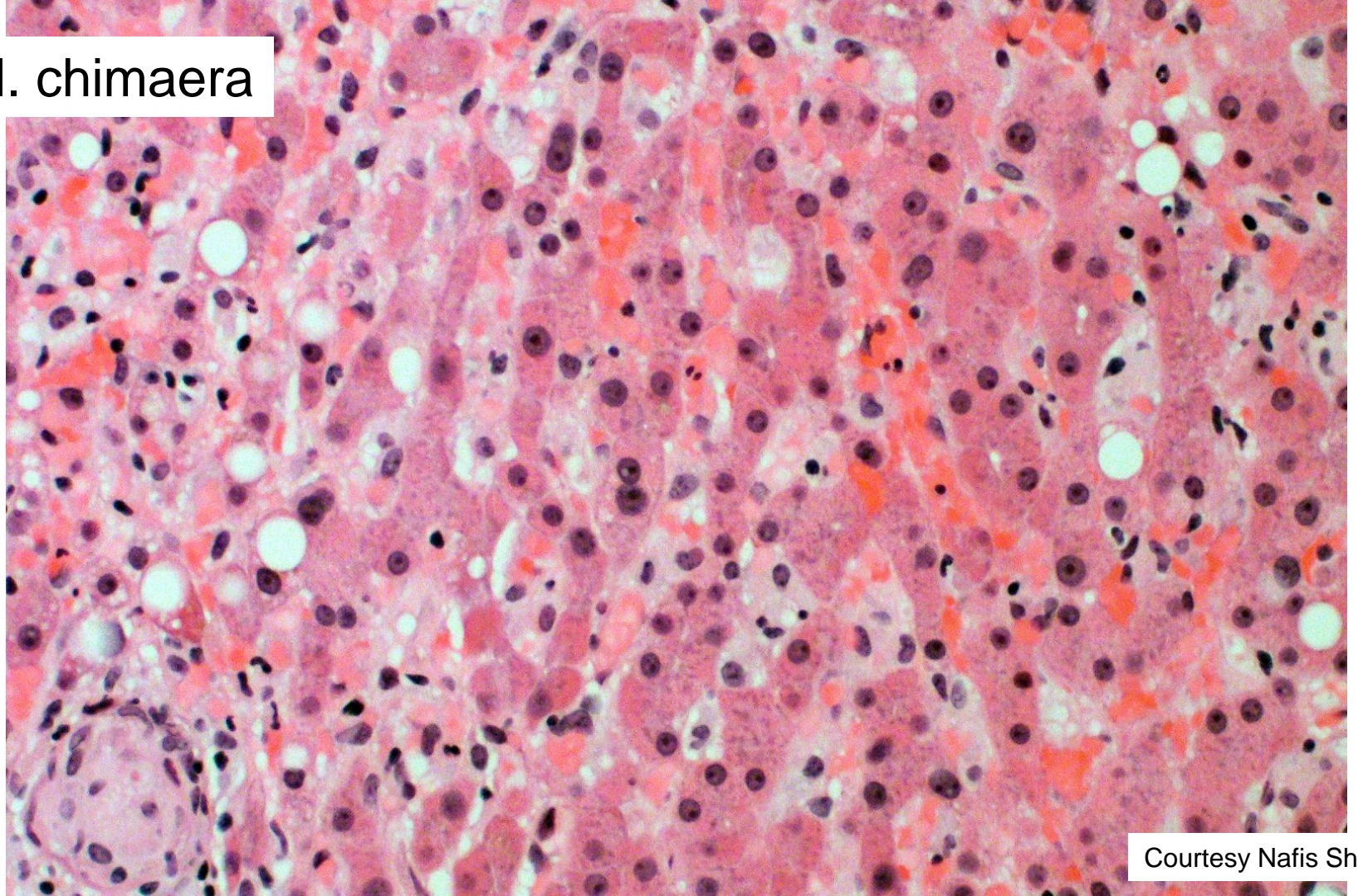


Allopurinol

Propylthiouracil



M. chimaera

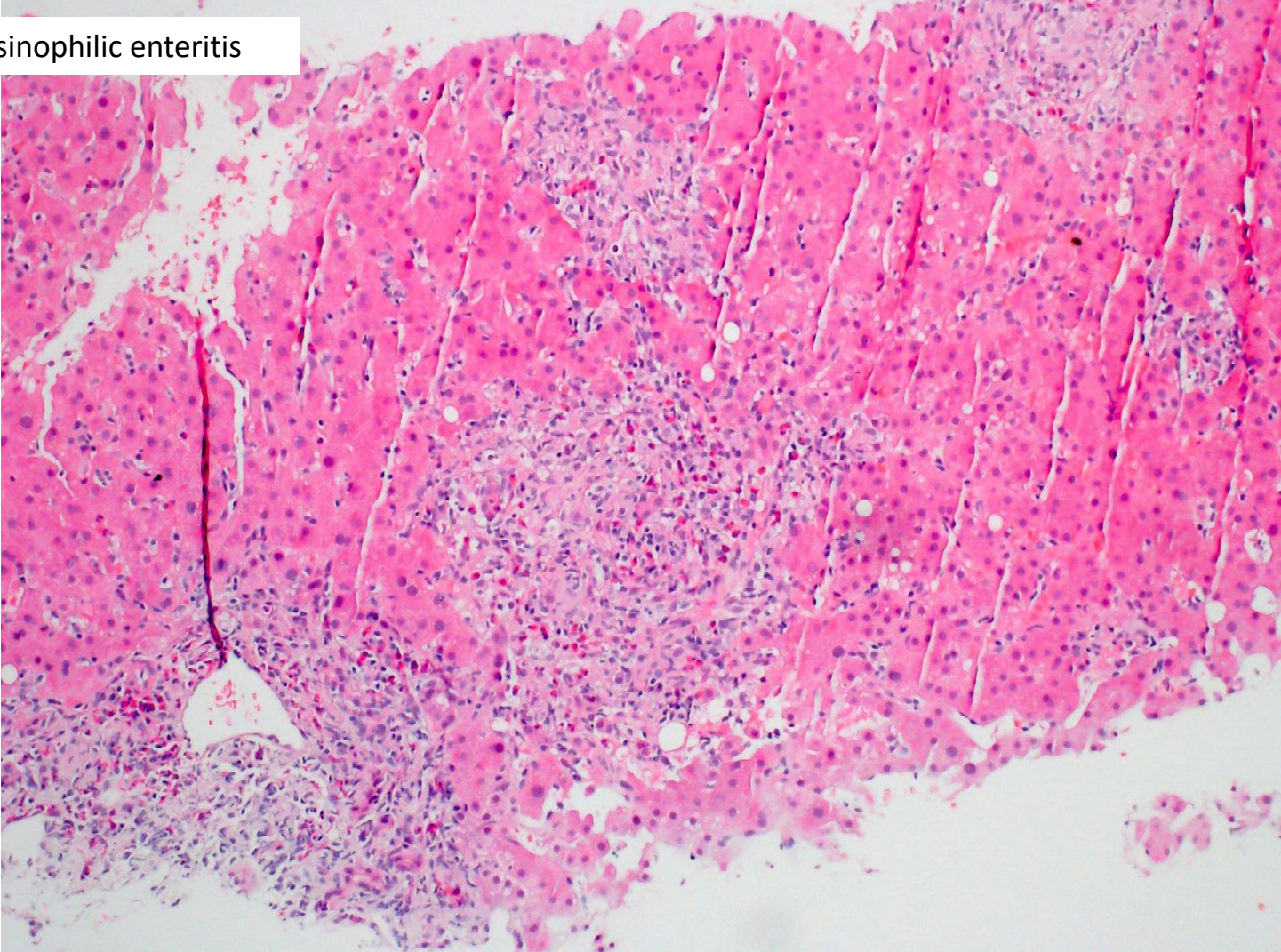


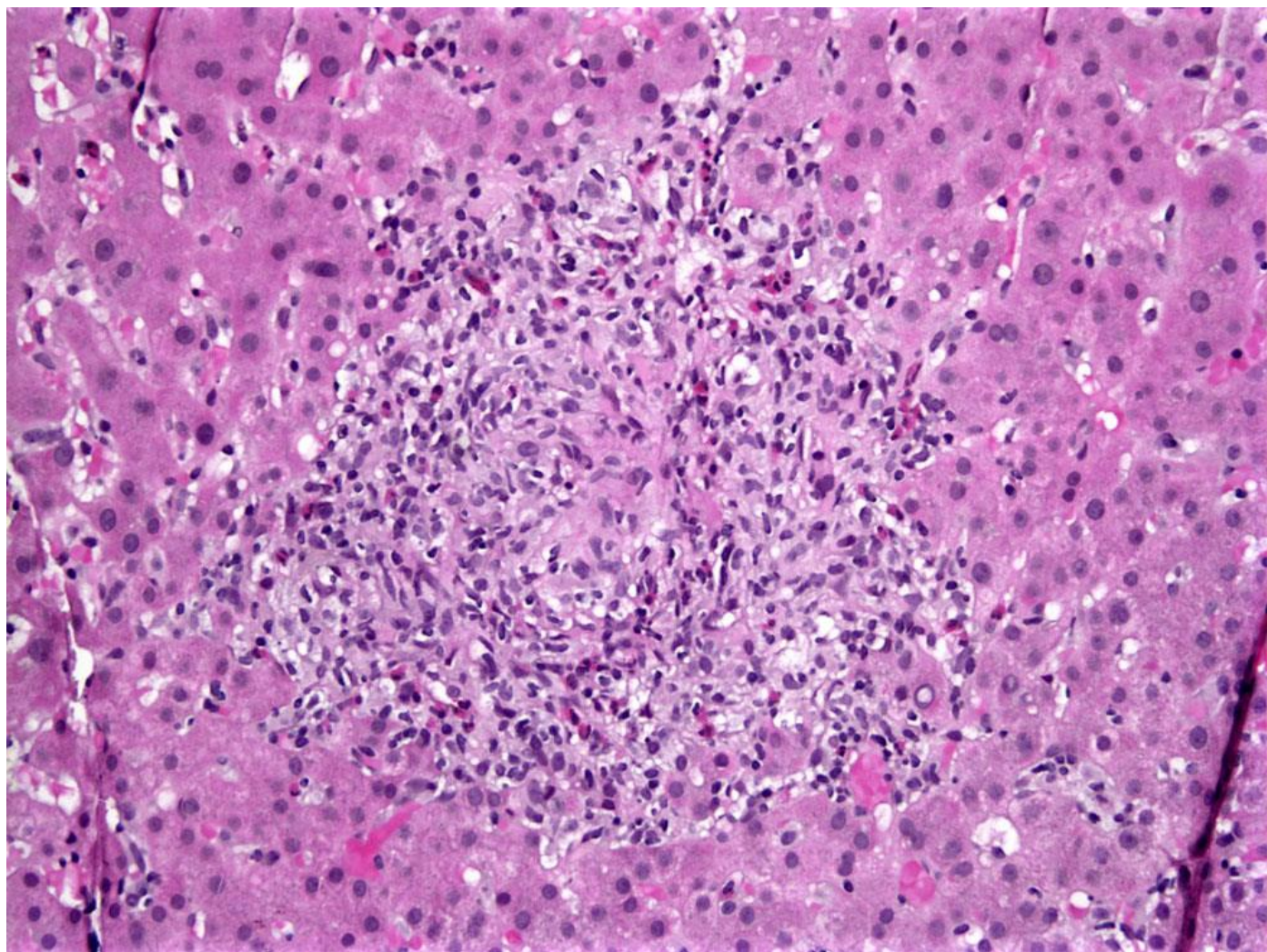
Courtesy Nafis Shafizadeh

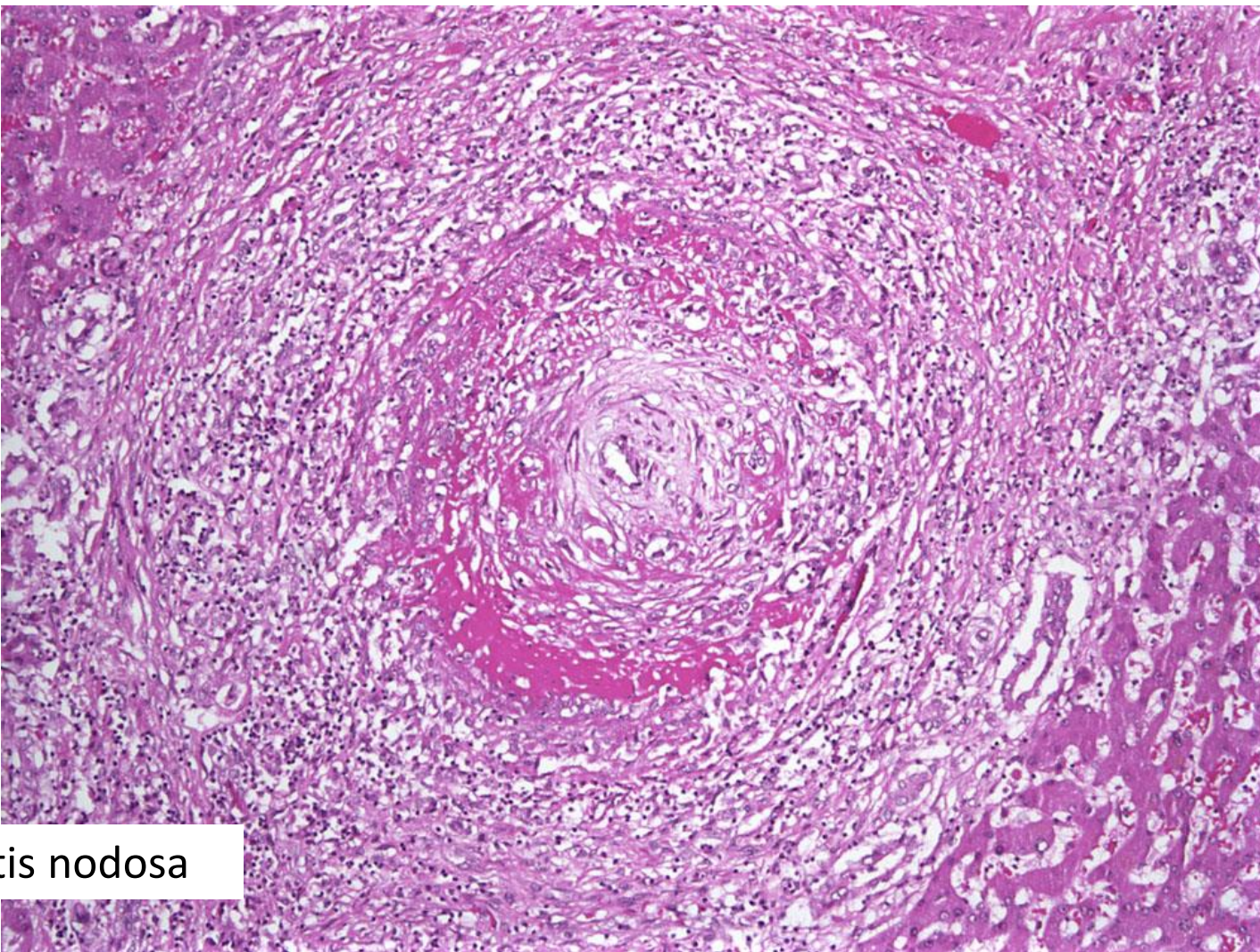
Other Noninfectious Etiologies

- Vasculitis/collagen vascular diseases (polyarteritis nodosa, Churg-Strauss, Lupus)
- Chronic biliary disease (PBC, PSC)
- Chronic GI diseases
 - IBD: not clear if granulomas are primary or associated with drugs, PSC, other in cases of UC, Crohn's with granulomas
 - Idiopathic eosinophilic enteritis may cause granulomas in biliary tree, liver
 - CVID

Idiopathic eosinophilic enteritis

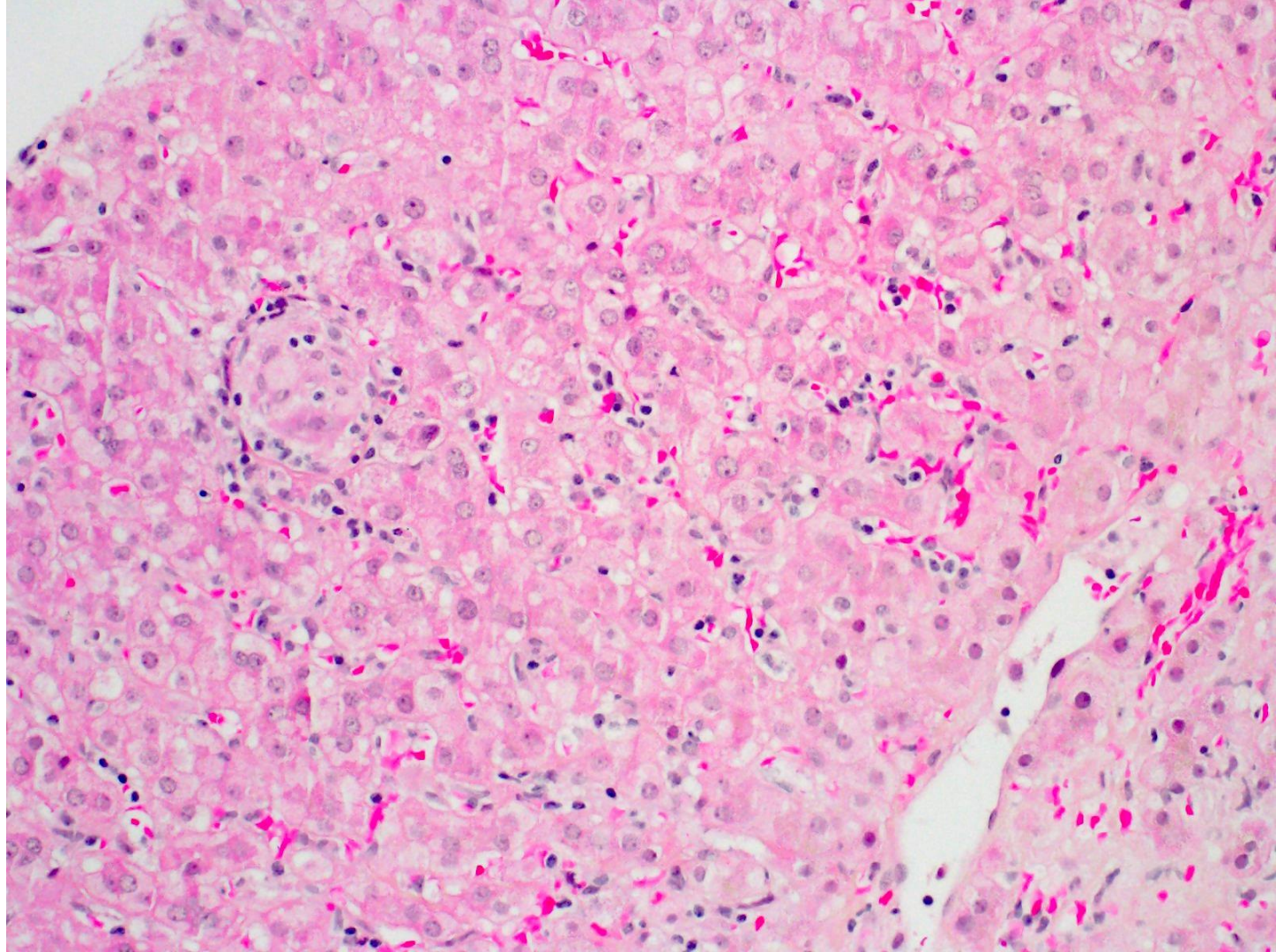






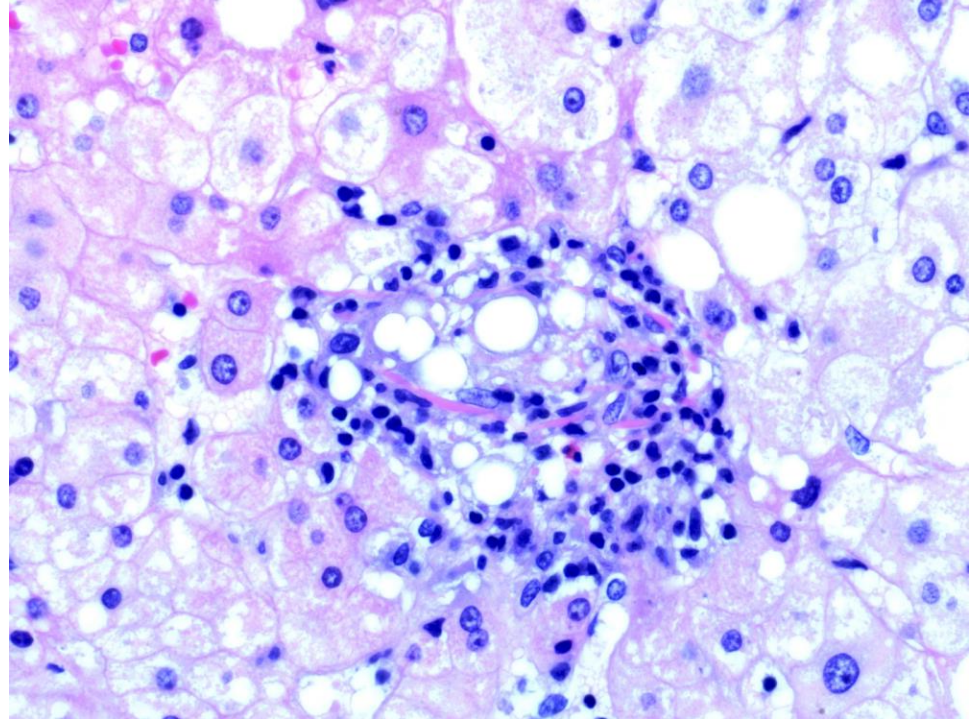
Polyarteritis nodosa

CVID



Morphological Classification of Granulomas

- Lipogranulomas
 - Contain lipid or mineral oil
 - Fatty liver disease
 - Hepatitis C



In Summary

- Morphology of granuloma can be clue to diagnosis/differential diagnosis
- Portal lymph node pathology may be helpful
- Low threshold for special stains
- Culture, molecular testing, and serologic studies may be useful diagnostic tools
- Clinical history may be the diagnostic tool that is most helpful, cheapest, but not always easiest to get



Questions?