FUO or FKO?

Andrew Beany

May 2017

Bnai Zion MC, Haifa

M. G.

- 19 yo female
- Obesity

Fever – *6 months*
Weight loss
Weakness
Dry cough
Diffuse non-specific (abdominal) pain

November 2016

August 2016

Work-up in a different hospital

- **HB=9.6 (MCV=69)**, WBC=7.73, **PLT=511**
- **CRP=240, ESR=110**
- **Albumin= 3.2**
- Folic acid- low
- T. Bil=0.48, ALT=32, AST=37, **ALP=152**
- **LDH=513**
- **Urinalysis: RBCs**

- Radiology
  - Chest and sinuses x-ray: Normal
  - Abdominal US: Normal
  - CT scan: Mild **splenomegaly**
  - PET-CT: Normal
  - TTE: Normal except sinus tachycardia
- E.N.T evaluation: Normal
- Normal work-up for infectious diseases
  - CMV, EBV, Toxoplasma, Mycoplasma, Brucella, C. burnetii (Q-fever), Rickettsia, Bartonella (cat-scratch), Pertussis, HIV, STD
- Work-up for inflammatory diseases
  - ANA, ENA, Anti-P3, Anti-MPO, RF, Anti-GBM, Celiac serology: Normal
  - ASLO, C3, C4: mildly high

August 2016

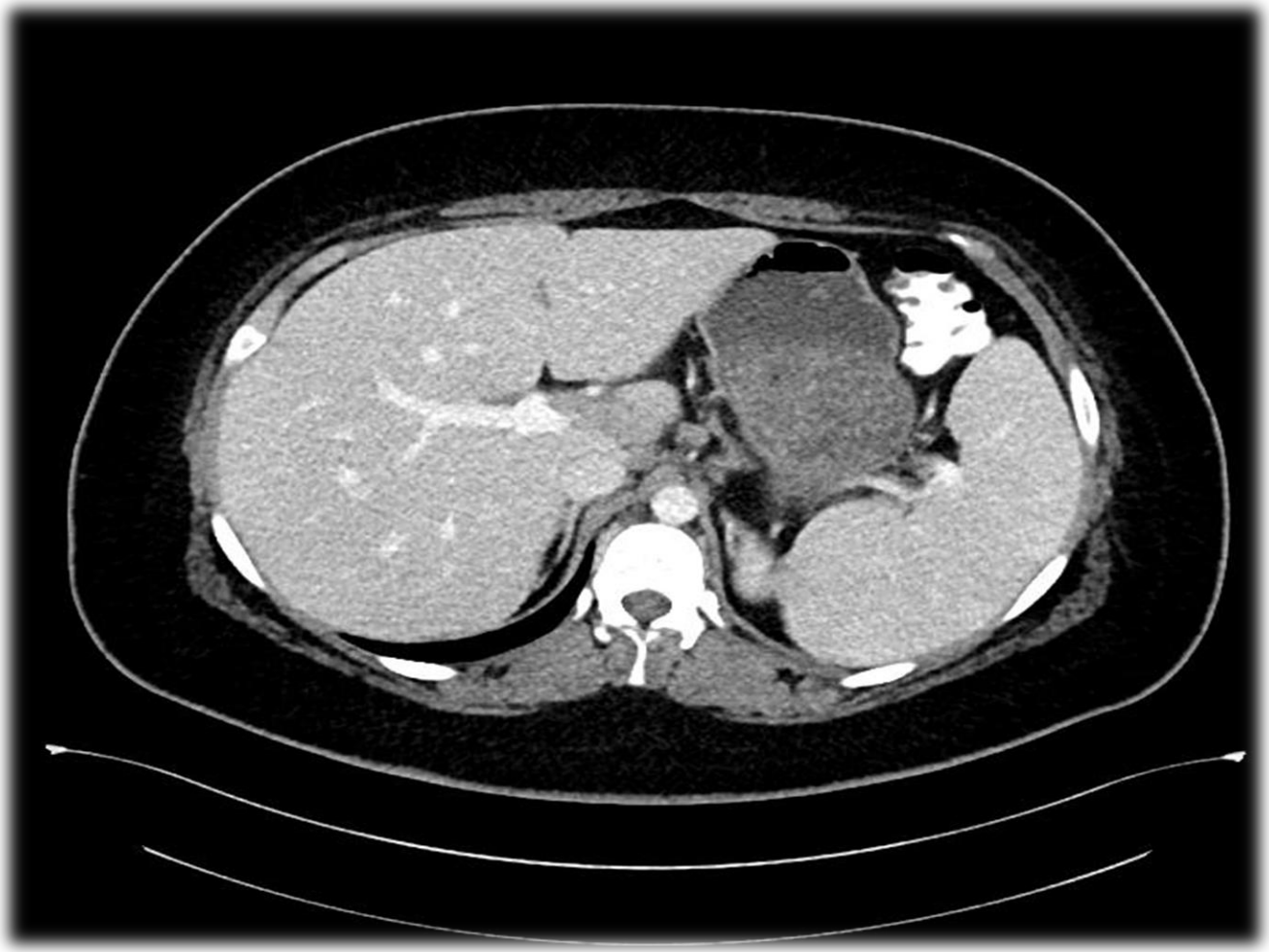
Work-up in a different hospital

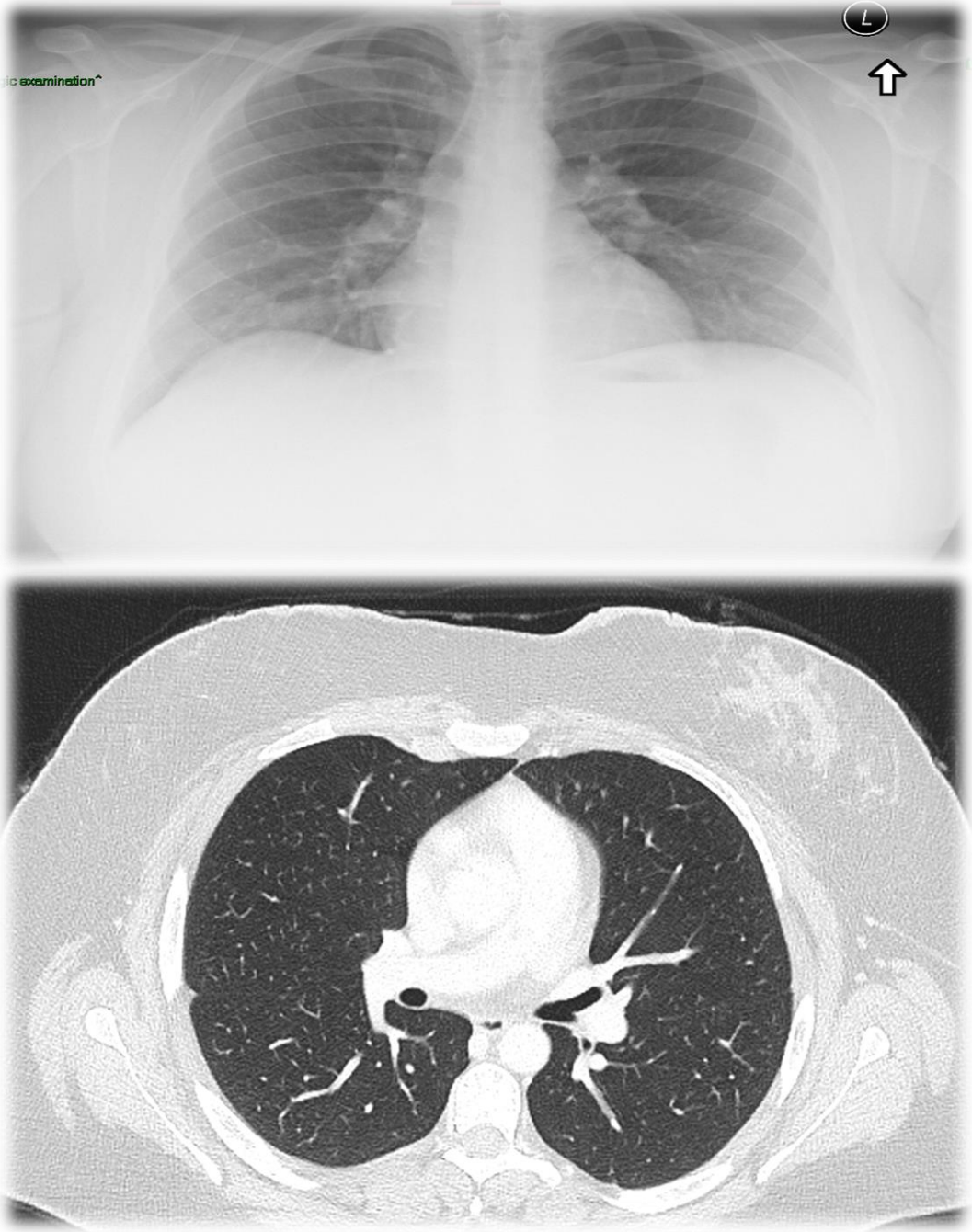
- PO Doxycycline 100 mg x 2/day
- Mild symptomatic improvement
- CRP=120

November 2017

Work-up in our hospital

- **HB=9.78 (MCV=69)**, WBC=8.32, **PLT=472**
- **Fe=31**, Transferrin=256, **Ferritin=203**, Vit B12=753, folic ac=6.3
- T.Bil=0.3, ALT=37, AST=45, **ALP=154**, **GGT=162**, LDH=313
- **CRP=93**
- **Urinalysis: RBCs**
- Work-up for inflammatory diseases
  - ANA, C3, C4, p/cANCA, CLP, RF, IgA/G/M, Anti-endomysial, Anti-TTG, LKM Ab, AMA, ASMA, Anti-RNP, Anti-Smith, Anti-RO, Anti-LA, Scl 70 Ab, Anti-centromer, Jo1 Ab- Normal
  - **ACE=85.4** (UNL: 55)
  - **ASLO= weakly positive**
- Work-up for infectious diseases
  - Blood and urine cultures, HBsAg, HBcAb, HCV Ab, EBV IgM, CMV IgM, Brucella, Pertusis, Parapertusis, C. burnetii (Q-fever), Rickettsia, Bartonella (cat-scratch), HIV- Negative
  - Quantiferon TB- negative
- Consultations
  - Ophthalmologist, gynecologist, pulmonologist (including spirometry): Normal
- Radiology
  - Chest x-ray: Normal
  - TTE: Normal
  - **Abdominal US: HSM**
  - **CT: HSM, lymphadenopathy**

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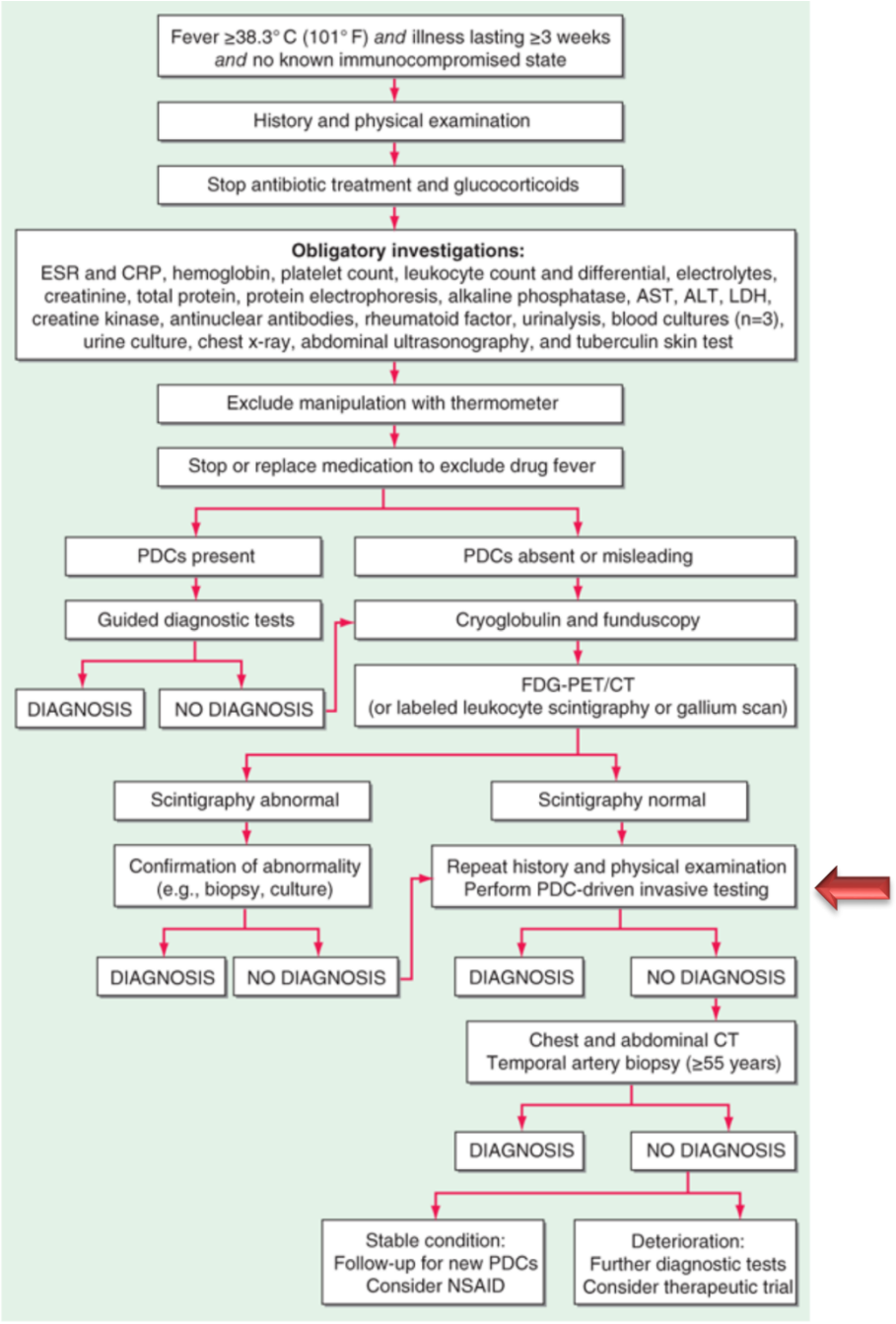
August 2016

Work-up in our hospital

- PO Doxycycline 100 mg x 2/day for 2 weeks
- No improvement in symptoms, CRP, LFT

Structured approach to patients with FUO



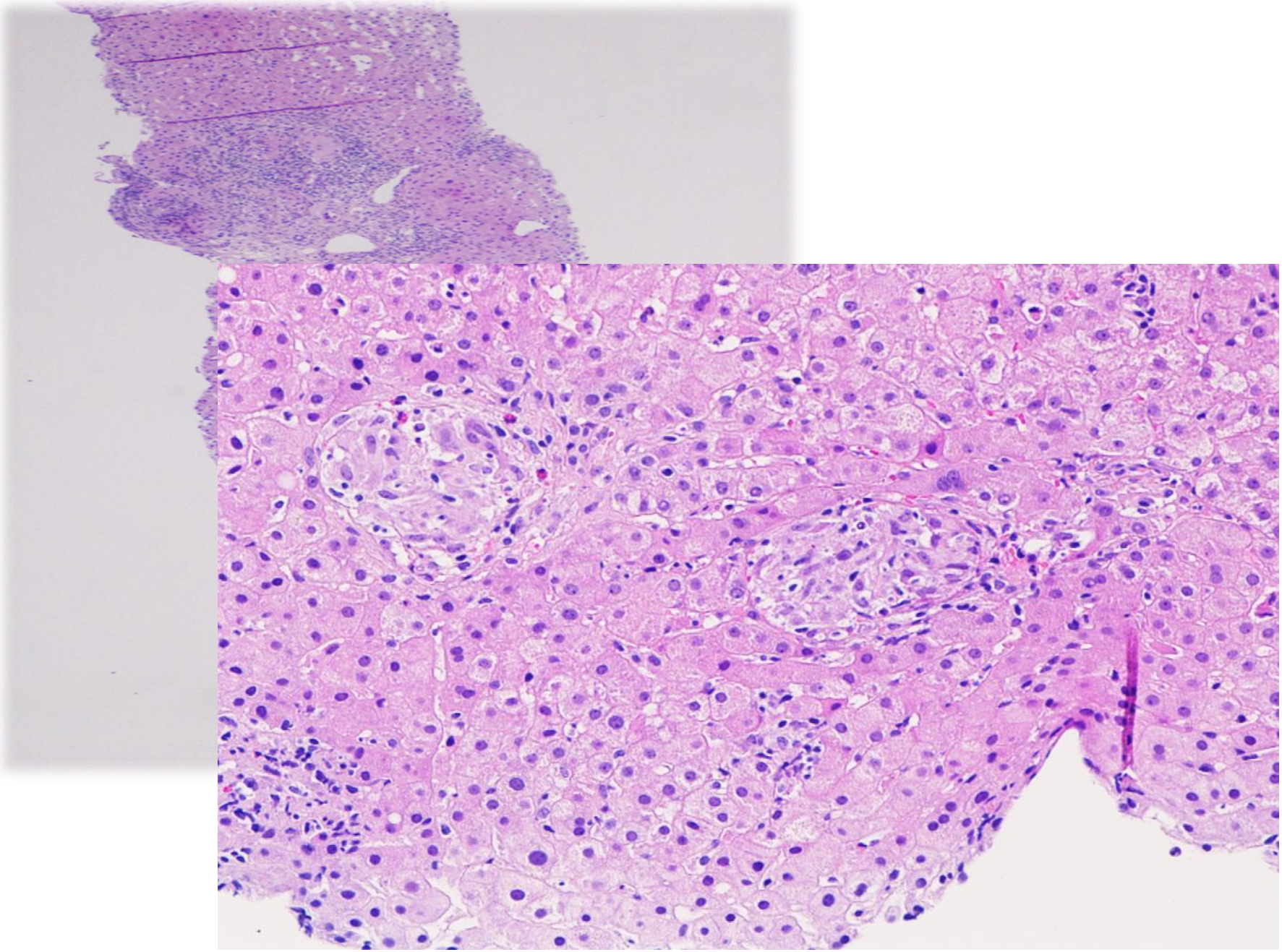
PDCs, potentially diagnostic clues

(all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis)

Harrison's Principles of Internal Medicine, 19e, 2015

Liver Biopsy

- Preserved lobular architecture and porto-central ratio
- **Marked inflammation** in portal areas and liver parenchyma zones 1, 2, 3
- The inflammatory infiltrate is composed of **lymphocytes** and **histiocytes**, few **plasma cells** and few **eosinophils** admixed with **non-caseating granulomas** (sarcoid like)
- In parenchyma, there is no evidence of increased apoptosis, ballooning or Mallory bodies



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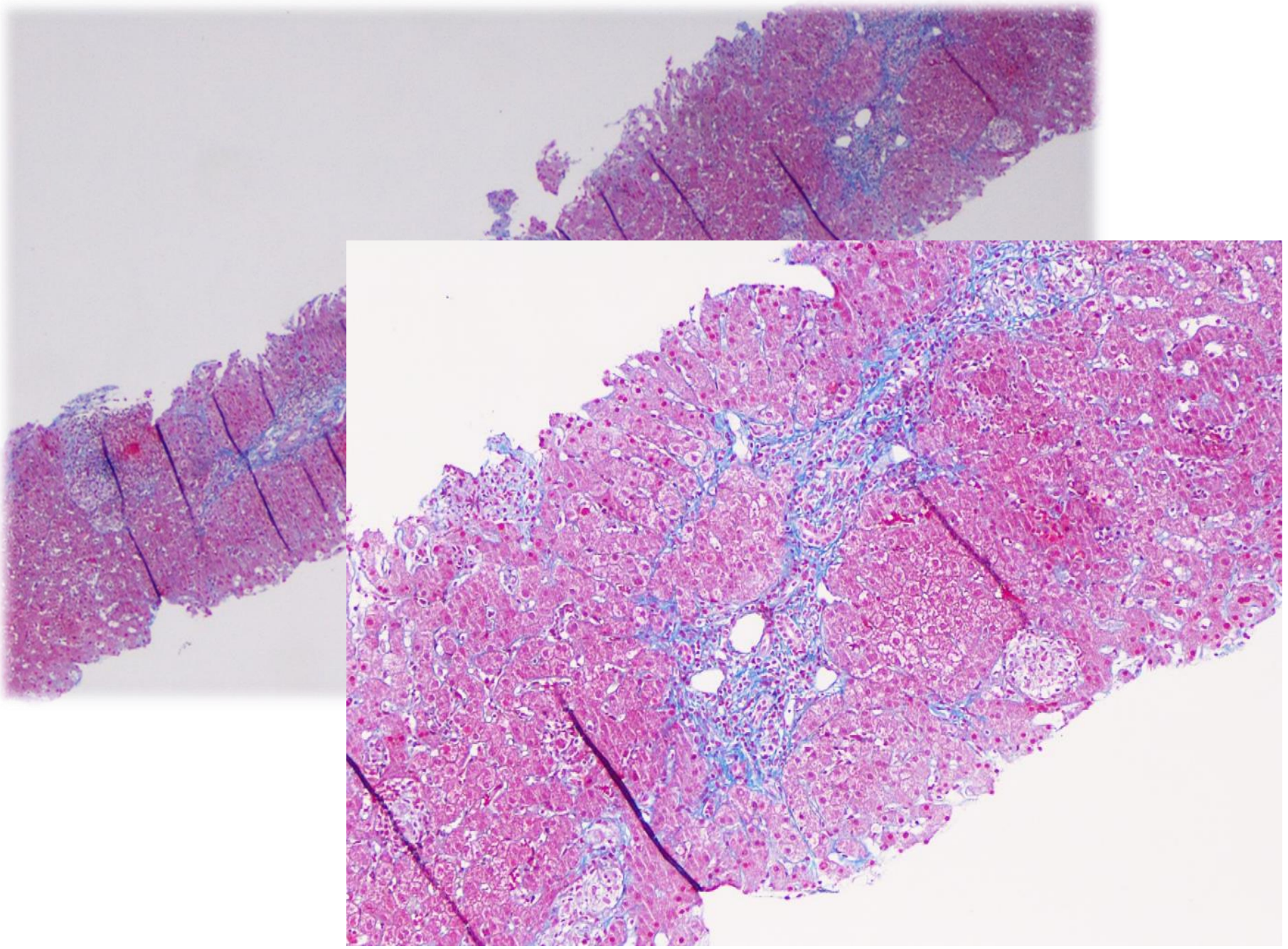
- In the portal areas the inflammatory process expand the portal spaces and involve the interface area with **porto-portal and porto-central bridging tendency**
- **Reticulum and Masson stains** show fibrous portal expansion and porto-portal **bridging fibrosis**
- ZN, PAS, CMV stains does not detect microbiota



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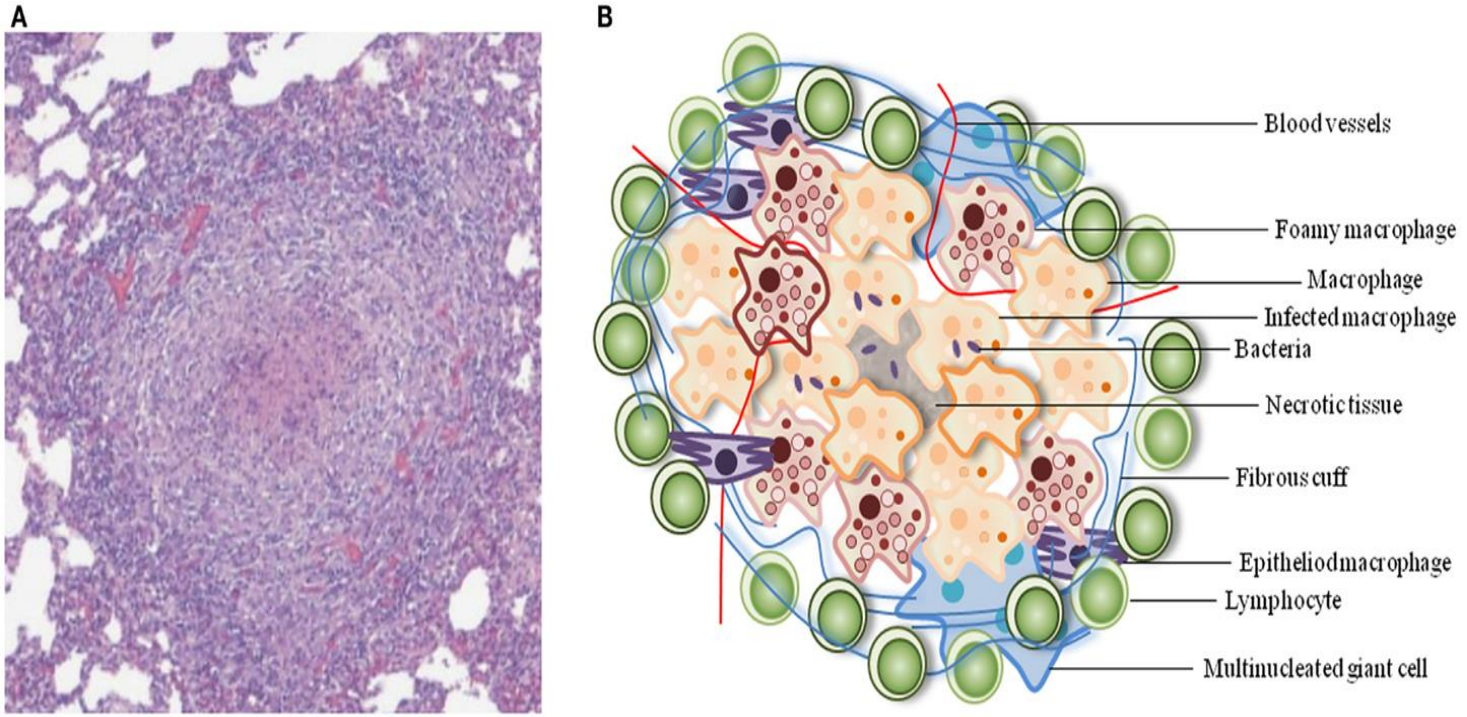
Non-caseating granulomatous hepatitis

DD: AIH, PBC, DILI
Less probably: sarcoidosis, infectious granulomas

Granulomas



A **circumscribed lesion** that forms as a result of an **inflammatory reaction**. It is characterized by a central accumulation of mononuclear cells, primarily **macrophages**, with a surrounding rim consisting of **lymphocytes** and **fibroblasts**

Hepatic granulomas

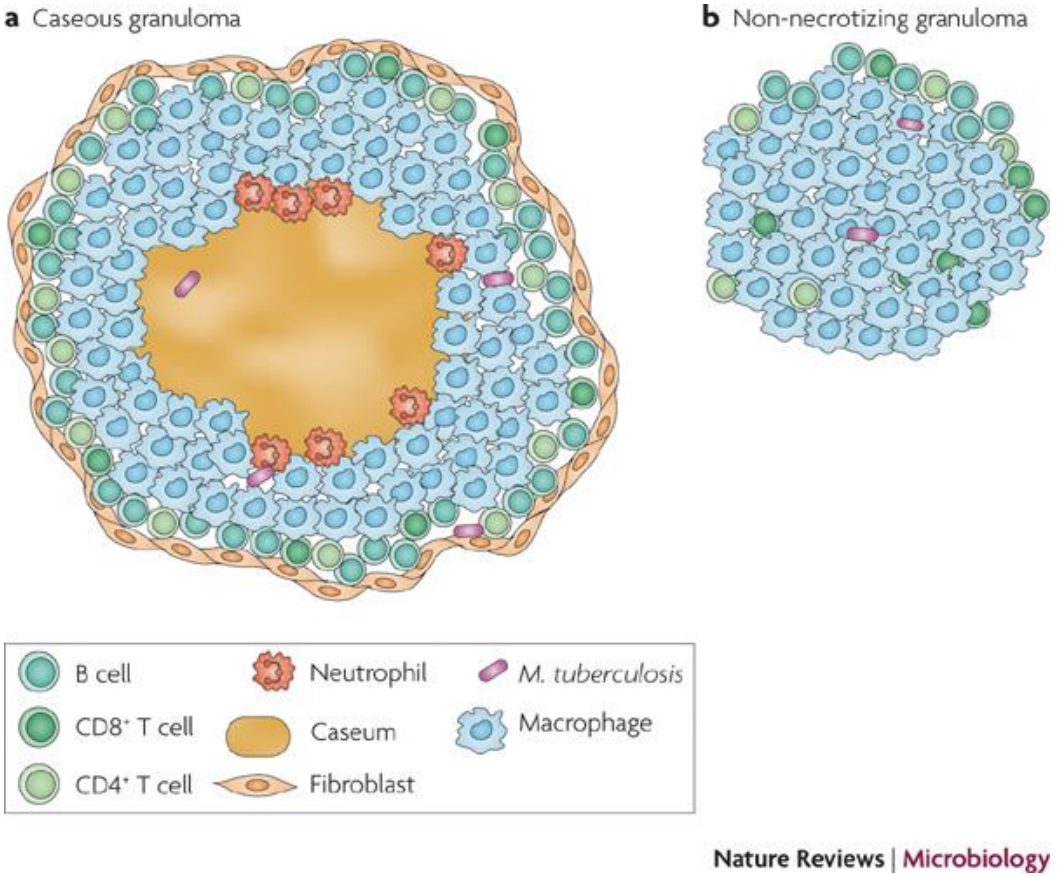
- 2-10% of patients who undergo a liver biopsy
- Caused by a variety of conditions
- May also be an incidental finding on otherwise normal liver biopsy specimens
  - An isolated granuloma (or perhaps two on a large liver biopsy specimen) does not necessarily indicate the presence of granulomatous liver disease

"The pathologist reading the liver biopsy should attempt to determine the location of the granulomas, the presence/absence of necrosis, the type of accompanying infiltrate, any organisms or foreign material in the granuloma, and associated findings"

Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th Edition

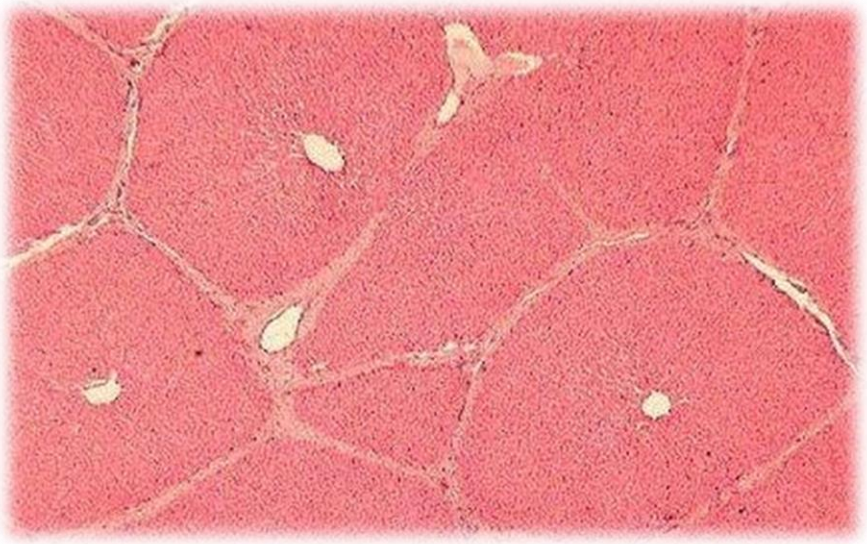
Histologic variants

- Noncaseating
  - Sarcoidosis
- Caseating
  - Tuberculosis
- Fibrin-ring
  - Hodgkin ly., CMV, HAV, Q fever, allopurinol
- Lipogranulomas
  - Mineral oil ingestion



Hepatic granulomas

- Can be located throughout the hepatic lobule
- A tendency to be located in specific sites is recognized in some disorders
  - Portal or periportal location: sarcoidosis
  - Portal location: PBC



Etiology

- What is the most common cause of granulomatous liver disease?

1. Primary Biliary Cholangitis
2. Infectious diseases
3. Sarcoidosis
4. All of the above ✓

"Probably the most common cause in the developed world is PBC"

Chapter 36, pp. 611

"The most common etiologies in the developing world (and in older studies) are infectious diseases, especially tuberculosis"

Chapter 36, pp. 611

"Sarcoidosis is the most common etiology"

Chapter 73, pp. 1249

Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th Edition

Granulomatous liver disease- causes

Infections

Bacterial
Tuberculosis
MAC
Brucellosis
Lepromatous leprosy
BCG infection
Listeriosis
Melioidosis
Tularemia
Yersiniosis
Psittacosis
Whipple disease
Catch scratch fever
Viral
CMV
EBV
Hepatitis A, B and C

Fungal
Histoplasmosis
Coccidioidomycosis
Cryptococcus
Nocardiosis
Candidiasis
Parasitic
Toxoplasmosis
Schistosomiasis
Visceral larva migrans
Visceral leishmaniasis
Rickettsial
Coxiella burnetii (Q fever)
Bontonneuse fever
Spirochetal
Secondary syphilis

Medications

Allopurinol
BCG
Carbamazepine
Chlorpropramide
Diltiazem
Gold
Halothane
Hydralazine
Interferon alfa
Mebendazole
Methyldopa
Nitrofurantoin
Phenylbutazone
Phenytoin
Procainamide
Quinidine
Sulfa drugs

Miscellaneous

Primary biliary cholangitis
Hodgkin disease
Non-Hodgkin lymphoma
Renal cell carcinoma
Berylliosis
Copper toxicity
Lipogranulomas (from ingestion of mineral oil)
Talc or other particulate matter
Crohn disease
After jejunoileal bypass
Inhalation of copper sulfate (vineyard workers)
Chronic granulomatous disease
Granulomatosis with polyangiitis (Wegener's)
Ingestion of "Green juice"
Intravesical administration of bacillus Calmette-Guerin
Idiopathic

UpToDate

Suggested laboratory evaluation in patients with granulomas on liver biopsy*

Chest film
Tuberculin skin test
Serum angiotensin converting enzyme concentration
Blood cultures (bacteria, fungi, mycobacteria)
Serologies (HIV, Brucella, syphilis, Coxiella, etc.)
Serum antimitochondrial antibodies
Serum IgM concentration
Acid-fast and fungal stains on liver biopsy

* Specific testing should consider clinical symptoms, travel history.

Sarcoidosis, mycobacterial infection (*M. tuberculosis* and Mycobacterium avium complex), PBC, and drug reactions, account for 50-75% of hepatic granulomas in the USA

Sarcoidosis

- Systemic granulomatous disease of unknown etiology
  - Noncaseating epithelioid granulomas
- Prevalnece: 10-20/100.000
- Age 20-60
- Women > men
- Lung disease in > 90% of all cases

Sarcoidosis

- 50-65% have granulomas on liver biopsy
- Symptoms: 5-15% of patients
- Most patients are asymptomatic and have only biochemical abnormalities
  - Usually an elevated ALP and GGT
- Rare patients develop cholestatic liver disease, cirrhosis, portal HTN, and/or hepatic vein thrombosis

Sarcoidosis

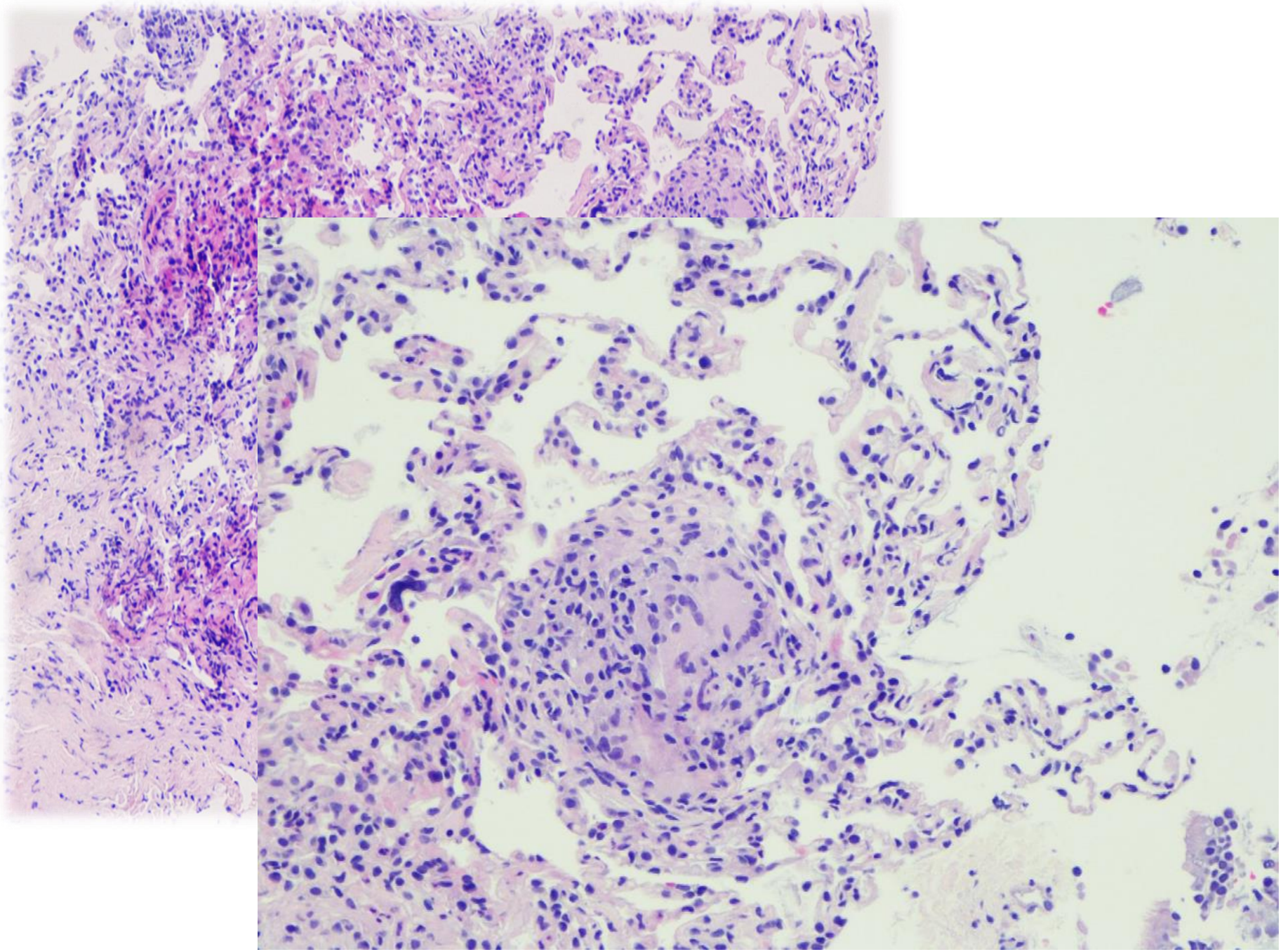
- No pathognomonic laboratory or histopathologic findings can establish the diagnosis of hepatic sarcoidosis
  - Sarcoid granulomas are often located in the portal tract
- Additional steps of identifying characteristic extrahepatic manifestations, and R/O other causes such as infection, drug-induced granulomas, and malignancy, are essential to making a definitive diagnosis

Trans-Bronchial Biopsy

- Interstitial granulomas, no evidence of inflammation, necrosis, or fibrosis
- Acid fast and silver stain are negative

Non-caseating granulomas in lung

DD: infectious granulomas, sarcoidosis



Bronchoalveolar Lavage

- Flow-cytometry analysis
  - CD4:CD8 ratio - 1:1
- Mycobacterial culture- negative
- Acid-Fast stain- negative

Management and follow-up

- PO Prednisone 40 mg

- Clinical improvement
- CRP- elevation

Liver Biopsy

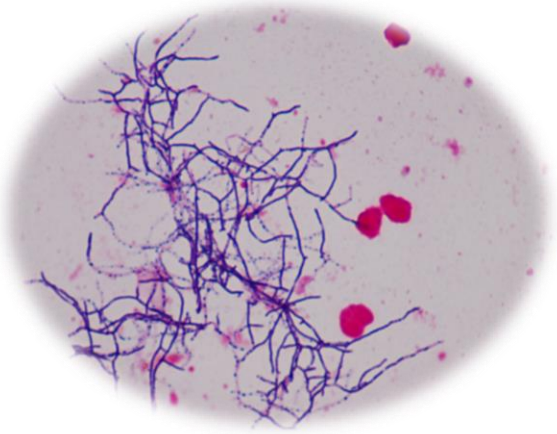
- Mycobacterial PCR- negative
- Bacterial DNA PCR- positive
  - *Nocardia Farcinica*
- Fungal DNA PCR- negative

Trans-Bronchial Biopsy

- Mycobacterial PCR- negative
- Bacterial DNA PCR- negative
- Fungal DNA PCR- negative

Nocardia

- Gram-positive, branching rods, aerobic bacteria
- Found worldwide in soil, decaying vegetable matter, and aquatic environments
- **Modes of entry**: inhalation, ingestion, and direct inoculation through the skin
  - Inhalation is the most common route of entry
- The majority of patients are immunocompromised, most often with cell-mediated abnormalities
  - Glucocorticoid therapy, malignancy, organ and hematopoietic stem cell transplantation, and HIV
- **Clinical manifestations**
  - Lungs- the primary site of infection in >2/3 of cases
    - Acute, subacute, or chronic
  - CNS disease- abscess, ~20% of cases
    - Mostly dissemination of infection from a pulmonary or cutaneous site
  - Cutaneous disease- mostly by trauma
  - Disseminated nocardiosis- two or more noncontiguous sites



Patient re-admitted for further evaluation

Trans-Bronchial Biopsy- 12.2016

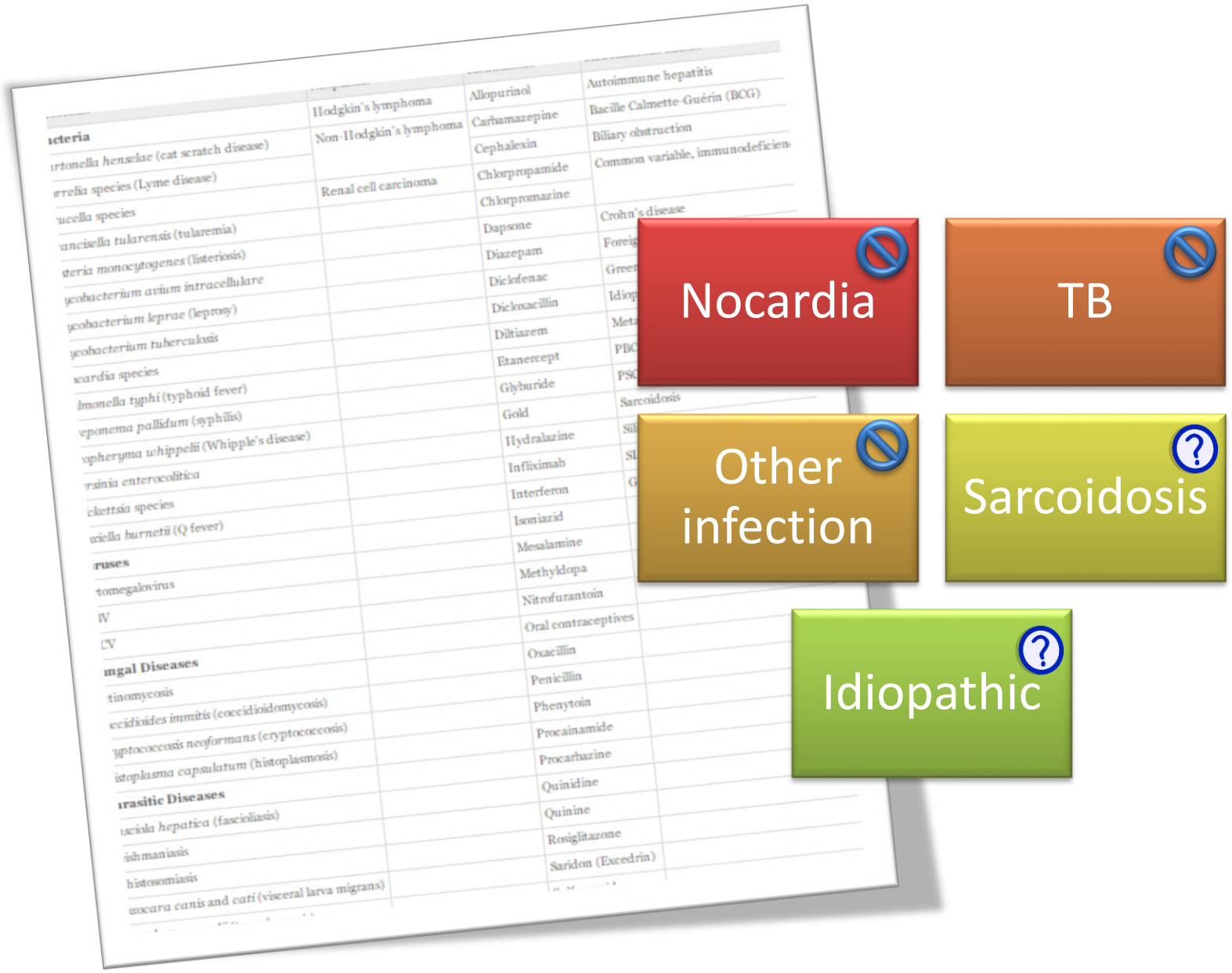
- No granulomas
- No *Nocardia*
  - Stains with methenamin silver, PAS, ZN, Gram- negative
  - Bacterial PCR- negative
- Mycobacterial PCR- negative

Brocho-alveolar Lavage- 12.2016

- Mycobacterial PCR- negative
- Bacterial DNA PCR- negative
  - No *Nocardia*
- *Nocardia* culture- negative

Re-evaluation

- Liver biopsy w/o paraffin
  - Pan-bacterial PCR- negative
  - No *Nocardia*
- Neutrophil function assessment- normal


Nocardia
TB
Other infection
Sarcoidosis
Idiopathic

Idiopathic granulomatous hepatitis

- The cause of hepatic granulomas may remain unclear despite careful evaluation
  - 10-36%
- A syndrome of prolonged febrile illness, myalgias, hepatosplenomegaly, and arthralgias of unclear etiology
  - Relapsing remitting course
- Laboratory findings are nonspecific. ESR is often markedly elevated

Idiopathic granulomatous hepatitis

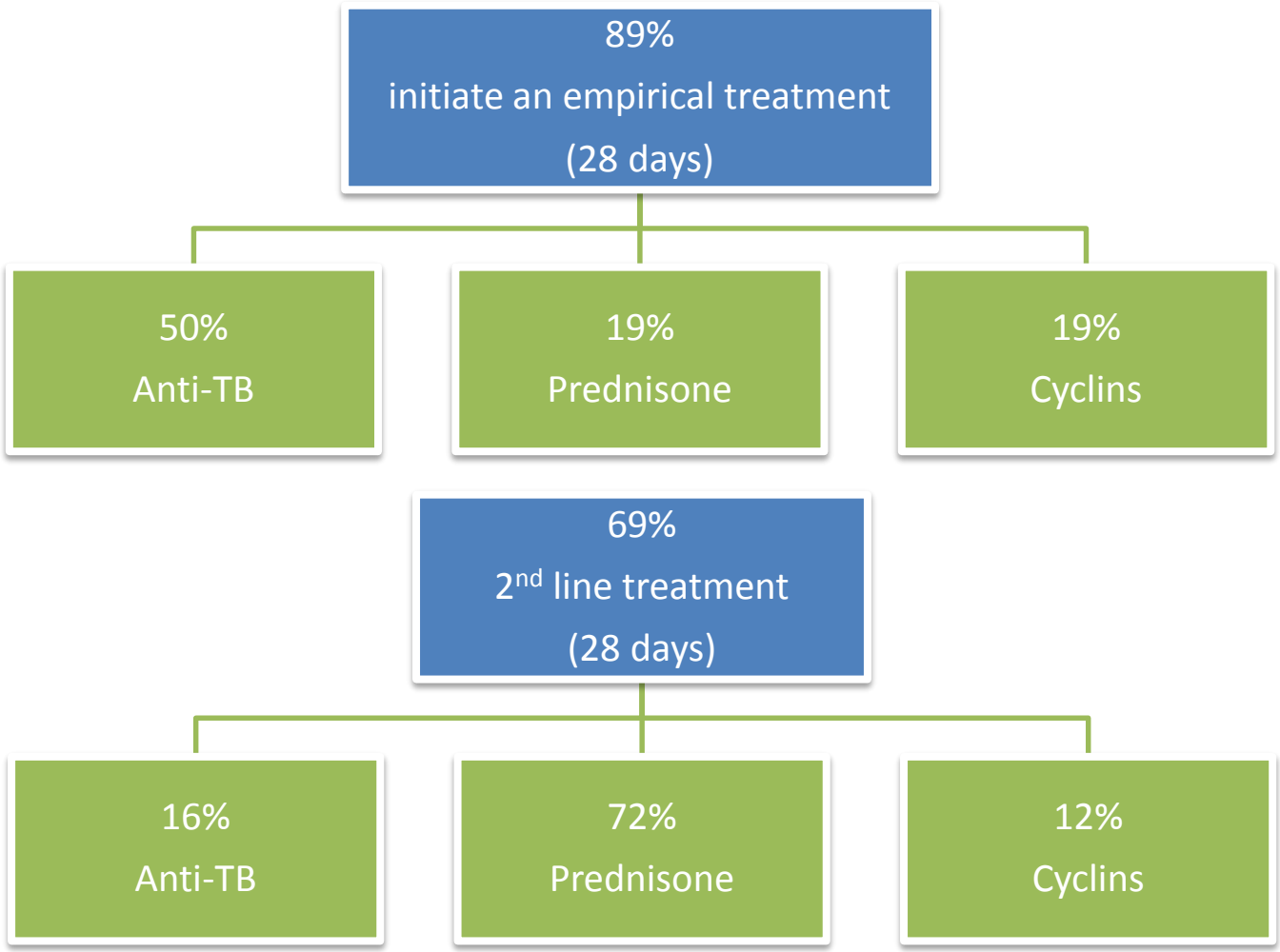
- The treatment of symptomatic cases involves immunosuppression
- It is reasonable to treat initially with an empiric course of antituberculous medications in patients in whom there is a concern about underlying tuberculosis
- If there is no clinical response after 4-8 weeks, empiric corticosteroids should be instituted, which usually lead to rapid improvement in symptoms and disappearance of the granulomas
  - Prednisone, 20 to 40 mg per daily
  - A biochemical response should be noted within several months
  - Once symptoms have improved, gradual weaning should be attempted
  - The prognosis in patients who respond to corticosteroids is good
  - Relapse is common and a repeat course of corticosteroids is often necessary
  - Methotrexate, as a steroid-sparing agent

Rev Med Interne. 2006 Apr;27(4):276-84. Epub 2006 Feb 9.

[Empirical treatment of granulomatous hepatitis of unknown origin: practice investigation in the French National Society of Internal Medicine].

[Article in French]

Agard C[1], Pottier P, Hamidou M, Papo T, Généreau T, de Faucal P, Boutoille D, Ponge T, Connault J, Brisseau JM, Planchon B, Barrier JH.



Management and follow-up

- PO Prednisone 30 mg (tapering down)
  - Mild clinical improvement
  - No improvement in CRP or LFT
- PO Azathioprine 50 mg (steroid-sparing)
  - Mild clinical improvement
  - Normal LFT
  - High CRP and ESR
- MTX- relative CI, d/t liver fibrosis
- Biological agent? (refractory sarcoidosis)

Lost to follow-up