Granulomas in the Liver-
with an emphasis on infectious etiologies

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Hepatic Granulomas

• Present in 2-10% of liver biopsies
• 13-36% have no discoverable etiology even after extensive workup of tissue and patient!
Causes of Hepatic Granulomas

- Infection
- Immunodeficiency
- Cholestatic liver disease (PBC)
- Tumors

- Drugs/toxins
- Metal exposure
- Foreign material
- Autoimmune diseases
- Other
  - Sarcoidosis
  - Chronic gastrointestinal diseases
Morphological Classification of Granulomas

- Epithelioid (+/-) necrosis
- Lipogranulomas
- Microgranulomas
- Fibrin ring granulomas
- Foamy macrophage aggregates
- Granulomatous inflammation
- Stellate abscess with granulomatous inflammation
Morphological Classification of Granulomas

- **Epithelioid (±) necrosis**
  - Discrete with distinct edges
  - Necrosis, lack of respect for architecture are often associated with infection
  - TB, sarcoidosis

- **Lipogranulomas**
  - Contain lipid
  - Mineral oil

- **Microgranulomas**
  - Some define as 3-7 cells in cross-section
  - Very nonspecific; often associated with other inflammatory cells
  - Drug reaction, Listeria
Morphological Classification of Granulomas

• Foamy macrophage aggregates
  – Often in immunocompromised patients
  – MAI, Rhodacoccus, histoplasmosis

• Granulomatous inflammation, +/- suppuration
  – Poorly formed, indistinct edges
  – Often admixed with other inflammatory cells
  – Some infections, drug

• Stellate abscess with granulomatous inflammation
  – Central abscess, surrounding granulomatous lesion
  – Cat scratch disease, Candida
Helpful questions to ask:

- Morphology of granuloma
- Accompanying inflammatory infiltrate
- Location of granulomas
- Nature of necrosis, if present
- Is there anything in the granuloma
- Other associated morphologic changes
- Need for special stains
Helpful clinical questions to ask:

• Immune status of patient
  • Exposure to animals
    • Foreign travel
  • Medication/drug history
Fibrin Ring Granuloma

• Epithelioid granuloma composed of lipid vacuole surrounded by fibrin ring
• Classically described in association with Q-fever
• Also associated with CMV, EBV, MAI, typhoid, drug reaction, Hodgkin’s disease
Is it time for wine and cheese yet?
Infectious Causes of Hepatic Granulomas

• **Viral**
  – CMV, EBV, HCV

• **Bacterial**
  – Cat scratch disease
  – Mycobacteria
  – Lyme disease
  – Brucella
  – Tularemia
  – Rickettsia
  – Whipple’s disease

• **Fungal**
  – Histoplasmosis
  – Candida

• **Parasitic**
  – Schistosomiasis
  – Ascaris
  – Pinworms
  – Toxoplasma
  – Fasciola hepatica
Mycobacterium tuberculosis

- Granulomas present in virtually all cases of miliary TB
- Signs/symptoms of liver disease may be dominant presenting feature
- Presentation ranges from asymptomatic to fever/RUQ pain/hepatomegaly
- Helpful tests: special stains, PCR, culture
MAI

- Most common in immunocompromised patients (but not always)
- Variable lesions:
  - Discrete granulomas
  - Foamy macrophage infiltrate
  - Fibrin ring granulomas
  - Spindle cell nodule
- Helpful tests: special stains, PCR, culture
MAI with epithelioid granulomas
MAI-foamy macrophages
MAI-fibrin ring granulomas
MAI-spindle cell nodule
Leprosy

• Both lepromatous and tuberculoid leprosy involve the liver; often subclinical
• Lesions depend on type of leprosy, but may be “in-between” the classic types
• Bacilli common in lepromatous leprosy, rare in tuberculoid
• Liver may harbor bacilli even when skin is clear
• Helpful tests: special stains, culture, PCR
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.
Cat Scratch Disease

- Small percentage of patients have disseminated disease
- Lack inoculation site
- Usually not immunocompromised
- Helpful tests: special stains, PCR, ELISA, history
Hepatic Cat Scratch Disease
Arrow = 153 bp DNA fragment of *B. henselae / B. quintana*

Lane 1 = *Bartonella henselae* purified DNA Positive Control
Lanes 2, 5 and 8 = reagent blank negative controls
Lanes 3 and 4 = Patient #36 at 1 ul and 10 ul respectively
Lanes 6 and 7 = Patient #37 at 1 ul and 10 ul respectively
Lane 9 = Patient #38 at 1 ul
Lane 10 = PhiX DNA size marker
Brucellosis

- Exposure to farm animals, contaminated food
- Dominant systemic symptoms; liver involved in about half of cases
- Helpful tests: history, serologies; special stains and culture not helpful
Courtesy Dr. David Walker
Tularemia

- Transmitted through contact with rodents/rabbits
- Patients often systemically ill, +/- hepatomegaly and elevated transaminases
- Helpful tests: serologies, PCR, culture; special stains not helpful
I think we need more beds.
Hepatic Fungal Infections

- Usually part of disseminated disease
- Patients usually immunocompromised
- Liver involvement manifests with hepatomegaly, abdominal pain, elevated transaminases and bilirubin
- Helpful tests: special stains, culture
Hepatic Fungal Infections

• Candida-granulomas with central suppuration
• Histoplasma-lymphohistiocytic nodules
• Aspergillus, Zygomycetes-suppurative; rare granulomas
• Cryptococcus-very variable, can involve biliary tree
H&E/methenamine silver
Cryptococcus
Schistosomiasis

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

- Both epithelioid and fibrin ring granulomas associated with EBV, CMV
- Also in a minority of HCV and HBV patients
- Must try and rule out other causes of hepatic granulomas, however
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 and nodes
- May cause fibrosis, cirrhosis, and cholestatic liver disease
- Helpful tests: chest xray, ACE assay; must rule out other causes of granulomas
Adverse Drug Reaction

- Many different granuloma morphologies; necrosis within granulomas is rare
- Look for associated inflammation, duct injury, vascular injury
- Combination of granulomatous inflammation + hepatocellular damage very suggestive of drug reaction
Coneflower Tea
Other Noninfectious Etiologies

- Vasculitis/collagen vascular diseases (polyarteritis nodosa, Churg-Strauss, Lupus)
- Chronic biliary disease (PBC, PSC)
- Chronic GI diseases
  - 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
In Summary

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

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