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

Courtesy Dr. Dhanpat Jain
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-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
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
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
Tularemia

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

- Dr. Joe Misdraji
- Dr. Lucas Campbell
- Dr. David Walker
- Dr. George F. Gray, Jr.
- Dr. Margie Scott