Granulomas in the Liver, with an Emphasis on Infectious Etiologies

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Granulomas are aggregates of macrophages, often admixed with other inflammatory cells, which usually result from chronic antigen presentation. Many diseases that produce granulomas involve the liver. Some are intrinsic hepatic diseases, whereas others are disseminated systemic diseases that involve the liver as well as other organs.

Hepatic granulomas are reportedly present in 2-10% of all liver biopsy specimens examined in general practice, and of those supposedly 13-36% have no discoverable etiology even after extensive evaluation of the specimen and the patient. However, pathologists and clinicians alike should remain diligent regarding the evaluation of liver specimens and patients with granulomatous diseases. The following section emphasizes infectious causes of granulomas, but it is also important to be aware of non-infectious entities in the differential diagnosis, such as sarcoidosis, primary biliary cirrhosis, adverse drug reaction, berylliosis, Hodgkin's disease, and foreign body reaction.

There are several classification schemes that address types of granulomas/granulomatous inflammation, but regardless of the scheme the morphology of the granulomas may provide clues to the diagnosis (see Table 1, below). Hepatic granulomas/granulomatous inflammation may be roughly divided into the following morphologic categories:

1. Epithelioid granulomas (with or without necrosis). These are discrete lesions with distinct edges. Necrotizing epithelioid granulomas most often have an infectious etiology, although no specific organism may be found. Necrotizing granulomas in infectious disease processes often do not respect the architecture of the liver, and may destroy adjacent structures.

2. Lipogranulomas. These contain lipid and are associated with mineral oils in foods. They are not believed to be associated with fatty liver disease.

3. Microgranulomas. Some have defined these as 3 to 7 cells in cross-section, often admixed with other inflammatory cells and/or apoptotic hepatocytes. This pattern is very nonspecific.

4. Fibrin ring granulomas. The distinctive hepatic fibrin ring granuloma deserves special mention. This lesion consists of an epithelioid granuloma with a central lipid vacuole surrounded by a fibrin ring. Although classically described in association with Q fever, these lesions are quite nonspecific and have been observed in the context of numerous diseases including leishmaniasis, Boutonneuse fever, Hodgkin's disease, allopurinol reaction, toxoplasmosis, CMV infection, mononucleosis, MAI infection, and typhoid fever.

5. Foamy macrophage aggregates. Infectious diseases causing this pattern of granulomatous inflammation are often immunocompromised, and there may be very little associated additional inflammatory response.

6. Granulomatous inflammation +/- prominent suppurative inflammation. In contrast to epithelioid granulomas, “granulomatous inflammation” suggests poorly formed
granulomas with indistinct edges, often with admixed inflammatory cells of other types. When suppurative inflammation predominates, certain infectious etiologies should be suspected (see table below). Granulomatous inflammation with associated hepatocellular and/or duct damage is often associated with drug-induced liver injury.

7. Stellate abscesses with associated granulomatous inflammation.

In addition to the morphology of the granulomas, the following questions can help guide the evaluation of the specimen:

1. What is the nature of the inflammatory infiltrate that accompanies the granulomas, if any?
2. Where are the granulomas?
3. What is the nature of the necrosis, if any?
4. Is there anything in the granulomas?
5. What other associated morphologic changes are present?

Special stains for microorganisms are of course invaluable in evaluating granulomatous processes in the liver, and the threshold for performing them should be very low. It is also important to decide whether or not the granuloma is incidental to some other chronic disease process (such as hepatitis C) or represents a second true pathologic process; in some cases, it is impossible to make this distinction morphologically.
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<th>Lipogranuloma</th>
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<td>Tularemia Listeriosis Melioidosis</td>
<td>M. tuberculosis (usually caseating)</td>
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<td>Toxoplasmosis</td>
<td>Listeria (rare)</td>
<td></td>
<td>Bartonella Tularemia Candida Other fungi</td>
<td>MAI (immunocompromised patients)</td>
<td></td>
<td>Brucellosis</td>
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<td>Salmonella</td>
<td>Other</td>
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<td>Lepromatous leprosy</td>
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<td>MAI (immunocompetent patients)</td>
<td>Sarcoidosis</td>
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<td>CMV</td>
<td>Usually a</td>
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<td>Histoplasmosis</td>
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<td>Listeria (rare)</td>
<td>Autoimmune diseases</td>
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<td>Other</td>
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<td>Drug reaction</td>
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<td>Whipple's disease (rare)</td>
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<td>Lupus</td>
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<td>Metastases</td>
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<td>Viral infections (rare)</td>
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Table 1. Classification of Granulomatous Processes in the Liver by Histologic Pattern
Selected Bacterial Infections Featuring Predominantly Granulomatous Inflammation

*Mycobacterium tuberculosis.* Signs and symptoms of liver disease may be the dominant or presenting features of tubercular infection. Liver involvement is seen in almost all cases of miliary tuberculosis, and is common in both localized extrapulmonary tuberculosis and in association with pulmonary tuberculosis. Patients may present with fever, hepatomegaly, and right upper quadrant pain, or they may be asymptomatic. Patients may have elevated bilirubin and transaminases, along with a disproportionately high alkaline phosphatase. Confluent granulomas can lead to masses (tuberculomas) and periportal lymphadenopathy. The histologic hallmark of hepatic tuberculosis is the epithelioid granuloma, often accompanied by caseation and giant cells. There may be a surrounding ring of lymphocytes and histiocytes. Granulomas are usually small, but may coalesce to form nodules with central liquefactive necrosis. Older lesions may show fibrosis and calcification. There is often an accompanying reactive hepatitis. It may be difficult to detect mycobacteria on special stains, thus culture and PCR assays may be of value.

*Mycobacterium Avium-Intracellulare.* MAI infection is most commonly associated with, but not limited to, AIDS patients. The liver is involved in over 50% of disseminated cases. Most liver biopsies show some degree of granulomatous inflammation. Some patients, particularly immunocompetent ones, have discrete, epithelioid granulomas with associated neutrophils and lymphocytes; giant cells and necrosis are rare. In immunocompromised patients, the granulomas are often composed of aggregates of foamy macrophages in the parenchyma and portal tracts. Fibrin ring granulomas are rarely seen as well. Organisms are usually abundant on acid-fast staining in immunocompromised patients, but rare in immunocompetent persons. Culture and PCR may be useful diagnostic adjuncts. The differential diagnosis includes other causes of foamy macrophage aggregates, such as *R. equi* and Whipple's disease. Other atypical mycobacteria occasionally cause liver disease, including *M. kansasii* and BCG.

*Mycobacterium leprae.* Over 60% of patients with lepromatous leprosy have hepatic involvement, and about 20% of patients with tuberculoid leprosy do as well. Liver disease is often subclinical. Histologically, the findings depend on the type of leprosy. In lepromatous leprosy, there are aggregates of foamy histiocytes (lepra cells) within portal tracts and lobules, containing numerous acid-fast bacilli. Giant cells and discrete granulomas are rarely seen, and accompanying inflammation is minimal. In tuberculoid leprosy, there are usually discrete, tuberculoid granulomas with associated giant cells. Bacilli are rare in this variant. Some patients manifest histologic features with features of both lepromatous and tuberculoid granulomatous lesions.

*Bartonella species.* *Bartonella henselae* is the most common cause of cat scratch disease (CSD). Patients usually present with isolated lymphadenopathy in an area draining a cat scratch inoculation, but a small percentage of patients (1-2%) develop disseminated infection. These patients usually lack the characteristic skin papule and superficial
adenopathy, but have generalized symptoms such as weight loss, fever, and malaise. Liver lesions are often multiple and have associated abdominal lymphadenopathy. Hepatic CSD patients are usually not immunocompromised. Patients generally respond well to antibiotic therapy. The characteristic histologic lesion of hepatic CSD consists of irregular, stellate microabscesses surrounded by an inner layer of palisading histiocytes, a surrounding rim of lymphocytes, and an outermost thick layer of fibrous tissue. This outer fibrous zone is very pronounced in the liver. The lesions may vary widely within the same specimen, ranging from early stellate microabscesses to older lesions consisting of fibrosis and granulation tissue. The differential diagnosis primarily includes other infections. Diagnostic aids include patient history with specific questions pertaining to cat exposure, silver impregnation stains (Warthin-Starry or Steiner), molecular assays, and ELISA at some centers.

**Brucella species.** This disease occurs primarily in domestic and barnyard animals; humans contract infection through occupational exposure and by ingesting contaminated food. Hepatic involvement is seen in approximately half of cases. Patients generally present with fever, malaise, headache, and arthralgias; lymphadenopathy and hepatosplenomegaly are variably present. Liver biopsies often (although not always) show noncaseating granulomatous inflammation, sometimes with accompanying giant cells. Granulomas may be discrete and epithelioid or small and poorly formed. Organisms are difficult to culture, and are rarely seen on special stains. Serologic studies and an appropriate exposure history are most helpful in making the diagnosis.

**Rickettsia and similar species.** Most rickettsial illnesses affect the liver, although involvement may be subclinical. *Coxiella burnetii* (causative agent of Q-fever) is associated with fibrin ring granulomas; many Q-fever granulomas are intermediate between epithelioid and fibrin-ring types. *Rickettsia conorii*, the causative agent of Boutonneuse fever and South African Tick Bite Fever, may also cause granulomas. Organisms are difficult to detect in the rickettsial illnesses, thus immunofluorescent stains and serologic studies may be very helpful.

### Bacterial Infections Featuring Mixed Suppurative and Granulomatous Inflammation

**Tularemia.** *Francisella tularensis* is a Gram-negative coccobacillus endemic in many areas of North America. It is transmitted to humans from rodents and rabbits. Hepatic involvement is often a component of disseminated infection. Patients have elevated transaminases, hepatomegaly, and rarely jaundice; hepatic involvement may be subclinical, however. Histologically, there are typically suppurative microabscesses with occasional surrounding macrophages; as the lesions evolve they may become more granulomatous. Organisms are rarely seen on special stains, thus cultures, serologic tests, and molecular testing are useful diagnostic modalities.

**Listeria monocytogenes.** Hepatic listeriosis may be seen in both neonates and adults, where it is frequently a feature of a disseminated infection in immunocompromised patients and diabetics. Histologically, scattered microabscesses are seen, often with small
granulomas. Sometimes an exclusively microgranulomatous pattern, and rarely true epithelioid granulomas, may be present. Occasionally, short pleomorphic Gram positive rods may be identified, but blood culture is the most important diagnostic test. DNA probes and immunohistochemistry may be useful but are not widely available.

Other hepatic bacterial infections that may cause granulomas include Whipple’s disease (*Tropheryma whippelii*), *Salmonella* (“typhoid nodules”), syphilis, *Chlamydia*, *Rhodacoccus equi*, which causes a granulomatous inflammatory pattern that mimics MAI; and *Pseudomonas pseudomallei* (*melioidosis*), which may cause either small neutrophilic microabscesses or granulomas.

**Hepatic Fungal Infections Featuring Granulomatous Inflammation**

Hepatic fungal infections are generally part of a disseminated process in immunocompromised patients, although cases are rarely described in immunocompetent persons. The clinical features are similar regardless of the organism involved, and include hepatomegaly, abdominal pain, and elevated transaminases and bilirubin. Fungi can sometimes be correctly classified in tissue sections based on morphology, and they are often visible on routine H&E sections when numerous. GMS and PAS stains remain invaluable diagnostic aids, however, and it should be stressed that culture should be relied upon as the gold standard of speciation. Antifungal therapy may vary according to the type of fungus.

The typical inflammatory reaction in hepatic candidiasis is granulomatous, often with a suppurative central area and variable necrosis. Giant cells are occasionally present. There may be surrounding palisading histiocytes and a fibrous scar, similar to hepatic cat scratch disease. Nonspecific findings such as cholestasis, portal inflammation, ductular proliferation, and sinusoidal dilatation near the inflammatory lesion are often present. Histoplasmosis features portal lymphohistiocytic inflammation and sinusoidal Kupffer cell hyperplasia. Discrete granulomas and giant cells are seen in only a minority of cases; organisms are generally present within both portal macrophages and Kupffer cells. The inflammatory response in aspergillosis ranges from minimal to a marked neutrophilic infiltrate; granulomatous inflammation is sometimes seen. The pathology of mucormycosis and related zygomycetes is similar to that of aspergillosis, The inflammatory reaction in *Cryptococcus* is variable and depends on the immune status of the host, ranging from a suppurative, necrotizing inflammatory reaction with granulomatous features, to virtually no reaction at all in immunocompromised hosts. Purely granulomatous responses are sometimes seen. Cryptococcosis may also involve the biliary tree.

Other fungal infections that are occasionally seen in the liver include *Pneumocystis carinii*, *Blastomyces dermatitidis*, *Paracoccidiodes brasiliensis* (South American blastomycosis), and *Coccidioidomycosis immitis*.

**Hepatic Parasitic Infections Featuring Granulomatous Inflammation**

Schistosomiasis. Schistosomiasis is the most common cause of portal hypertension in the world. Most hepatobiliary disease is caused by either *S. mansoni*, *japonicum*, or *mekongi*, as they prefer mesenteric and portal veins. Once settled in their vein of choice, adult worms copulate and produce thousands of eggs in their lifetimes; approximately 50% of the eggs remain within the body. Hypersensitivity to the eggs themselves is actually the underlying cause of disease, and resultant inflammation leads to fibrosis and obstructive hepatobiliary disease. Symptomatic patients present with splenomegaly and signs of portal hypertension, particularly bleeding; hepatic function is usually preserved.

Grossly, livers are enlarged and nodular; on cut surface, the typical portal fibrosis known as pipestem or Symmers' fibrosis may be seen. Histologic features vary with duration of disease, and in chronic schistosomiasis there is typically a granulomatous reaction to the eggs, which are present in varying numbers both within granulomas and fibrotic areas. Ultimately, portal tracts become large and densely sclerotic, and fibrous septa link portal tracts together. Sinusoidal fibrosis may also develop. As fibrosis progresses, eggs may be difficult to find. Granulomas and fibrosis also affect portal vein branches, leading to phlebitis, sclerosis, and thrombosis. Eventually portal veins are obstructed and destroyed, with subsequent proliferation of hepatic arterial branches.

Visceral leishmaniasis (kala-azar). Visceral leishmaniasis is most often seen in AIDS patients. The typical hepatic pathologic finding is hyperplastic Kupffer cells containing organisms; the organism-laden macrophages may form small nodules or loosely formed granulomas. Fibrin ring and epithelioid granulomas have also been described.

Enterobius vermicularis (pinworms). Pinworms are one of the most common human parasites. The rare hepatic pinworm granuloma consists of a hyalinized nodule with peripheral inflammation. Central necrosis with eggs and worm remnants may be present.

Other parasites that can cause granulomatous hepatic inflammation include *Fasciola hepatica*, which may cause calculi, cholangitis, obstructive jaundice, and a granulomatous hepatitis; *Toxoplasma gondii*, *Capillaria hepatica*, *Ascaris*, *Strongyloides stercoralis*; and *Giardia lamblia*, which rarely causes granulomatous hepatitis and cholangitis.

Granulomas in Viral Infections

Although the most characteristic histologic feature in healthy patients with EBV hepatitis is a diffuse lymphocytic sinusoidal infiltrate in a single file, "string-of-beads" pattern, small Kupffer cell clusters, and rarely discrete non-caseating granulomas or fibrin-ring granulomas, can be seen. Epithelioid and fibrin ring granulomas have also been described in association with CMV. In addition, granulomas that are not attributable to any other underlying etiology have been reported in a minority of hepatitis C biopsies (in which they may portend a favorable response to interferon therapy), and occasionally in cases of hepatitis B.
Noninfectious causes of hepatic granulomas are myriad, and are summarized in Table 2. A limited discussion of a few of these entities follows.

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<th>Cause</th>
<th>Examples</th>
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<td>Primary cholestatic disorders</td>
<td>Primary biliary cirrhosis, primary sclerosing cholangitis</td>
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<td>Chronic gastrointestinal diseases</td>
<td>Idiopathic eosinophilic gastroenteritis</td>
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<tr>
<td>Vasculitides</td>
<td>Polyarteritis nodosa, lupus</td>
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<tr>
<td>Drug induced injury</td>
<td>Isoniazid, quinidine, allopurinol</td>
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<tr>
<td>Metal toxicity</td>
<td>Beryllium, copper toxicity</td>
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<tr>
<td>Foreign material</td>
<td>Talc, starch</td>
</tr>
<tr>
<td>Extruded cell components</td>
<td>Lipogranulomas, bile granulomas</td>
</tr>
<tr>
<td>Inherited diseases</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>Hodgkin’s disease, primary hepatic tumors, metastases</td>
</tr>
<tr>
<td>Other</td>
<td>Sarcoïdosis</td>
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</tbody>
</table>

**Sarcoïdosis.** The incidence of hepatic granulomas in sarcoïdosis varies from 50-100%, but autopsy studies have shown that the liver is secondary only to the lungs and lymph nodes in frequency of involvement by granulomas. Sarcoïd granulomas are epithelioid with variable giant cells, and severe lesions may be confluent. Caseation is usually absent, but there may be central fibrinoid necrosis. They are often located in portal tracts, and there may be associated spotty lobular inflammation and portal lymphocytic inflammation. Many types of inclusions have been described, most commonly the asteroid body. Sarcoïd granulomas are often accompanied by fibrosis, which may lead to cirrhosis. A subset of sarcoïd patients develops a chronic cholestatic process that resembles primary biliary cirrhosis, with progressive destruction of bile ducts by granulomas.

**Chronic biliary diseases.** Granulomas are reported in 18-64% of PBC cases. They may be portal or lobular, but are often associated with duct lesions. Granulomas are also seen in a minority of cases of PSC, in which they are usually well formed, non-necrotizing, and epithelioid.

**Chronic gastrointestinal diseases.** Granulomas have been reported in a small minority of patients with ulcerative colitis, Crohn’s disease, and idiopathic eosinophilic gastroenteritis. It is unclear whether the granulomas associated with chronic idiopathic inflammatory bowel disease could be due to other causes such as PSC or an adverse drug reaction, however. The granulomas seen in idiopathic eosinophilic enteritis represent involvement of the biliary tree by the disease.

**Vasculitis/collagen vascular diseases.** Granulomas may involve the hepatic vasculature in collagen vascular diseases or vasculitic diseases including (but not limited to) polyarteritis nodosa, giant cell arteritis, Churg-Strauss disease, and lupus.
**Adverse drug reaction.** A complete discussion of granulomatous lesions caused by drugs and toxins is beyond the scope of this lecture. The granulomas associated with adverse drug reactions may be well or poorly formed. Necrosis is very rare. Giant cells may be present, and there is a variable associated inflammatory infiltrate that may include lymphocytes, plasma cells, and eosinophils. There may be associated duct and/or vascular injury. The combination of granulomatous inflammation with significant hepatocellular injury should strongly suggest drug associated liver injury. A few notable drug culprits include allopurinol, nitrofurantoin, isoniazid, phenytoin, quinidine, and hydralazine.

**Selected References**


Take home messages:
1. Many diseases that produce granulomas involve the liver, both intrinsic hepatic diseases and disseminated systemic diseases that involve the liver as well as other organs.

2. Hepatic granulomas are reportedly present in 2-10% of all liver biopsy specimens examined in general practice, but up to 13-36% have no discoverable etiology even after extensive evaluation of the specimen.

3. The morphology of the granulomatous lesion, as well as the location, accompanying inflammatory infiltrate, presence or absence of necrosis, and features of the surrounding liver may provide clues to the diagnosis.
Granulomas in the Liver-
with an emphasis on infectious etiologies

Hans Popper Hepatopathology Society

March 2, 2008

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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
Fibrin Ring Granuloma

- Epithelioid granuloma composed of lipid vacuole surrounded by fibrin ring
- Classically described in association with Q-fever
- Also associated with viral infection, MAI, typhoid, drug reaction, Hodgkin’s disease
Morphological Classification of Granulomas

- Epithelioid (+/-) necrosis
  - Infectious, sarcoidosis
- Lipogranulomas
  - Mineral oil
- Microgranulomas
  - Drug reaction, Listeria
- Fibrin ring granulomas
  - Q-fever, CMV, EBV
- Foamy macrophage aggregates
  - MAI, Whipple’s disease, histoplasmosis
- Granulomatous inflammation, +/- suppuration
  - Tularemia, drug
- Stellate abscess with granulomatous inflammation
  - Cat scratch disease, Candida
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
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

- Present in virtually all cases of miliary disease
- 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
- Helpful tests: special stains, PCR, culture
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
• 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
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
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)
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