Hepatic Granulomas

A Review With Emphasis on Infectious Causes

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Granulomas are reportedly present in 2% to 10% of all liver biopsy specimens examined in general practice, and of those, it is reported that 13% to 36% have no discoverable etiology even after extensive evaluation of the specimen and the patient.1-7 Hepatic granulomas may represent an infectious process, either primary or systemic; an adverse drug effect; a reaction to foreign material or nearby tumor; or have no clinical importance whatsoever. This review emphasizes infectious causes of granulomas but also includes some important noninfectious entities included in the differential diagnosis.

Granulomas are aggregates of macrophages, often admixed with other inflammatory cells, which typically are a result of 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. 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.2-5 (Table 1). Hepatic granulomas/granulomatous inflammation may be roughly divided into the following morphologic categories:

- Epithelioid granulomas, with or without necrosis. These are discrete lesions with distinct edges. Necrotizing epithelioid granulomas in infectious disease processes often do not respect the architecture of the liver and may destroy adjacent structures. Necrotizing epithelioid granulomas quite frequently have an infectious etiology, although no specific organism may be found.
- Stellate abscesses with associated granulomatous inflammation. This pattern is also most often associated with infectious etiologies.
- Granulomatous inflammation with or without 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 (Table 1). Granulomatous inflammation with associated hepatocellular and/or duct damage is often associated with drug-induced liver injury.
- 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.
- Foamy macrophage aggregates. This pattern of granulomatous inflammation is usually due to infection, frequently in immunocompromised patients. There may be very little associated additional inflammatory response, particularly if the patient is severely immunocompromised.
- Fibrin-ring granulomas. This distinctive form of hepatic granuloma deserves special mention. This lesion consists of an epithelioid granuloma with a central lipid vacuole surrounded by a fibrin ring (Figure 1). Although classically described in association with Q fever, these lesions are quite nonspecific and have been observed in the context of a growing list of diseases including leishmaniasis, *Rickettsia* typhus, boutonneuse fever, Hodgkin disease, allopurinol reaction, toxoplasmosis, cytomegalovirus infection, mononucleosis, *Mycobacteri*—Lamps 867

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um avium-intracellulare infection, and typhoid fever.2–5,8,9

- Lipogranulomas. These contain lipids and are associated with mineral oils in foods. An association with fatty liver disease and with hepatitis C infection has also been proposed.

In addition to the morphology of the granulomas, pathologists should evaluate the location of the granulomas; the presence or absence of necrosis; the nature of the infiltrate that accompanies the granulomas, if any; if there is anything in the granulomas, such as organisms or foreign material; and other associated morphologic changes in the liver biopsy specimen. Special stains for microorganisms and, more and more frequently, molecular testing for infectious causes are also invaluable in evaluating granulomatous processes in the liver. It is also important to decide whether or not the presence of granulomas represents a true pathologic process, or is incidental to another primary disease process (such as hepatitis C infection). It may be difficult, if not impossible, to make this distinction on morphologic grounds alone.

### SELECTED EXAMPLES OF BACTERIAL INFECTIONS FEATURING PREDOMINANTLY GRANULOMATOUS INFLAMMATION

#### Mycobacterium tuberculosis

Liver involvement is seen in almost all cases of miliary tuberculosis and is common in both localized extra pulmonary tuberculosis and in association with pulmonary tuberculosis.2,10,11 Signs and symptoms of liver disease may be the dominant or presenting features of tuberculous infection and may rarely occur in the absence of pulmonary findings. Patients may present with fever, hepatomegaly, and right upper quadrant pain, or may be asymptomatic. Bilirubin and transaminases are variably elevated, often with a disproportionately high alkaline phosphatase concentration.2,10 Confluent granulomas can lead to radiographically apparent masses (tuberculomas) and perportal lymphadenopathy.1,12

The histologic hallmark of hepatic tuberculosis is the epithelioid granuloma, often with caseation and giant cells (Figure 2, A). 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 be fibrotic or calcified.2 Similar lesions are often found in perportal lymph nodes (Figure 2, B). There is often an accompanying nonspecific reactive hepatitis. It may be difficult to detect mycobacteria on special stains for acid-fast bacillus; thus, culture and polymerase chain reaction assays may be invaluable. However, performing polymerase chain reaction on acid-fast bacillus–negative tissue sections often will not yield a positive result.13 It is also important to recognize that current culture methods and molecular tests cannot distinguish bacillus Calmette-Guerin from M tuberculosis.

#### Mycobacterium avium-intracellulare

Infection with M avium-intracellulare is most commonly associated with, but not limited to, patients with AIDS. The liver is involved in more than 50% of disseminated cases.14,15 Most involved liver biopsy specimens show some form of granulomatous inflammation. Occasional patients, particularly those who are immunocompetent, have discrete, epithelioid granulomas with associated neutrophils and lymphocytes; giant cells and necrosis are rare in these cases. In immunocompromised patients, the granulomatous inflammation often consists of aggregates of foamy macrophages in the parenchyma and portal tracts (Figure 3, A).8,9 Fibrin-ring granulomas are rarely seen as well. Organisms are usually abundant on acid-fast stains in immunocompromised patients (Figure 3, B) but are rare in immunocompetent persons. Culture and polymerase chain reaction may be useful diagnostic adjuncts. The differential diagnosis includes other causes of foamy macrophage aggregates, such as Rhodococcus equi and Whipple disease. Other nontuberculous mycobacteria occasionally cause liver disease as well, including Mycobacterium kansasii and bacillus Calmette-Guerin.

#### Mycobacterium leprae

Liver involvement in leprosy is often subclinical, yet more than 60% of patients with lepromatous leprosy have hepatic involvement, and approximately 20% of patients with tuberculoid leprosy do as well.16–18 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 (Figure 4). Bacilli are rare in this variant. Some cases have features of both lepromatous and tuberculoid granulomatous lesions.

**Bartonella Species**

*Bartonella henselae* is the most common cause of cat scratch disease. Although patients usually present with isolated lymphadenopathy in an area draining a cat scratch inoculation, 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. Patients with hepatic cat scratch disease are typically not immunocompromised, and generally respond well to antibiotic therapy.

The characteristic histologic lesion consists of irregular, stellate microabscesses surrounded by an inner layer of palisading histiocytes, a middle layer of mononuclear cells, and an outermost layer of thick fibrous tissue (Figure 5). 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), immunohistochemistry, molecular assays, and enzyme-linked immunosorbent assay at some centers.

**Brucella Species**

Hepatic involvement is seen in approximately 50% of cases of brucellosis. Because disease occurs primarily in domestic and barnyard animals, humans contract infection through occupational exposure and/or by ingesting contaminated food. Patients generally present with fever, malaise, headache, and arthralgias; lymphadenopathy and hepatosplenomegaly are variably present. Liver biopsy specimens 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 only rarely seen on special stains. Serologic...
studies and an appropriate exposure history are most helpful in making the diagnosis.

**Rickettsia Organisms 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.

**SELECTED EXAMPLES OF BACTERIAL INFECTIONS FEATURING MIXED SUPPURATIVE AND GRANULOMATOUS INFLAMMATION**

**Tularemia**

Tularemia remains a rare but potentially fatal disease that is endemic in many areas of North America. *Francisella tularensis* is a gram-negative coccobacillus that is primarily transmitted to humans from rodents and rabbits. Hepatic involvement is often a component of disseminated infection. Patients with hepatic involvement typically have elevated transaminase levels, hepatomegaly, and rarely jaundice; hepatic involvement may be subclinical, however. Histologically, there are typically supplicative microabscesses with occasional surrounding macrophages (Figure 6, A); as the lesions evolve they may become more granulomatous. Periportal lymph nodes may show discrete, well-delineated areas of cortical necrosis (Figure 6, B). Organisms are rarely seen on special stains; thus, cultures, serologic tests, and molecular testing are useful diagnostic modalities.

**Listeria monocytogenes**

Listeria is a foodborne illness that primarily affects immunocompromised patients, including neonates, pregnant women, and patients with underlying malignancies, diabetes, organ transplants, and cirrhosis. 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 disease (*Tropheryma whippe-lii*), "typhoid nodules" (*Salmonella*), syphilis, *Chlamydia* infection, *R equi* infection, with a granulomatous inflammatory pattern that mimics that of *M avium-intracellulare*;...
and melioidosis (Pseudomonas pseudomallei), with either small neutrophilic microabscesses or granulomas.²,³

SELECTED EXAMPLES OF HEPATIC FUNGAL INFECTIONS FEATURING GRANULOMATOUS INFLAMMATION

Hepatic fungal infections are usually part of a disseminated process in immunocompromised patients, although cases are rarely described in immunocompetent persons. The clinical features are similar regardless of the fungus involved and include hepatomegaly, abdominal pain, and elevated transaminase and bilirubin levels. Fungi can sometimes be correctly classified in tissue sections by morphology; they are often visible on routine hematoxylin-eosin sections when numerous, but Grocott methenamine silver and periodic acid–Schiff stains remain invaluable diagnostic aids. It should be emphasized, however, that culture or molecular diagnosis are more reliable tools for accurate speciation, which is extremely important as antifungal therapy may vary according to the type of fungus.

The typical inflammatory reaction in hepatic candidiasis is granulomatous, often with a necrotic central area.¹³,¹⁴ (Figure 7). Giant cells are occasionally present. There may be surrounding palisading histiocytes and a fibrous scar, similar to hepatic cat scratch disease.¹⁴ Nonspecific findings such as cholestasis, portal inflammation, ductular proliferation, and sinusoidal dilatation near the inflammatory lesion are often present in the hepatic parenchyma.

Histoplasmosis features portal lymphohistiocytic inflammation and sinusoidal Kupffer cell hyperplasia, and organisms are generally present within both portal macrophages and Kupffer cells (Figure 8, A and B).¹⁵ Discrete granulomas and giant cells are seen in only a minority of cases.

The inflammatory response in aspergillosis ranges from minimal to a marked neutrophilic infiltrate; granulomatous inflammation is sometimes seen, and the pathology of mucormycosis, and related zygomycetes infections, is

Figure 7. The inflammatory reaction in hepatic candidiasis is typically granulomatous, often with a necrotic central area and peripheral fibrosis. There may be surrounding palisading histiocytes, similar to hepatic cat scratch disease (courtesy of Lisa Yerian, MD) (hematoxylin-eosin, original magnification ×30).

Figure 8. A, Portal lymphohistiocytic aggregates typical of hepatic histoplasmosis. B, Hematoxylin-eosin/methenamine silver stain highlights organisms within both portal and sinusoidal macrophages (hematoxylin-eosin, original magnification ×60 [A]; original magnification ×300 [B]).

Figure 9. This liver biopsy specimen shows infection with Cryptococcus, with only focal positivity with mucicarmine stain, indicating a capsule-deficient strain. Note that there is essentially no inflammatory reaction in this severely immunocompromised patient (original magnification ×600).
similar to that of aspergillosis. The inflammatory reaction in Cryptococcus infection 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. (Figure 9). Purely granulomatous responses are sometimes seen. Cryptococcosis may also involve the biliary tree. Some strains are capsule deficient and are either negative for mucicarmine or only focally positive, and thus a Fontana-Masson stain may be useful in diagnosis.

Other fungal infections that are rarely seen in the liver include those caused by Pneumocystis carinii, Blastomyces dermatitidis, Paracoccidioides brasiliensis (South American blastomycosis), and Coccidioides immitis.

SELECTED EXAMPLES OF 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 Schistosoma mansoni, Schistosoma japonicum, or Schistosoma mekongi, as these prefer mesenteric and portal veins. Adult worms copulate within portal and mesenteric veins and produce thousands of eggs in their lifetimes. Approximately 50% of the eggs remain within the patient’s body, thus reaction to the eggs themselves is the underlying cause of disease, and the 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 pattern of 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 (Figure 10, A). Ultimately, portal tracts become large and densely sclerotic, and fibrous septa link portal tracts together; eggs are often calcified (Figure 10, B). Sinusoidal fibrosis may also develop. As the fibrosis progresses, eggs may be increasingly difficult to find. Granulomas and fibrosis affect portal vein branches as well, leading to phlebitis, sclerosis, and thrombosis. Eventually portal veins are obstructed and destroyed, with subsequent proliferation of hepatic arterial branches. Schistosome pigment, which is a product of hemoglobin catabolism by adult worms, is often visible as a brown pigment in both granulomas and sinusoidal Kupffer cells (Figure 10, C).

Visceral Leishmaniasis (Kala-Azar)

Visceral leishmaniasis is most often seen in patients with AIDS. The liver typically shows hyperplastic Kupffer cells containing organisms; organism-laden macrophages may form small nodules or loosely formed granulomas (Figure 11). 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.

Figure 10. A, Granulomatous reaction to Schistosoma eggs in hepatic schistosomiasis (courtesy of Joseph Misdraji, MD). B, As lesions age, they become fibrotic, often with numerous calcified eggs. C, Schistosome pigment is often seen within Kupffer cells (courtesy of Joseph Misdraji, MD) (hematoxylin-eosin, original magnifications ×150 [A and B] and ×300 [C]).
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**

Small Kupffer cell clusters and, rarely, discrete noncaseating granulomas or fibrin-ring granulomas, may be seen in Epstein-Barr virus infection of the liver. Epithelioid and fibrin-ring granulomas have also been described in association with cytomegalovirus. Furthermore, granulomas that are not attributable to any other underlying etiology have been reported in a minority of hepatitis C and hepatitis B biopsies; in the former, they may portend a favorable response to interferon therapy.

**SELECTED NONINFECTION CAUSES OF HEPATIC GRANULOMAS**

A comprehensive discussion of noninfectious causes of hepatic granulomas is beyond the scope of this review, but some of the more important noninfectious entities that are in the differential diagnosis of infectious granulomas in the liver are summarized in Table 2, and a limited discussion of some of these entities follows.

**Sarcoidosis**

The liver is secondary only to the lungs and lymph nodes in frequency of involvement by granulomas, and the incidence of hepatic granulomas in sarcoidosis has been reported to be 50% to 100%. Sarcoid granulomas are epithelioid with variable giant cells, and lesions may be confluent (Figure 13, A). Caseation is usually absent, but there may be central fibrinoid...
necrosis. Many types of inclusions have been described, most commonly the asteroid body. Granulomas are often located in portal tracts with associated lymphocytic inflammation, and there may be associated spotty lobular inflammation and hepatocyte necrosis. Sarcoid granulomas are often accompanied by fibrosis (Figure 13, B), which may lead to cirrhosis.25-27 Some patients with chronic hepatic sarcoidosis manifest signs of portal hypertension in the absence of cirrhosis, which may be due to compression of the portal vein by involved portal lymph nodes, or to compression of small portal vein branches by parenchymal granulomas.28 A subset of patients with sarcoid develop a chronic cholestatic process that resembles primary biliary cirrhosis, with progressive destruction of bile ducts (Figure 13, C).27

**Chronic Biliary Diseases**

Granulomas are reported in 18% to 64% of primary biliary cirrhosis cases. They may be portal or lobular, but are often associated with duct lesions. Granulomas are also seen in a minority of cases of primary sclerosing cholangitis, in which they are usually well formed, nonnecrotizing, and epithelioid.2-4

**Chronic Gastrointestinal Diseases**

Granulomas have been reported in a small minority of patients with ulcerative colitis, Crohn disease, and idiopathic eosinophilic gastroenteritis.2-4 It is unclear whether the granulomas associated with chronic idiopathic inflammatory bowel disease could be due to diseases such as primary sclerosing cholangitis or an adverse drug reaction. Granulomas may also be a feature of idiopathic eosinophilic enteritis involving the hepatobiliary tree by the disease (Figure 14).59 Sarcoidlike granulomas are also well described in the liver in patients with common variable immunodeficiency.60

**Vasculitis/Collagen Vascular Diseases**

Granulomas may involve the hepatic vasculature in collagen vascular diseases or vasculitic diseases including (but not limited to) polyarteritis nodosa (Figure 15), giant cell arteritis, Churg-Strauss disease, and lupus.2-4

**Adverse Drug Reaction**

A complete discussion of granulomatous lesions caused by drugs and toxins is beyond the scope of this review, and the pathology of drug-associated granulomatous processes is very diverse (Figure 16, A and B). Granulomas associated with adverse drug reactions may be well or poorly formed, but 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.1-4,61

**References**
