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REVIEW ARTICLE

Granulomatous liver diseases: A review

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Granulomas that consist of focal accumulations of macrophages are commonly found in the liver due to stimulation of the immune system by a number of agents. Manifestations are variable depending on whether the underlying cause is a systemic disease or a primary hepatic granulomatous reaction. This article describes the common causes, presentation, histopathology, and manifestations of granulomatous diseases as well as various diagnostic and management strategies.

Introduction

Granulomas are aggregates of modified macrophages (epithelioid cells) and other inflammatory cells that accumulate after chronic exposure to antigens. The underlying trigger may be exposure to noxious agents that cannot be biochemically degraded or to immune dysfunction. The ultimate result is a release of a variety cytokines that stimulate mononuclear cells that fuse to form multinucleated giant cells with a surrounding rim of lymphocytes and fibroblasts. The extent of inflammation associated with granuloma formation is variable. Hepatic granulomas may be accompanied by severe inflammation within or surrounding granulomatous structures which is termed granulomatous hepatitis (Fig. 1A). In other cases, there may be little or no accompanying inflammation in which the granulomas are referred to as bland granulomas. The term "granulomatoid reaction" is used to describe poorly delineated granulomas.[1]

From clinical studies, the prevalence of granulomas ranges from 2.4%–15% of all liver biopsy specimens.[2–10] Conn and others[10] reported that 66% of their cases of granulomatous reaction were secondary to a systemic disease, 28% to primary liver disorders, and 6% were idiopathic. Sartin and colleagues[4] reported that follow-up of patients may reveal the cause in additional 10%–15% of the cases indicating the importance of long-term follow-up in determining a cause. The frequency has been reported to be higher in specific groups such as patients with fever of unknown origin or those infected with HIV where granulomas are noted to be between 16%–75%.[11] In the United States, however, 75% of cases are a result of sarcoidosis,

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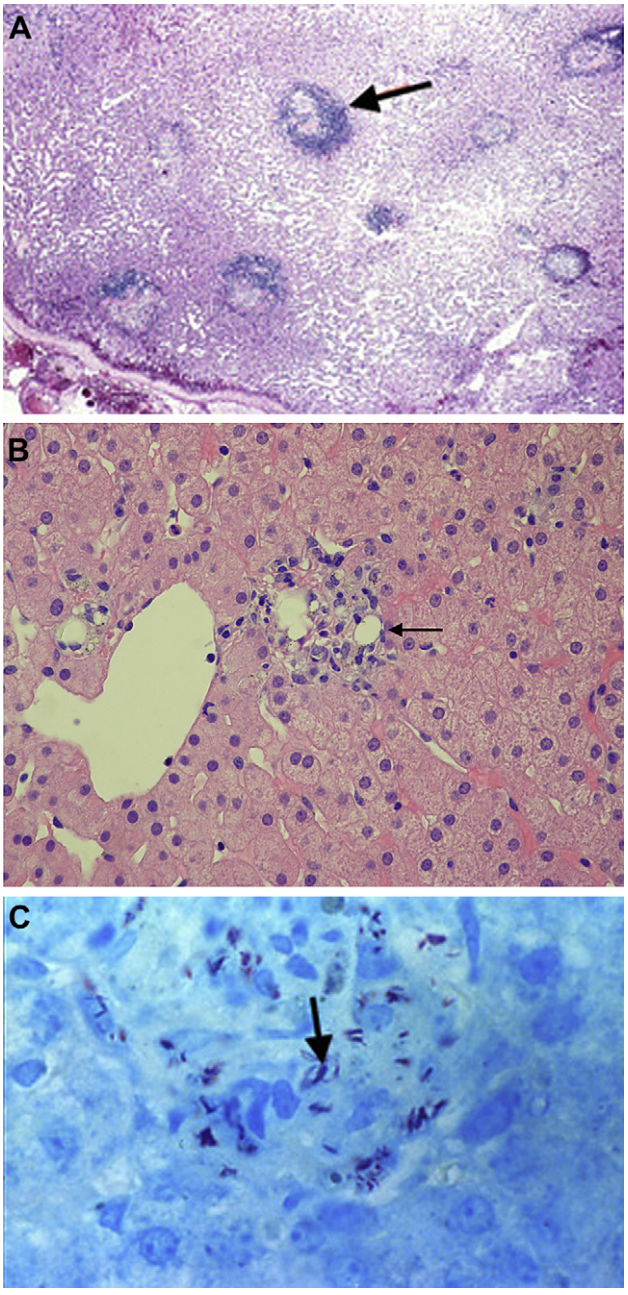

Figure 1 (A) Granulomatous hepatitis. Note the primarily lobular distribution and a generous lymphocytic cuff (arrow; H and E, ×40); (B) lipogranuloma. Note the fat vacuoles (arrow; H and E, ×400); (C) Note the *Mycobacterium tuberculosis* bacilli (arrow; Fite acid-fast stain, ×1000).

mycobacterial infection, primary biliary cirrhosis, and drug-induced liver injury.[12–15] In India, it has been reported in retrospective analyses that tuberculosis was the most common cause (55%) of cases. Other important causes were leprosy, sarcoidosis, histoplasmosis, brucellosis, amebic liver abscess, lymphoma, and malignant granuloma.[16]

Morphology

Granulomas are compact spherical masses of aggregated epithelioid histiocytes measuring anywhere from 50 to 300 mm. This is equivalent to 0.5–6 times the diameter of a liver core needle biopsy.[17] Often, but not always, they contain multinucleated giant cells and are surrounded by a cuff of lymphocytes and plasma cells (Fig. 1A). Such large granulomas are often formed by conglomeration of smaller ones. Four morphologic types of hepatic granulomas have been described.[18] One type is a foreign body granuloma consisting of inclusions of particulate material within cytoplasmic vacuoles. Examples of indigestible particulate materials include mineral oil, starch, and silicone.[18] Another type is the lipogranuloma, which is associated with hepatic steatosis (Fig. 1B). Histiocytes and macrophages surround a vacuole of triglycerides. These lipogranulomas do not cause bile duct injury or cholestasis and their medical significance is uncertain.[13] A third type of granuloma is an epithelioid granuloma in which there is differentiation of activated macrophages into secretory cells leading to synthesis and secretion of large amounts of cytokines (Fig. 2).[19] Due to the fact that there are no inclusions within these cells, there is a homogeneous appearance to the cytoplasm, which is the reason that this type of granuloma acquired its epithelioid designation. The plasma membranes of these cell types can fuse leading to the formation of giant cells or Langhans cells. Deposition of collagen or fibrin can occur at the periphery leading to a fibrin-ring granuloma as is seen in Q fever, although such granulomas are not specific for this condition.[19] A fourth type of granuloma, lymphohistiocytic granuloma, is clinically similar to epithelioid granuloma. However, epithelioid cells are not found in the accumulations of macrophages and lymphocytes.[19]

The morphology of granulomas is not specific enough to identify the cause, although it can help in developing a differential diagnosis. For example, the presence of necrosis or caseation points to infection with *Mycobacterium tuberculosis*. Poorly formed granulomatous reaction without necrosis is typical in patients with defective immune systems such as patients with AIDS. (Fig. 3A) These granulomas typically contain a large number of acid-fast organisms, *M avium intracellulare*. The presence of plasma cells in the lymphocytic cuff favors syphilis, while numerous eosinophils might indicate a hypersensitivity to medication (Figs. 4A and B) or parasitic disease. The

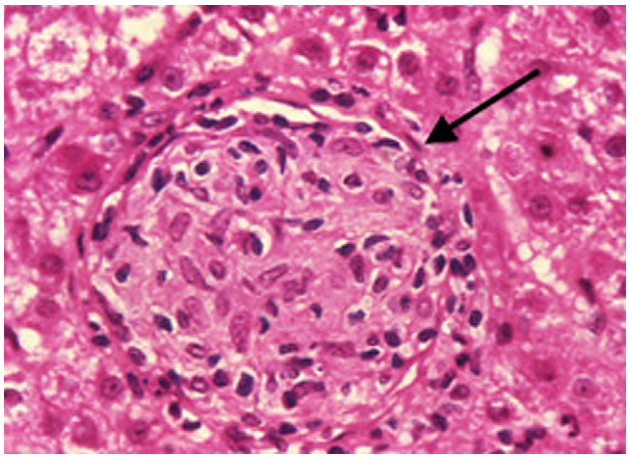

Figure 2 An epithelioid granuloma (arrow; H and E, ×400).

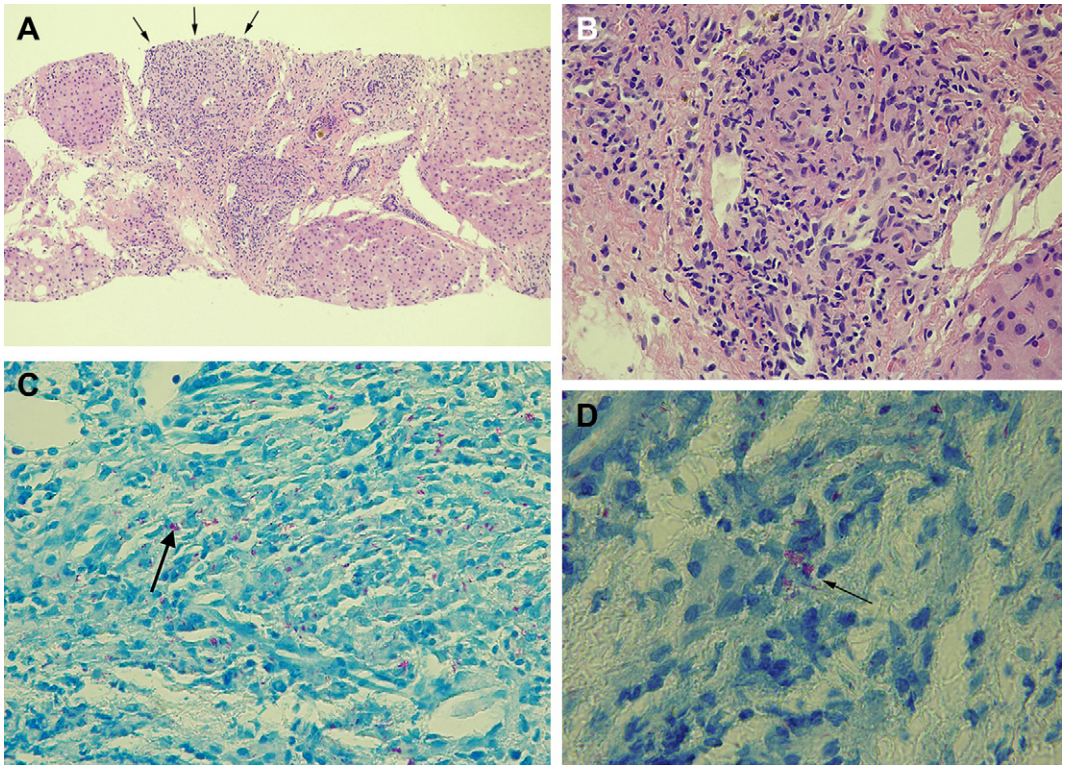

Figure 3 (A) Granulomatous hepatitis associated with AIDS. Note the ill-defined, nature of granulomas (arrows; H and E, ×40); (B) example of a better-defined granuloma in granulomatous hepatitis of AIDS (H and E, ×400); (C) large numbers of *Mycobacterium avium intracellulare* within and around loosely arranged aggregates of epithelioid histiocytes (arrow) (Fite acid fast stain, ×400); (D) clusters of acid fast bacilli (arrow; Fite acid fast stain, ×1000).

presence of a fibrin ring, a fibrin doughnut, suggests Q fever. Well-formed granulomas with little lymphocytic cuff and no necrosis in the portal areas with fibrosis point to sarcoidosis (Figs. 5A and B). Foreign body granulomas often show detectable foreign material microscopically under normal or polarized light (Table 1 and 2).

Lipogranulomas are a specific form of granulomatous reaction containing fat vacuoles and often no giant cells (Fig. 2). These are associated with fatty liver disease that is increasing in incidence and, are more common in alcoholic fatty liver disease than other types. Because of lack of specificity, clinical and laboratory modalities need to be employed to determine the cause. Granulomas can often accumulate in the liver near portal tracts, and can be associated with elevated alkaline phosphatase.[12] Cells within the granuloma can secrete a variety of proteins and enzymes such as lysozyme, collagenase, and angiotensin-converting enzyme as can be seen in sarcoidosis.[20] There can also be various forms of necrosis that provide clues as to the cause of the granulomas. These findings include "caseating" necrosis as is found in pulmonary tuberculosis, or "noncaseating" necrosis as can be seen in sarcoid granulomas.[13]

The location of granulomas on histologic evaluation can also be helpful as a general guide to diagnosis. For example, in primary biliary cirrhosis (Fig. 6A) and sarcoidosis (Fig. 5A), granulomas are observed near portal regions, whereas drug-induced granulomas are more often poorly defined and are found within the hepatic lobules. (Fig. 4A).[13]

Pathogenesis

As mentioned above, granuloma formation is due to a chronic inflammatory reaction with the presence of epithelioid cells or giant multinucleated cells surrounded by lymphocytes, monocytes and plasma cells.[20] The term "epithelioid histiocytes" refers to modified tissue monocytes, macrophages, and histiocytes that arise from blood monocytes. They can be considered immunologically activated histiocytes and macrophages. Their immunologic and phagocytic activity is enhanced under the influence of T-cell interleukins.[21]

Granuloma formation occurs when the humoral or cellular immune response fails to eliminate the offending foreign material.[20] This is largely a delayed hypersensitivity cellular immune response, which attempts to isolate and neutralize pathogenic material and is otherwise difficult to eradicate.

There are two main types of granulomatous reaction: (1) a reaction to immunologically inert, large foreign bodies, and (2) a reaction to immunologically active antigenic, poorly degradable particles. The two types also differ in their pathogenesis.[21]

The type of immune response that occurs depends on whether the foreign particles are intra- or extracellular in origin. The Th1 response usually targets intracellular pathogens leading to secretion of various cytokines such as interferon gamma, interleukin (IL)-2, and IL-12. Extracellular pathogens evoke a Th2 response with the secretion of

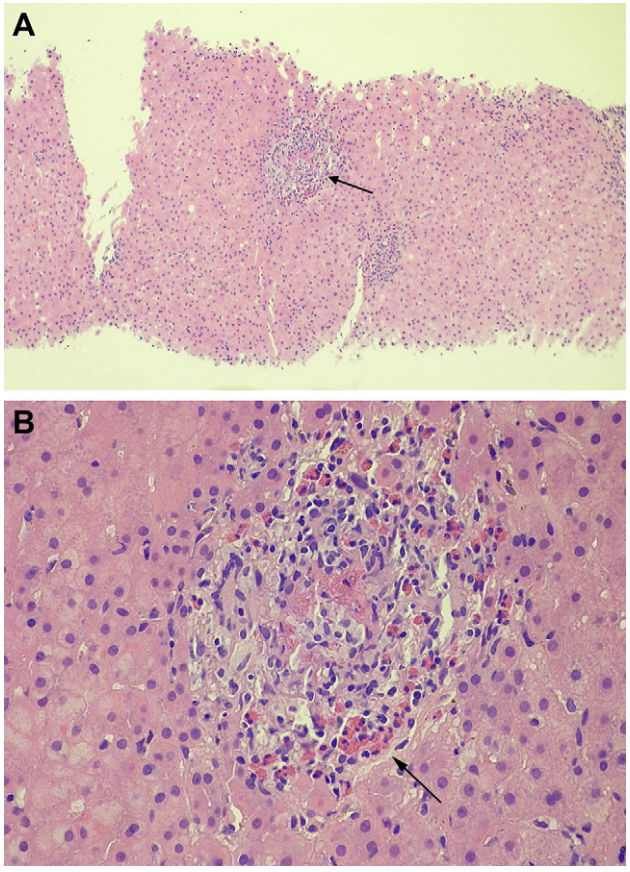

Figure 4 (A) Granulomatous hepatitis, hypersensitivity to medication. Notice the lobular distribution of granuloma (arrow; H and E, ×40); (B) extensive eosinophilic reaction in the inflammatory cuff of the granuloma (arrow; H and E, ×400).

IL-4, 5, 6, and 10. Both reactions elicit a positive feedback response on T-cells perpetuated by cytokines. The formation and maintenance of granulomas in the liver is based on cytokine release.[13] In the immunologically active type, granuloma formation appears to begin with phagocytosis of immunologically active materials by ordinary macrophages. The macrophages then process the offending agent into simple antigenic peptides, which are then presented to T-lymphocytes. This causes activation of T-lymphocytes, stimulating them to produce various cytokines leading to activation of other T-cells and conversion of ordinary histiocytes and macrophages into epithelioid histiocytes, a more potent cell type. These epithelioid histiocytes aggregate into a granuloma and can fuse to form giant cells. Additionally, this granulomatous reaction is typically surrounded by a cuff of lymphocytes, a few plasma cells, and eosinophils. The makeup of this cuff is to some extent determined by the causative agent. Epithelioid histiocytes are capable of causing tissue necrosis leading to the so-called "necrotizing" granulomas as is typical with infectious agents.[21]

Accumulation of these effector cells in the portal tract leads to injury of the septal and interlobular bile ducts that can cause cholestasis. Potential modifiers of this inflammatory response are being investigated as pharmacologic targets for therapeutic modulation of or interference with cytokine production.[13]

Clinical presentation

The symptoms of granulomatous liver disease depend on the underlying disease. Patients are frequently asymptomatic, and they may not even have laboratory evidence of hepatic dysfunction. When manifestations of granulomatous disorders affecting the liver do occur, they are usually due to cytokine release by activated macrophages and lymphocytes that may cause liver injury.[22] Symptoms such as fever, weight loss, anorexia, night sweats, and adenopathy may be present in the case of systemic disease. Laboratory signs of inflammation, as well as elevated alkaline phosphatase and hepatomegaly, have been reported in 60% of cases.[14] Jaundice is rare unless there is bile duct injury. Severe pain in the right upper quadrant can be present even without biliary injury.[12,14,15,23]

Diagnosis of hepatic granulomatosis

A comprehensive medical history and physical examination should be pursued along with an extensive medication and travel history. A reasonable initial approach is to search first for the most common causes of granulomatous liver disease in a particular population to avoid unnecessary testing. Asymptomatic patients are usually discovered because of abnormal liver enzyme tests or a family or

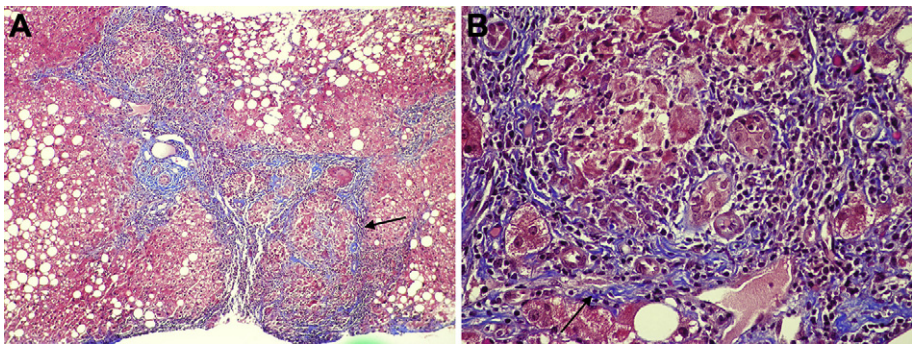

Figure 5 (A) Sarcoidosis. Note the portal distribution and excessive fibrosis around granuloma (arrow; trichrome stain, ×100); (B) sarcoidosis, extensive fibrosis (arrow; trichrome stain, ×400).

Table 1 Granuloma types and characteristics.

Granuloma types	Granuloma characteristics
Foreign body	Internal particulate material: mineral oil, starch, silicone
Lipogranuloma	Vacuoles of triglycerides
Epithelioid	Activated macrophages that can secrete cytokines and aggregate to form giant cells, or Langhans cells. Fibrin rings may form due to fibrin deposition
Lymphohistiocytic	Macrophage and lymphocyte accumulation

personal history of increased risk for granulomatous disease. Symptoms may be helpful in developing a differential diagnosis. For example, if fever is present, the investigation should focus on infectious causes or sarcoidosis. If there are signs of portal hypertension on physical examination, causes such as schistosomiasis, sarcoidosis, or primary biliary cirrhosis (PBC) may considered higher on the list of differential diagnoses.[13]

Initial testing may include a chest radiography, cultures for bacteria, mycobacteria, viruses, and fungi. Serologies for hepatitis B, C, as well as syphilis, Q fever, and brucella can also be pursued. Other studies including antimitochondrial antibody, angiotensin-converting enzyme levels, and a tuberculin skin test can be helpful. Although the above tests can provide helpful clues as to the possible existence of granulomatous liver disease, the diagnosis can only be made by histologic examination of liver biopsies. Stains of liver biopsies for acid-fast bacilli, fungi, spirochetes, and Bartonella as well as careful examination for ova, foreign bodies, eosinophils, lipid vacuoles, and fibrin are also important in the diagnostic work-up.[24]

There is no characteristic pattern of liver biochemical abnormalities suggestive of any specific cause of granulomatous liver disease. Elevated alkaline phosphatase may be more common in patients with granulomas related to sarcoidosis or PBC or drug-induced injury due to bile ductule involvement. However, elevated aminotransferase levels can be found in schistosomiasis or drug-induced hepatotoxicity.[13]

Imaging studies can show liver sizes that range from normal to massive hepatomegaly. A homogenous or coarse appearance may be noted, and calcifications can be seen on plain radiographs. Granulomas of 0.5 cm in diameter or greater can be detected on magnetic resonance imaging (MRI) as multiple nodular lesions or, less commonly, isolated hepatic granulomas. The former may have an appearance suggesting the presence of a malignant neoplasm. Caseating granulomas as in tuberculosis have a high or low signal in T1-weighted magnetic resonance images, and no enhancement, or sometimes peripheral enhancement after gadolinium injection in comparison to noncaseating granulomas in sarcoidosis which have intermediate signals on T1-weighted images with gadolinium enhancement that may or may not persist on late images.[25–27]

Etiologies

The etiologies of granulomatous liver disease are diverse, and they can be a result of primary liver disease or other

Table 2 Granuloma etiologies and characteristics.

Granuloma etiologies	Granuloma characteristics
Autoimmune	
Sarcoid	Noncaseating epithelioid granulomas
Primary biliary cirrhosis	Noncaseating granulomas near portal triads
Infectious	
Mycobacterium tuberculosis	AFB inside epithelioid granulomas and giant cells often with ring of lymphocytes and histiocytes
M avium intracellulare	Aggregates of foamy macrophages in parenchyma and portal triads with +AFB stain
M leprae	Foamy histiocytes in portal tracts and lobules with multiple AFB found
Brucella	Noncaseating granulomas
Rickettsia	Fibrin ring surrounding vesicle of fat
Francisella	Suppurative microabscesses with surrounding macrophages
Listeria	Microabscesses with small granulomas
Bartonella henselae	Stellate abscesses with three distinct zones
Tropheryma whipplei	Epithelioid granulomas
Histoplasma	Macrophages and lymphocytes with histoplasma and epithelioid cells in center
Schistosoma	Eosinophils with fibrosis and collagen deposition in peri-portal and peri-sinusoidal areas often with egg at the center
Leishmania	Fibrin ring or epithelioid granulomas
Hepatitis C	Epithelioid granulomas
Drugs and Chemicals	Granulomas with eosinophils
Malignancy	Non-necrotic granulomas

AFB = Acid-fast bacilli.

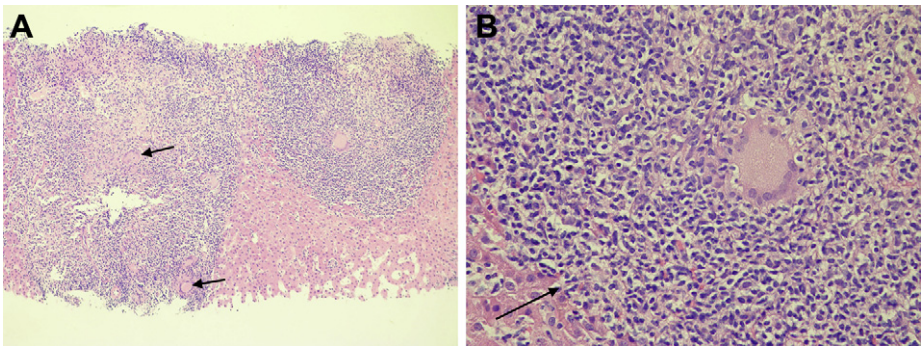

Figure 6 (A) Primary biliary cirrhosis. Note the significant inflammatory response and expansion of portal areas in a granulomatous reaction (arrows; H and E, ×100); (B) note the inflammatory cells spilling over into the adjacent liver lobule resulting in an interface hepatitis (arrow) and scarcity of bile ducts (H and E, ×400).

systemic diseases; 13%–36% have an unclear etiology despite extensive evaluations.[12,28,29] In the Western world, the two major causes of granulomas in liver biopsies are sarcoidosis and tuberculosis. However, the frequency with which other causes are found depends on the geographic area. For instance, schistosomiasis is a frequent cause of granulomas in areas where this parasitic infection is endemic.[13]

The presence of hepatic granulomas may be an incidental finding and may not require treatment. However, many diseases can be associated with hepatic granulomas. Primary liver diseases rarely cause hepatic granulomatous disease except for primary biliary cirrhosis, and hepatitis C. Tuberculosis and schistosomiasis are the most common infectious causes of hepatic granulomatous inflammation worldwide primarily in non-Western countries. Other important causes include malignancy such as Hodgkin lymphoma and drug-related injury.

It is helpful to classify the causes of granulomatous hepatitis into several broad categories such as autoimmune disorders, systemic infections, medications, malignancy, idiopathic causes and, rare causes, which encompass a broad category of systemic granulomatous diseases, connective tissue diseases causing a systemic inflammatory disorder, and digestive disorders.[13]

Autoimmune disorders

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown cause that can affect several organs, including the liver. Although the disease mainly affects the lungs and lymphoid tissue, involvement of the liver can be demonstrated in 80% of people who undergo liver biopsy. Noncaseating epithelioid granulomas are the characteristic histologic findings.[12] Sarcoid is thought to account for 12%–30% of the cases of granulomatous liver disease. The granulomas are located around portal tracts (Fig. 5A) and in mediolobular areas. Clinically relevant hepatobiliary disease is rare, but, if present, it is usually related to complications of portal hypertension or cholestasis.[30] The diagnosis of hepatic sarcoidosis is made based on liver biopsy findings in the presence of extrahepatic involvement such as pulmonary sarcoidosis, an elevated angiotensin-converting enzyme level, and exclusion of infectious causes of hepatic granulomas. Patients with symptomatic disease or liver complications can be treated with corticosteroids or ursodeoxycholic acid. However, therapy is not recommended for asymptomatic cases of granulomatosis and no evidence of hepatocellular injury.[14,30]

PBC

PBC is a progressive autoimmune disease involving inflammation of the intralobular bile ducts with damage of small intrahepatic bile ducts within the portal tracts (Figs. 6A and B). The diagnosis can be made by detection of antimitochondrial antibodies, in combination with a characteristic liver biopsy. On liver biopsy, 25%–50% of patients with PBC will have granulomas. They are noncaseating and are located within the portal tracts in close proximity to septal and interlobular bile ducts. Clinical cholestatic manifestations are the hallmark of advanced PBC. Medical therapy for PBC consists of ursodeoxycholic acid, which is used for its favorable effect on cholestasis, deceleration of liver disease progression, and prevention of the need for liver transplantation in cases treated in early stages.[31–33]

Infectious etiologies

Microorganisms that require a macrophage-based pathway for clearance may cause granulomas. There are many infectious causes of hepatic granulomas including mycobacterial, viral, fungal and parasitic infections. Patients with AIDS are especially prone to granulomatous disease associated with opportunistic infections. Patients who receive treatment with immunosuppressive medications such as tumor necrosis factor antagonists are at increased risk of infectious granulomatous complications. More common in developing countries are hepatic granulomas due to leprosy, brucellosis, and Q fever.[34,35] Certain bacterial infections due to agents such as mycobacteria, Bartonella, brucella, and rickettsia cause predominantly granulomatous inflammation, while others, such as tularemia and listeria, create a mixed suppurative and granulomatous inflammation.[36]

M tuberculosis

M tuberculosis infection can lead to hepatic granulomas and less commonly tuberculomas (confluent granulomas

that form masses) and abscesses involving the liver. Rarely, tuberculous lymph nodes can compress the *porta hepatis* causing biliary tract disease and/or portal hypertension.[37] Up to 90% of all patients with miliary tuberculosis have hepatic granulomas as well as a significant proportion of the HIV population especially in the developing world.[14,38] Classic symptoms of fever, night sweats and weight loss may be present as well as hepatomegaly and right upper quadrant pain. Laboratory abnormalities include elevated bilirubin and aminotransferases with a disproportionately high alkaline phosphatase.[20] On histologic examination, characteristic epithelioid granulomas (Fig. 1B) and giant cells are noted, often surrounded by a ring of lymphocytes and histiocytes and usually without caseation. The latter are, however, not always universal findings on liver biopsy. Acid-fast bacilli (AFB) are often seen within the granuloma as well (Fig. 1C).[34] The detection of tuberculosis in patients with hepatic granulomas may be difficult due to the lack of caseation necrosis on biopsy or lack of a positive Ziehl-Neelsen stain or culture. Polymerase chain reaction (PCR) assay has been reported to detect *M tuberculosis* with a sensitivity of 88% and specificity of 100%.[39]

M bovis

The attenuated strain of *M bovis*, which is used as a live vaccine in the form of Bacillus Calmette-Guerin (BCG), as well as a therapy for bladder cancer or melanoma, can cause systemic infection. Clinical presentation includes jaundice; on liver biopsy, hepatic granulomas can be detected.[40]

M avium-intracellulare

M avium-intracellulare, an infection common among AIDS (Figs. 3A and B) patients, can involve the liver in more than 50% of disseminated cases. In these immunocompromised patients, granulomatous inflammation is composed of aggregates of foamy macrophages in the parenchyma and portal tracts, and the organisms can be detected by acid-fast staining (Figs. 3C and D). Immunocompetent patients, however, tend to have discrete epithelioid granulomas with associated neutrophils and lymphocytes without giant cells or necrosis, and the organism is difficult to detect by acid-fast stain.[41,42]

M leprae (leprosy)

M leprae infection can cause lepromatous leprosy in which more than 60% of patients have hepatic involvement or tuberculoid leprosy, in which 20% of patients with hepatic involvement. Aggregates of foamy histiocytes within portal tracts, and lobules with numerous acid-fast bacilli are found in lepromatous leprosy, whereas discrete tuberculoid granulomas with associated giant cells are characteristic of tuberculoid leprosy in which the bacilli are rarely detected.[43,44]

Brucella (brucellosis)

Infections with brucella species can occur as a result of occupational exposure to livestock, specifically through inhalation of barnyard dust or by ingestion of their unpasteurized products. Clinical presentation includes fever, malaise, headache, arthralgia, lymphadenopathy, or hepatosplenomegaly, in which 50% of cases exhibit hepatic granulomas on biopsy often with noncaseating granulomatous inflammation. Detection of brucella is difficult and relies on isolation of brucella from the blood to obtain a positive serology because it is rarely demonstrated within the liver.[45]

Rickettsia and similar species

Infection with *Coxiella burnetii*, the causative agent of Q fever, is commonly asymptomatic. However, when there is hepatic involvement, granulomas can appear as a fibrin ring of granulomas surrounding a vesicle of fat. This fibrin deposition can also be scattered among epithelioid cells.[46] Boutonneuse fever and South African tick bite fever that are caused by *Rickettsia conorii* can also cause hepatic granulomas. In these cases, the diagnosis is based on serology.[47]

Francisella tularensis (tularemia)

Francisella tularensis is a Gram-negative coccobacillus found in many areas of North America in rodents and rabbits, which are the vectors for human transmission. With disseminated infections, hepatic involvement can be subclinical or may present with elevated aminotransferases, hepatomegaly, and occasionally jaundice. The histologic picture on liver biopsy is one of suppurative microabscesses with occasional surrounding macrophages that may become granulomatous. The diagnosis is based on serology.[48]

Listeria monocytogenes (listeriosis)

In neonates or immunocompromised adults, disseminated listeriosis can involve the liver in the formation of microabscesses with small granulomas. Detection of listeria is made by blood culture.[49]

Bartonella henselae (cat scratch disease)

B henselae infection, the causative agent of cat scratch disease, has been known to cause regional lymphadenitis, and, in disseminated disease, it can have hepatic involvement. There have been case reports of liver biopsies showing multiple granulomas with characteristic stellate abscesses surrounded by three distinct zones: an inner layer of palisading histiocytes, an intermediate lymphocytic rim, and an outermost zone of fibrosis. Most cases also have nonspecific parenchymal changes such as lymphocytic infiltrates with expanded fibrotic portal triads and dilated sinusoids surrounding the granulomas.[50]

Tropheryma whipplei (Whipple disease)

Hepatic involvement with Whipple disease caused by *Tropheryma whipplei* is rare. Patients may present with hepatomegaly and fever in the absence of intestinal symptoms. Epithelioid granulomas have been reported on biopsy and diagnosis can be made by Periodic acid-Schiff (PAS) stain showing positive macrophages.[51]

Other bacterial infections

Salmonella typhimurium, Rhodococcus equi, which causes granulomatous patterns similar to Mycobacterium avium-

intracellulare (MAI), and *Pseudomonas pseudomallei* (melioidosis), which causes small neutrophilic microabscesses or granulomas, and chlamydia and syphilis are examples of other bacterial infections reported to cause granulomatous hepatitis.[20,52,53]

Histoplasma capsulatum (histoplasmosis)

Histoplasmosis is the most commonly recognized fungal disease associated with hepatic granulomatous infection. It is endemic in the Ohio and Mississippi River valleys. Hepatic involvement by histoplasmosis manifests with granuloma formation dominated by macrophages and lymphocytes with *H capsulatum* organisms and epithelioid cells located central to the lesion.[54]

Other fungal infections

Hepatic candidiasis is characterized by granulomas with suppurative central areas containing variable necrosis and giant cells. There may be a histologic appearance to similar cat scratch disease with palisading histiocytes and a fibrous scar. Aspergillosis is characterized by a marked neutrophilic infiltrate or granulomatous inflammation, which is similar to that in mucormycosis and zygomycetosis. Cryptococcus causes histologic features that range from necrotizing inflammatory reaction with granulomatous features in immunocompromised adults to purely granulomatous reactions. Occasionally, other fungal infections such as *Pneumocystis carinii*, *Blastomycosis dermatitidis*, and *Paracoccidioides brasiliensis* can cause hepatic granulomas.[20,52,55]

Schistosomiasis

Infections with *Schistosoma mansoni* and *S japonicum* are frequent in the developing world where waterborne parasitic diseases are prevalent. Chronic schistosomiasis causing granulomas and related fibrosis is the most common cause of portal hypertension in the world, presenting with splenomegaly and bleeding.[56] The parasites enter the human host through the skin and circulate until they reach the mesenteric venules where the produce eggs that are inadvertently swept by the mesenteric venous blood flow, eventually lodging in the hepatic sinusoids. Thousands of eggs can be produced by adult worms. This leads to a granulomatous reaction rich in eosinophils and is associated with fibrosis and collagen deposition in the periovular, periportal, and perisinusoidal areas. This is termed "pipestem or Symmer fibrosis." In liver biopsy specimens, the schistosome eggs (Fig. 7) are commonly found at the center of the granulomas.[56,57] The small branches of the portal vein become obliterated with subsequent proliferation of hepatic arterial branches. Presinusoidal portal hypertension with spreading fibrosis develops, leading to a grossly nodular appearance of the liver.[58]

Leishmania donovani (Leishmaniasis)

Visceral leishmaniasis infection with *Leishmania donovani* or *L infantum* is a parasitic infection causing disease in various intra-abdominal solid organs, and it is often seen in immunocompromised patients with AIDS. Several case reports have documented fibrin-ring granulomatous hepatitis, which more commonly occurs with Q fever, Hodgkin disease, Cytomegalovirus (CMV) hepatitis, and allopurinol treatment.

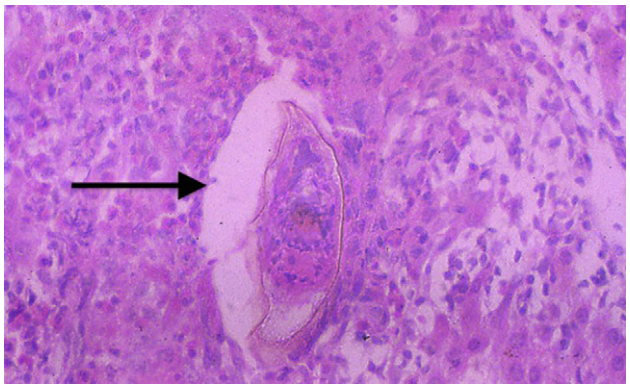

Figure 7 Schistosomiasis of liver. Note *Schistosoma hematobium* egg with terminal spine in the center (arrow; H and E, ×400).

Other studies have noted epithelioid granulomas as well as hyperplastic Kupffer cells, and organism-filled macrophages, forming small nodules or granulomas.[59,60]

Other parasitic infections

Enterobius vermicularis (pinworm) has been shown in rare case reports to cause hepatic granulomas consisting of hyalinized nodules with peripheral inflammation. The center of the granuloma exhibits necrosis with *E vermicularis* ova and nematode remnants.[61] *Fasciola hepatica* infection, fascioliasis, can cause biliary calculi, cholangitis, obstructive jaundice, and has been shown to cause tumor-like granulomatous lesions due to transhepatic migration of the larvae.[62] Other rare causes of parasitic granulomatous hepatitis include *Toxoplasma gondii*, *Capillaria hepatica*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Giardia lamblia*.[63–66]

Hepatitis C

Retrospective and prospective studies have reported granulomas in the liver biopsies with a frequency of 1%–10% in patients with HCV, but no other known systemic or hepatic diseases. One larger retrospective review described epithelioid granulomas in 63 of 1662 liver biopsies performed for HCV staging. Antiviral therapy with interferon-alpha may also contribute to granuloma formation in the livers of patients with HCV. *De novo* induction of granulomas can occur with interferon-based therapy as well as development or activation of subclinical sarcoid due to the release of cytokines that occurs with enhancement of the Th1 inflammatory response initiated by the interferon therapy. Usually the sarcoidosis and granulomas regress upon cessation of interferon therapy. Granulomatous disease associated with HCV infection has been linked to a higher mortality rate.[12,38,67–70]

Hepatitis B

The data for hepatic granuloma formation in hepatitis B infection is limited. However, a study by Goldin and colleagues[67] reported hepatic granulomas in 2% (3/151) of patients with chronic hepatitis B infection. As with hepatitis C, it is imperative that other granulomatous diseases such as tuberculosis, brucellosis, sarcoidosis and drug reactions be excluded.[67]

Other viral infections

Cytomegalovirus and Epstein-Barr virus can be associated, although rarely, with epithelioid granulomas in immunocompetent patients as well as fibrin-ring granulomas. With Epstein-Barr virus infection, the hepatitis results in a diffuse lymphocytic sinusoidal infiltrate in a single file "string of beads" pattern with small Kupffer cell clusters and discrete noncaseating granulomas.[71,72]

Drugs and chemicals

Numerous drugs have been implicated in the development of granulomas in the liver or granulomatous hepatitis. The overall incidence of drug-induced hepatic granulomas is thought to be 10%.[52] The clinical presentation may be one of hepatocellular or cholestatic liver injury. Jaundice is relatively rare. Histology reveals granulomas infiltrated with eosinophils. Eosinophils in the peripheral blood or surrounding the granulomas may or may not be present, and should not be considered to be pathognomic for drug-induced granulomatous hepatitis.[14,52,73] Chemicals such as beryllium and thorotrast as well as drugs such as phenylbutazone, allopurinol, sulfonamides, phenytoin, carbamazepine, chlorpropamide, quinidine, methyldopa, nitrofurantoin, isoniazid, amiodarone, and diazepam among others have been linked to hepatic granulomas. There have been several case reports implicating acetaminophen, norfloxacin, rosiglitazone, and mesalamine as culprits as well.[13] It may be difficult to establish with certainty a cause-and-effect relationship between drug usage and formation of granulomas. However, resolution of granulomas after discontinuation of the drug may be helpful in establishing the diagnosis. Other causes should be ruled out even when patients may have been exposed to drugs listed above. The management includes discontinuation of the suspected drug with close monitoring of the clinical course. Repeat liver biopsy may be helpful if the diagnosis was unclear at the beginning.[13]

Malignancy

Hodgkin lymphoma, non-Hodgkin lymphoma, and renal cell carcinoma have all been associated with hepatic granulomas. These types of granulomas are non-necrotic and are considered to be distinct from malignant cells. The relationship between malignant lesions and the development of hepatic granulomas is unclear (Figs. 8A and B). However, the presence of these granulomas appears to have no relationship to the prognosis of the tumor.[12,74]

Idiopathic causes

A substantial proportion of patients—about 3%—37%—with granulomatous liver disease will never have a cause identified despite extensive work-up. The term "granulomatous hepatitis" is often used to refer to a syndrome characterized by a prolonged febrile illness, myalgias, hepatosplenomegaly, and arthralgias of unclear etiology. Laboratory work may reveal a markedly elevated sedimentation rate. It is thought that many of these cases may be related to a subset of autoimmune disease or sarcoid,

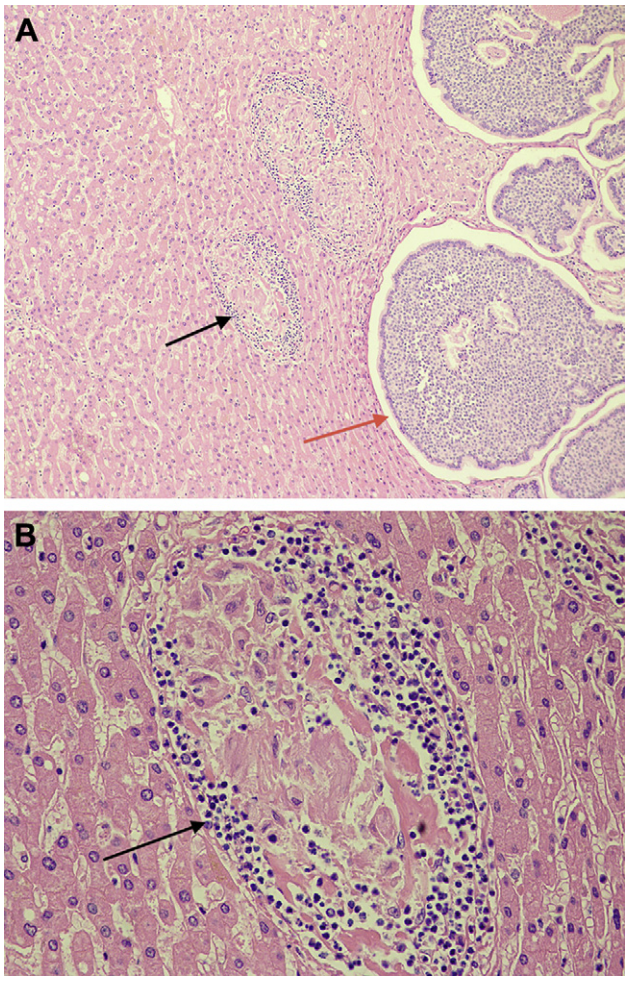

Figure 8 (A) Granulomatous response in liver (black arrow) associated with a metastatic malignant neoplasm, an islet cell carcinoma, a neuroendocrine neoplasm (red arrow; H and E, ×40); (B) higher power view of the epithelioid granuloma (arrow; H and E, ×400).

and some authors have recommended an empirically careful therapeutic trial of corticosteroids or methotrexate.[75,76] Others have suggested that an empiric trial of antimicrobial therapy against *M tuberculosis* may have benefit in anergic patients or in those with a positive tuberculin skin test.[76] In other cases where granulomas are an incidental finding without clinical manifestations or laboratory abnormalities, periodic monitoring is sufficient.[13]

Rare causes

Systemic inflammatory and rheumatologic conditions like Wegener granulomatosis and connective tissue diseases such as polymyalgia rheumatica, temporal arteritis, systemic lupus erythematosus, Sjögren disease, and erythema nodosum have been associated with hepatic granulomas. Another rare cause is chronic granulomatous disease, which is a rare inherited disorder caused by a defect of the reduced nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) complex leading to loss of the capacity of macrophages to kill phagocytized bacteria and

fungi. Although the latter disease is uncommon, 75% of patients have hepatic granulomas.[77,78] Crohn disease and ulcerative colitis have also been linked to granulomatous disease in various case reports, although a true association is unproven. This finding has more specifically been reported in patients with Crohn ileitis.[33,79]

Conclusion

Although the causes of hepatic granulomatous disease are numerous, the most common causes include sarcoidosis, primary biliary cirrhosis, and tuberculosis. Work-up should include a thorough clinical history, pertinent laboratory work, and eventually a liver biopsy when this diagnosis is suspected. Treatment should be focused on the specific inciting agent with the goal of prevention of complications such as portal hypertension and liver failure.

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