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REVIEW

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Granulomatous liver diseases

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Abstract

A granuloma is a discrete collection of activated macrophages and other inflammatory cells. Hepatic granulomas can be a manifestation of localized liver disease or be a part of a systemic process, usually infectious or autoimmune. A liver biopsy is required for the detection and evaluation of granulomatous liver diseases. The prevalence of granulomas on liver biopsy varies from 1% to 15%. They may be an incidental finding in an asymptomatic individual, or they may represent granulomatous hepatitis with potential to progress to liver failure, or in chronic disease, to cirrhosis. This review focuses on pathogenesis, histological features of granulomatous liver diseases, and most common etiologies, knowledge that is essential for timely diagnosis and intervention.

INTRODUCTION

Granulomas are a collection of activated macrophages and other inflammatory cells and may be the result of a variety of conditions, usually infectious or autoimmune. Granulomas are found in diseases isolated to the liver or may reflect systemic illness, and the disease severity may range from an asymptomatic state to severe granulomatous hepatitis with portal hypertensive complications.

Diagnosis of hepatic granulomas relies on liver biopsy and the most common scenario leading to the discovery of granulomas is that of a liver biopsy performed for the workup of abnormal liver enzymes or for confirmation of hepatic involvement in a systemic process that shows granulomas. When granulomas are found incidentally, there is often a diagnostic challenge; a comprehensive history and physical exam are crucial for making the correct underlying diagnosis. The physician's role is to stratify the risks and to decide whether the incidental finding of granulomas requires further investigation. This review details pathogenesis, established common and emerging causes of granulomatous liver diseases (GLD), and histological features.

EPIDEMIOLOGY

The prevalence of granulomas on liver biopsy ranges from 1% to 15%.[1,2] It is challenging to make accurate estimates of the real prevalence of hepatic granulomas since not every patient evaluated by a hepatologist undergoes a liver biopsy. The etiologies of hepatic granulomas differ geographically. While in the Western world, noninfectious autoimmune

Abbreviations: BCG, Bacillus Calmette-Guerin; CGD, chronic granulomatous disease; CT, computerized tomography; CVID, common variable immunodeficiency; FUO, fever of unknown origin; GLD, granulomatous liver diseases; ICI, immune checkpoint inhibitors; NCPH, noncirrhotic portal hypertension; PBC, primary biliary cholangitis; PH, portal hypertension; TB, tuberculosis; Th1, T helper type 1; Th2, T helper type 2; TNF-α, tumor necrosis factor-alpha; UDCA, ursodeoxycholic acid; US, ultrasound.

conditions such as primary biliary cholangitis (PBC) are prevalent, in the Middle East and Asia infections remain the leading causes of hepatic granulomas. Tuberculosis (TB), leishmaniasis, and viral hepatitis account for the most frequent causes in the developing world (Table 1).

The prevalence and etiology differ among different patient subpopulations, especially those who are predisposed to hepatic granulomas by virtue of an underlying condition, usually an inborn or acquired immunodeficiency or immunosuppression. GLD was found in about one-third of the patients infected with HIV, who had a liver biopsy as a workup of hepatomegaly, fever of unknown origin (FUO), or elevated transaminases.[14,15] Opportunistic infection with various mycobacteria, especially *Mycobacterium tuberculosis*, remains the leading cause of liver granulomas in patients with HIV prior to and during the antiretroviral therapy eras.[14–17] In a single-center study of 301 patients with HIV, hepatic granulomatous inflammation was present in 29% of the patients, with more than half having TB immune reconstitution inflammatory syndrome.[18] In another study, the prevalence of granulomas in solid organ and hemopoietic stem cell transplant recipients was explored. Hepatic granulomas were found in 0.8% of all recipients of transplantation, with most of them thought to be noninfectious (72%). Eighty-nine percent were found in recipients of liver transplant with the most frequent underlying cause being graft-versus-host disease and idiopathic, presumed noninfectious.[19]

PATHOGENESIS

Exposure to a foreign body, bacteria, mycobacteria, fungi, or antigenic stimuli triggers an initial immune response and recruitment of inflammatory cells. Granulomas are a manifestation of inflammation, most often part of an effort to biochemically degrade a foreign substance, bacteria, or persistent antigenic stimulus. The latter may be exemplified by sarcoidosis or DILI.[1,2,20] The pathophysiological cascade in GLD involves innate and adaptive immunity and consists of several steps: initial innate immune response, macrophage activation, T-cell and B-cell activation, and finally, granuloma formation, all of which may eventually result in hepatic fibrosis.

Granuloma formation represents helper T-cell–mediated delayed hypersensitivity reaction, and the two primary components of this process are resident macrophages and CD4+ T-cells.[20] Antigenic stimulus through toll-like receptors attracts macrophages to the site of inflammation as a part of an innate immune response. Macrophages engulf and try to destroy the invader through phagocytosis. Macrophages, B-cells, and dendritic cells serve as Ag-presenting cells in the generation of the adaptive immune response and play a role in $CD4^+$ T helper cell modulation and initiation of CD4+ T helper type 1 (Th1) and 2 (Th2) cytokine responses. Activation of macrophages by cytokines is further required for granuloma formation (Figure 1). Th1 activation dominates in granulomatous inflammation

TABLE 1 Top etiologies of hepatic granulomas in cohorts from different countries

References	Top cause	Other
United States[3]	Idiopathic (50%)	Sarcoidosis (22%), drug-related (6%), PBC (5%), histoplasmosis (5%), and TB (3%).
Pakistan[4]	TB (88.9%)	Sarcoidosis (7.4%), PBC (3.7%).
Iran[5]	TB (53%)	Visceral leishmaniasis (8.3%), visceral larva migrans, PBC, and hepatitis C (4.2% each).
Saudi Arabia[6]	TB (42.6%)	Hepatitis C (14.8%), idiopathic (14.8%), schistosomiasis (5%), sarcoidosis (5%).
Greece[7]	PBC (62%)	Sarcoidosis (7.5%), hepatitis B and C (7.5%), autoimmune hepatitis (6%), idiopathic (6%).
Turkey[8]	PBC (44.2%)	Infections - mycobacterial, echinococcal, and hepatitis C (39.5%) malignancy—HCC, cholangiocarcinoma, and others (5.8%), sarcoidosis (4.7%), and foreign body (3.5%).
Portugal[9]	TB (35.8%)	PBC (15.0%), idiopathic (12.5%), hepatitis C (6.3%).
Germany[10]	PBC (48.6%)	Undiagnosed/idiopathic (36%), sarcoidosis (8.4%).
Ireland[11]	PBC (23.8%)	Sarcoidosis (11.1%), idiopathic (11.1%), hepatitis C (9.5%), drug-related (7.9%), PBC/autoimmune hepatitis overlap (6.3%), Hodgkin disease (6.3%), autoimmune hepatitis (4.8%), TB (4.8%).
Australia[12]	Chronic liver disease: alcoholic hepatitis/cirrhosis, hepatitis B, secondary hemochromatosis (20%)	Sarcoidosis (12%), infections - cytomegalovirus, Q fever, hepatitis B, Coxsackie B (12%), malignancy (8%), drug-related (7%), TB (7%).
India[13]	TB (55%)	Leprosy (17.6%), Hodgkin's disease (3.6%).

Abbreviations: PBC, primary biliary cholangitis; TB, tuberculosis.

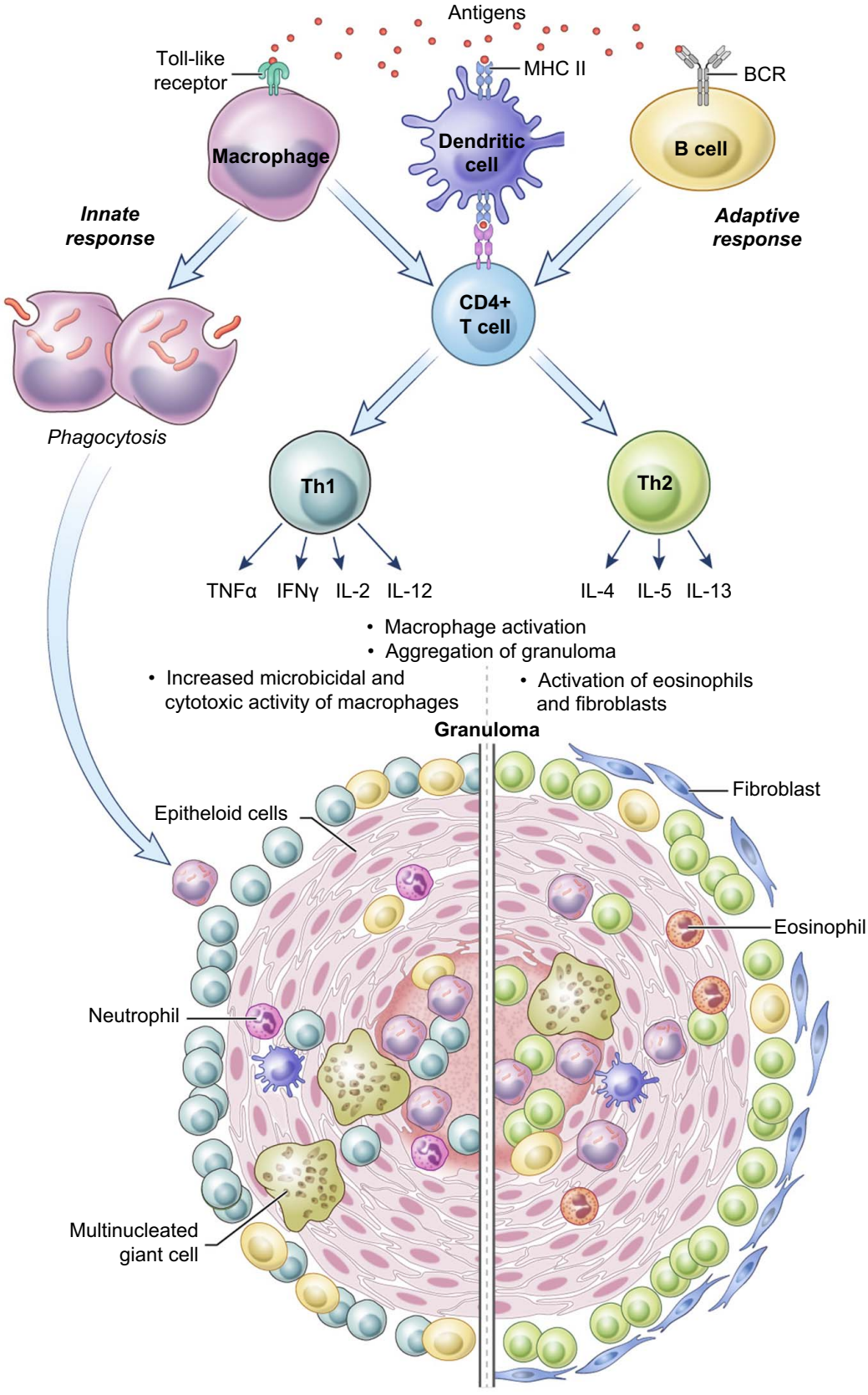

FIGURE 1 Pathogenesis of granuloma formation. Bacteria or any foreign organism can be phagocytosed by macrophages as a part of the innate immune response. In the adaptive response, antigen is presented to the CD4+ T-cells through Ag-presenting cells: macrophages, dendritic cells, and B-cells. The Th1 pathway involves the release of TNF-α, INF-γ, IL-2, IL-12, and other pro-inflammatory cytokines and it is critical in sarcoidosis and tuberculosis. The Th2 response is mediated through IL-4, IL-5, and IL-13, and it plays a role in helminth infections such as schistosomiasis. Abbreviations: INF-γ, interferon-gamma; Th2, T helper type 2; TNF-α, tumor necrosis factor-alpha).

that usually involves intracellular pathogens such as mycobacteria, leishmania, or idiopathic inflammatory diseases like sarcoidosis. It is mainly facilitated by pro-inflammatory cytokines interferon-gamma, tumor necrosis factor-alpha (TNF-α), and IL-2, IL-6, and IL-12. Th2 cytokine response with IL-4, IL-5, IL-10, and IL-13 is most prominent in parasitic infections, such as schistosomiasis.[21] Interestingly, in schistosomiasis the initial response is Th1, then ova Ags promote the switch to Th2 response shortly after an infection. In schistosomiasis, the ova cause the most pronounced granulomatous response, and the Th2 response helps to prevent further inflammation. An additional source of IL-4 in parasitic infections is eosinophils.[22] Interferon-gamma-γ may play a protective role against fibrosis in schistosomiasis, while IL-10 may control excessive Th1 and Th2 polarization of granulomatous response.[23] In animal studies, levels of IL-13 correlate with collagen deposition, fibrosis, and the severity of portal hypertension in schistosomiasis.[24]

Activated macrophages further aggregate to form organized granulomas. Granulomas are dynamic structures, and they may undergo fibrosis, a common outcome, or necrosis as they mature. Fibrosis is facilitated through the secretion of growth factors and extracellular matrix proteins by macrophages, and it may occur in both noninfectious settings, such as foreign body granulomas, and in infection-related granulomas.[25] In schistosomiasis, the fibrotic response is coordinated by HSC, which secrete a range of profibrotic chemokines, including chemokine (C-X-C motif) ligand 1 and chemokine (C-C motif) ligand 2.[26] Granulomas, especially those of infectious etiology, can undergo necrosis. One of the remarkable examples is the caseating tuberculous granuloma, where necrosis is associated with increased bacterial proliferation. Proteomic analysis of necrotic foci has shown large amounts of pro-inflammatory eicosanoids, such as leukotriene B4, and prostanoids, such as cyclooxygenase-1 and 2. Animal models have shown an abundance of TNF-α and reactive oxygen species within necrotic foci, which play microbicidal roles, but also may be destructive to the tissues.[27]

A genetic predisposition may contribute to susceptibility to granulomatous disease. Human leukocyte Ag DRB1 was recognized as a marker of predisposition to sarcoidosis.[28] Analysis of familial and sporadic cases of sarcoidosis identified a variant of butyrophilin-like 2 gene *BTNL2* that is a risk factor for sarcoidosis independent of Human leukocyte Ag predisposition.[29] Whole exome sequencing in patients with common variable immunodeficiency (CVID) has shown that patients with identifiable underlying monogenic causes (about 30% of CVID cases) are more likely to have complicated courses, including granulomatous infiltrates, rather than infections only.[30] Potential genes associated with hepatic granulomas in CVID include, but are not limited to, *recombination-activating gene 1* and *nuclear factor kappa B subunit 1*.[31]

HISTOPATHOLOGY

Liver biopsy plays a pivotal role in the diagnosis of GLD. It can be done for investigation of a systemic disorder with liver involvement, or an isolated hepatic process. The histological term used for activated macrophages, "epithelioid histiocyte," is based on their appearance and it is reflected in the names of some types of granulomas (Table 2 and Figure 2). Compared to the inactive macrophages, the epithelioid histiocytes have more cytoplasm with fewer lysosomes, a regular elongated shape, and sometimes multiple, peripherally-located nuclei.[32,33] They also lose their pseudopods, giving the cell a smooth outline. The location of granulomas in the liver depends on the etiology. Suture granulomas are found in the vicinity of prior surgery, while talc granulomas are most of the time located in portal areas. Sarcoidosis, PBC, and infectious granulomas often spread diffusely in the liver affecting portal, intra-acinar, periductal, and ductal areas.[32] The peri-granulomatous liver tissue may be unchanged, or it may show increased lymphocytic inflammation.[1]

Microgranulomas are small collections of macrophages, only 3 to 7 cells in cross-section, and they represent a nonspecific reaction to a liver injury.[20] They are frequently seen in metabolic dysfunction–associated steatotic liver disease, PBC, and DILI. They do not have independent significance and are unlikely to be associated with major parenchymal abnormalities.[12]

Lipogranulomas represent a collection of vacuolated fat droplets, and they were initially considered an incidental finding without clinical significance. The use of mineral oil in the food industry was thought to be responsible for the increased incidence of lipogranulomas in liver biopsies.[34] It was subsequently shown that lipogranulomas are associated with steatosis of any etiology, including metabolic dysfunction–associated

TABLE 2 Histological types of granulomas and the associated conditions

Type of granuloma	Associated disease
Microgranuloma	Nonspecific
Lipogranuloma	Steatotic liver disease, hepatitis C
Fibrin-ring granuloma	Q fever (*Coxiella*), leishmaniasis, toxoplasmosis, Hodgkin disease, ICIs-related granulomas
Epithelioid necrotizing granuloma	TB, nocardiosis, fungal infections
Epithelioid non-necrotizing granuloma	Sarcoidosis, hepatitis C, PBC, DILI

Abbreviations: ICIs, immune checkpoint inhibitors; PBC, primary biliary cholangitis; TB, tuberculosis.

steatotic liver disease, and less frequently, alcohol.[35] They are usually located within portal or acinar areas, especially adjacent to hepatic veins. Large portal lipogranulomas may lead to portal expansion and give a false impression of "fibrosis." Variable amounts of collagen fibers may be seen within and around lipogranulomas, as well as rare eosinophils.[32,36,37] In 58 patients with lipogranulomas on the liver biopsy, the most frequent underlying etiology was either hepatitis C or steatotic liver disease.[38] Lipogranulomas were evident in 19% of biopsies done for the workup of DILI.[39]

Fibrin-ring granulomas were initially described in association with granulomatous hepatitis in *Coxiella burnetii* infection (Q fever) by Bernstein.[40] Their distinct feature is the presence of a central round fat vacuole surrounded by a fibrin ring and an outer layer of histiocytes. They are usually small in size and intralobular. Masson trichrome stain is useful for staining the eosinophilic fibrin ring.[20,41] Although highly suggestive of Q fever, they are found in other etiologies as well. In a study of 23 biopsies with evidence of fibrin-ring granulomas, Q fever accounted for 43% of the cases, followed by visceral leishmaniasis in 22% and boutonneuse fever, caused by various species of *Rickettsia*, in 13%. A smaller proportion of cases were associated with toxoplasmosis, allopurinol-induced liver injury, and Hodgkin's disease.[41] Association with autoimmune conditions such as systemic lupus erythematosus and giant cell arteritis are also reported.[42,43] The current focus has shifted from infections toward DILI: fibrin-ring granulomas are reported in patients with granulomatous hepatitis due to immune checkpoint inhibitors (ICI), both anti-CTLA-4 and anti-PD-L1.[44,45]

Epithelioid granulomas are mostly composed of epithelioid cells but may also contain lymphocytes and other inflammatory cells and fibroblasts. They are often associated with specific infectious and noninfectious disorders, and they are categorized as non-necrotizing

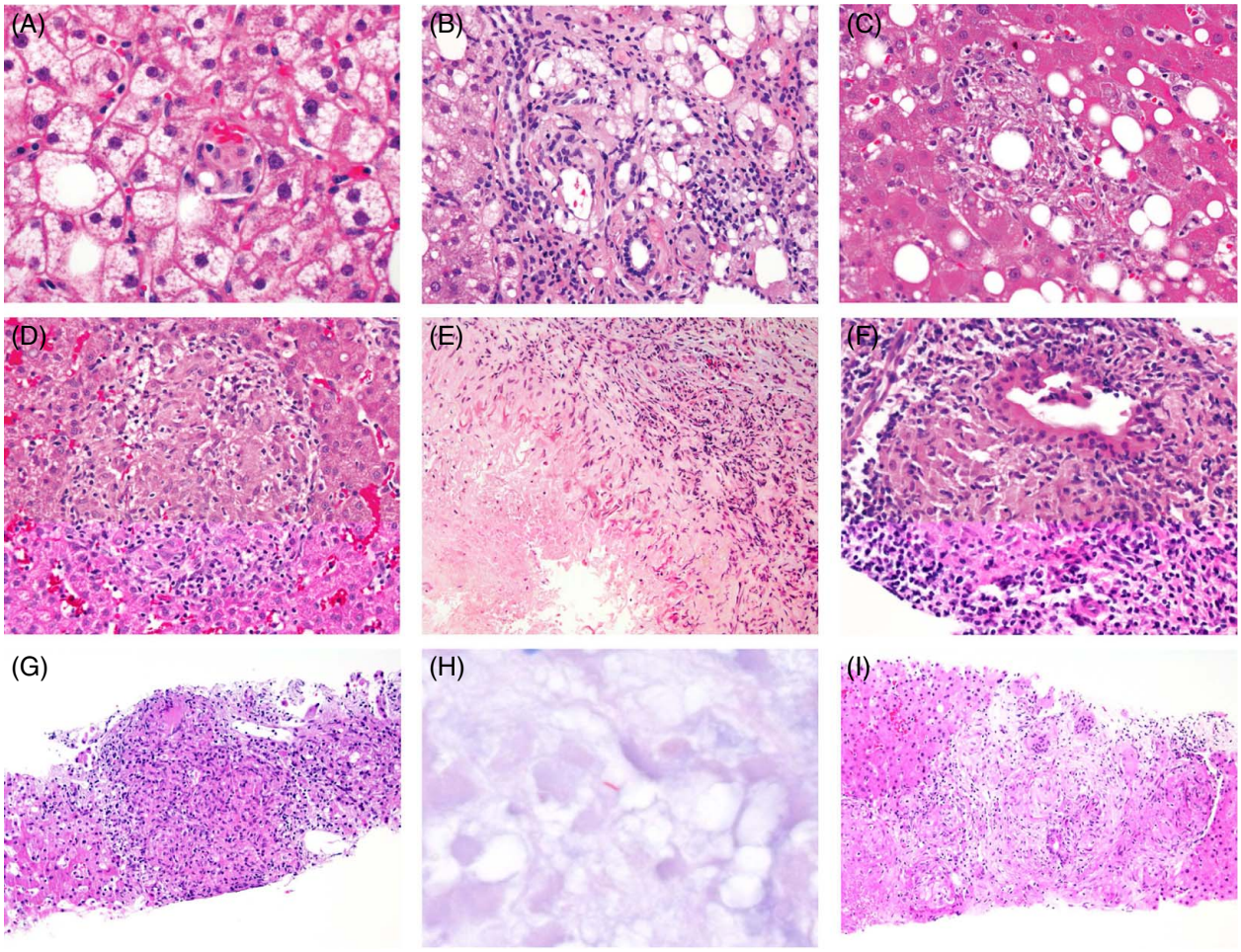

FIGURE 2 Histological features of hepatic granulomas. (A) Microgranuloma in metabolic dysfunction–associated steatohepatitis, H&E, ×600. (B) Lipogranuloma in metabolic dysfunction–associated steatohepatitis, H&E, ×400. (C) Fibrin-ring granuloma in drug-induced injury due to the ICIs ipilimumab and nivolumab, H&E, ×400. (D) Non-necrotizing epithelioid granuloma in autoimmune lymphoproliferative syndrome, H&E, ×400. (E) Necrotizing epithelioid granuloma in eosinophilic hepatitis, H&E, ×200. (F) Florid duct lesion of primary biliary cholangitis, H&E, ×400. (G) Mycobacterial granuloma, H&E, ×200. (H) *Mycobacterium tuberculosis* on acid-fast bacilli stain, ×600. (I) Granulomas in sarcoidosis, H&E, ×200. Abbreviations: H&E, hematoxylin and eosin; ICI, immune checkpoint inhibitors.

and necrotizing. Necrosis is found in the center of the epithelioid granuloma. "Caseating necrosis" is a term to describe the macroscopic picture associated with complete loss of tissue structure, with TB being a classic example.[46] Necrotizing epithelioid granulomas are prevalent in infections such as nocardiosis, fungal infections, including histoplasmosis, and fascioliasis; an association with DILI has been reported as well.[47–50] Non-necrotizing epithelioid granulomas may be either poorly or well-formed. Well-formed granulomas are seen in sarcoidosis and infections like hepatitis C.[20,51] Poorly formed granulomas are infiltrated by lymphocytes, which can obscure the normal cohesive granuloma structure. They may be found in immune-mediated conditions, PBC, DILI, or T-cell–mediated rejection after a liver transplant.[2,52] "Granulomatous inflammation" refers to an inflammatory reaction involving epithelioid cells when granulomas fail to form.[32] Epithelioid granulomas that are not associated with a known etiology should be stained for infectious organisms.

ETIOLOGY

The etiologies of hepatic granulomas can be broadly categorized as infectious and noninfectious (Table 3). The diagnosis of idiopathic granuloma is made when no underlying cause can be identified. In this section, the focus is made on the most common etiologies.

Foreign body granuloma

Granuloma formation is a localized inflammatory response that occurs in an attempt to react and isolate exogenous material. It includes materials like sutures, sponges, implants, or other particles that enter the body during an injury.[92,93] Hepatic and splenic granulomas containing microscopic metallic particles were found in 38% of the autopsies of patients with a history of hip or knee replacement. Foreign body granulomas may also cause hepatitis with fatigue, jaundice, and weight loss.[94] Isolated elevation of alkaline phosphatase and non-necrotizing granulomas containing silicone material are described in patients with ruptured breast implants.[95]

Sarcoidosis

Sarcoidosis is a systemic disorder, mostly prevalent in women of young and middle age between 20 and 50 years. The pathogenesis of sarcoidosis is poorly understood, and it is thought to develop due to a combination of factors, including genetic predisposition, environmental, and even bacterial triggers.[96] It usually affects the lungs and mediastinal lymph nodes, but it can also involve the liver in 6%–18% of the cases with the majority of the patients being asymptomatic.[97,98] Having hepatic involvement at the time of diagnosis is a predictor of chronic disease in sarcoidosis.[98] Symptomatic patients often present with nonspecific complaints such as fatigue, night sweats, and fever. Hepatic symptoms often resemble cholestatic liver disease, PBC, or primary sclerosing cholangitis, manifesting with pruritus, jaundice, anorexia, and elevated alkaline phosphatase.[99] Sarcoidosis may involve up to 90% of the liver volume, which can lead to intrahepatic and extrahepatic biliary obstruction. Non-necrotizing granulomas are a predominant feature of hepatic sarcoidosis, although bile duct injury, chronic portal inflammation, and vascular changes, such as sinusoidal dilation and nodular regenerative hyperplasia, may also be seen on the biopsy.[100] Fibrosis and cirrhosis are encountered in 20–29% of the biopsies,[100,101] and may eventually become complicated by portal hypertension (PH). In a case series of 12 patients with PH due to sarcoidosis, 7 patients died, 6 of them due to complications of PH, and 2 patients received liver transplants.[102] Sarcoidosis is also a known cause of noncirrhotic portal hypertension (NCPH);[99] reversal of NCPH in sarcoidosis with steroid treatment has been reported.[103]

Primary biliary cholangitis

PBC, formerly known as primary biliary cirrhosis or nonsuppurative destructive cholangitis, is an autoimmune slowly progressive, cholestatic liver disease associated with inflammation and destruction of the small bile ducts. Granulomas are usually evident in early disease, characterized by portal inflammation, sometimes called the florid duct lesion stage.[62] The florid duct lesion is a diagnostic histological feature of PBC and represents a damaged bile duct, surrounded by lymphocytes and plasma cells, with adjacent granulomas. Granulomas are mostly epithelioid, non-necrotizing, and are poorly formed, with many infiltrating lymphocytes that disrupt the structure. As the disease evolves, granulomas become less prominent.[104] Immunological studies showed that dendritic cells and immunoglobulin M are key factors in the formation and evolution of granulomas in PBC.[105] The presence of granulomas is thought to be associated with better patient survival;[106] this is likely explained by the fact that the granulomas are an early finding in PBC. While granulomas are a hallmark of PBC, in primary sclerosing cholangitis they are usually an incidental finding.[20]

Inborn errors of immunity

Advancements in medicine and the use of prophylactic antibiotics have dramatically increased survival in

TABLE 3 Most common etiologies of hepatic granulomas

Infectious etiologies	Noninfectious etiologies
Bacterial infections	Autoimmune disease
Nocardiosis[47]	Sarcoidosis[53]
Mycobacterial infections, including *M. tuberculosis*, *M. bovis*, *M. avium*[17,54]	Eosinophilic granulomatosis with polyangiitis[55]
Brucellosis[56]	Giant cell arteritis[57]
Q fever (*Coxiella burnetii*)[12]	Granulomatosis with polyangiitis[58]
Cat-scratch disease (Bartonellosis)[59]	Crohn's disease[60]
Syphilis[61]	Primary biliary cholangitis[62]
Actinomycosis[63]	Immunodeficiencies, inborn and acquired
Fungal infections	Common variable immunodeficiency[64]
Histoplasmosis[65]	Chronic granulomatous disease[66]
Blastomycosis[67]	Human immunodeficiency virus infection[18]
Coccidioidomycosis[68]	Medications
Candidiasis (in the setting of neutropenia)[69]	Acetaminophen[70]
Viral infections	Allopurinol[71]
Hepatitis A, B, C[6,51,72]	Albendazole[73]
Epstein-Barr virus[74]	Amoxicillin-clavulanate[75]
Cytomegalovirus[76]	Diltiazem[77]
Parasitic infections:	Etanercept[78]
Helminthic infections:	Infliximab[79]
Ascaridosis[80]	Ipilimumab[81]
Fascioliasis[82]	Mebendazole[83]
Schistosomiasis, including *S. japonicum* and *S. mansoni*[67]	Mesalamine[84]
Protozoal infections:	Nivolumab[81]
Toxoplasmosis[85]	Vemurafenib[86]
Leishmaniasis[87]	Rosiglitazone[88]
	Sulfasalazine[89]
	Quinidine[90]
	Hodgkin's disease[91]
	Foreign body
	Talc[20]
	Surgical material[92,93]
	Prosthetic devices[94]
	Implants[95]
	Idiopathic granulomas

patients with inborn errors of immunity, and as a result, recognition of hepatic disorders. Hepatic granulomas are a signature of CVID and chronic granulomatous disease (CGD).[107] CVID refers to a spectrum of disorders typically associated with adult-onset antibody deficiency, but a subgroup of cases have granulomas in the lung, liver, and spleen. Liver disease has been associated with higher mortality in CVID.[108] Up to 22% of the patients with CVID may develop granulomas, with about one-third of them located in the liver. Hepatic granulomatosis in CVID is frequently associated with nodular regenerative hyperplasia. These conditions altogether lead to NCPH, the most common and morbid sequela of which are variceal bleeding, ascites, and spontaneous bacterial peritonitis.[64,109,110] CGD is due to defects in the NADPH oxidase complex, which is required for the production of reactive oxygen species by phagocytes. CGD leads to impaired innate and adaptive immune responses and with resulting susceptibility to infection with organisms such as *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia* complex, *Nocardia* species, and *Aspergillus* and other

fungi.[66] Along with liver abscesses, non-necrotizing granulomas are the most common histological finding in CGD and are found in up to 74% of the patients. Granulomas may alter the architecture of small portal veins and lead to an obliterative portal venopathy and nodular regenerative hyperplasia, and as a result lead to NCPH.[111,112]

Inflammatory bowel disease

Abnormal liver enzymes have been reported in up to 30% of all patients with inflammatory bowel disease, with chronic liver disease developing only in 6% of the patients.[113] GLD is an infrequent complication that is encountered more in Crohn's disease than in ulcerative colitis. Hepatic granulomas have been reported in 6% of liver biopsies of patients with Crohn's disease.[60] In a study from Northern Ireland, only 1.8% of GLD was accounted for by Crohn's disease. Well-circumscribed epithelioid granulomas within portal tracts were a characteristic feature found on biopsy.[114] Symptomatic patients usually present with signs of cholestasis. Granulomatous hepatitis may also be induced by sulfasalazine or mesalamine therapies used for the treatment of inflammatory bowel disease.[84,89]

Drug-induced liver injury

Granulomas due to DILI are suspected when there is a temporal association with exposure to a drug and other, more common causes of GLD have been excluded. Several medications have been linked to GLD, the most common are mentioned in Table 2. Granulomatous injury may have acute or delayed onset and it may be accompanied by features of hypersensitivity such as rash, eosinophilia, and fever. Liver enzymes are often elevated in a cholestatic pattern. Drug-induced granulomas are usually non-necrotizing, epithelioid, and located in portal areas, and they may lead to vascular or duct injury. The presence of eosinophils supports a drug etiology.[20,115] In the study by Kleiner et al, the finding of granulomas and eosinophils in DILI was linked to mild cases.[39]

Several cases of GLD have been reported in association with the anti-TNF modulators, infliximab, and etanercept, used for psoriasis and rheumatoid arthritis, among other diseases; discontinuation of the medications led to normalization of liver function.[78,79,116] At the same time, infliximab has been successfully used for off-label treatment in sarcoid granulomatosis and idiopathic granulomatous hepatitis.[117,118] Variations in pro-inflammatory and immunoregulatory TNF properties in different diseases may correlate with the variability in the response to anti-TNF therapies.

Iatrogenic granulomatous hepatitis was reported after injection of Bacillus Calmette-Guerin (BCG), a live attenuated *Mycobacterium bovis* used for vaccination against TB and also as immunotherapy for bladder cancer and melanoma.[119–121] Mutations in genes responsible for the generation and response to INF-gamma and IL-12 are associated with an increased risk of disseminated BCG infection.[122] Animal studies showed that liver injury in BCG infection is likely mediated through TNF-receptor 1.[123] In the case of disseminated infection following BCG instillation for bladder cancer, granulomatous hepatitis is usually an early complication with occurrence after a median of 1 week, compared to cardiovascular and bone injury that develops after a year. Up to 18% of all cases of disseminated BCG infection after use for bladder cancer involve the liver.[54]

Tyrosine kinase inhibitors and ICIs are medications of current interest in DILI research. They improve survival in patients with melanoma, head and neck cancer, non-small-cell lung cancer, and many others, but at the same time, they are associated with immune-mediated adverse events. ICI treatment in particular may be complicated by systemic granulomatous sarcoid-like reactions.[124] Granulomatous hepatitis was reported in association with the tyrosine kinase inhibitors vemurafenib, and the ICIs nivolumab and ipilimumab.[81,86] The granulomatous injury with ICIs may present in hepatocellular, cholestatic, or mixed patterns.[125] The presence of pre-existing antinuclear antibodies along with granulomas on histology may serve as potential markers of ICI-related hepatitis.[126]

Bacterial infections

Granuloma formation is a distinct feature of multisystem mycobacterial infections like TB or leprosy. TB remains a global health challenge: the estimated death toll in 2021 was 1.6 million people.[127] It usually presents as a pulmonary infection, with hepatic TB in an extrapulmonary location. Up to 85% of hepatic TB occurs as part of systemic infection, and rarely as an isolated finding. Symptomatic patients present with fever, weight loss, jaundice, and hepatosplenomegaly, sometimes associated with portal hypertension.[128,129] Hepatic TB can be disseminated, miliary, or focal in the form of tuberculoma or abscess; the main histological feature of both forms is the epithelioid necrotizing granuloma.[17] Its function is to contain infection: in TB the inner part of granuloma has a pro-inflammatory environment, while the outside layer is anti-inflammatory. The balance between these two is thought to be responsible for the host's ability to isolate infection and prevent dissemination.[27] The histological diagnosis is confirmed with acid-fast bacilli stain and culture, although the acid-fast bacilli stain cannot distinguish between the

different types of mycobacteria. PCR and the PCR-based MTB/RIF assay are more sensitive in the diagnosis of pulmonary and extrapulmonary TB than acid-fast bacilli stain alone.[130]

Hepatic granulomas are associated with many other bacterial infections. Fibrin-ring granulomas are typical lesions of *Coxiella burnettii* infection or Q fever, although granulomas without characteristic annular arrangement or fibrinoid material can be also found.[131] Up to half of the patients with liver disease due to brucellosis present with tender hepatomegaly and increased serum liver enzymes. In the study by Cervantes et al, non-necrotizing granulomas were found in 70% of the liver biopsies and most of them had disease durations less than 100 days. This suggests that granulomas in brucellosis may be a feature of acute disease.[56] Cat-scratch disease, due to *Bartonella henselae*, is usually a self-limiting disease, although rare cases of granulomatous hepatitis have been reported in children and young adults. Positive *Bartonella* serologies and bacteria visible on the silver stain confirm the diagnosis.[59,132] Actinomycosis is typically associated with cervicofacial infections, but it also causes abdominal disease with the liver being involved in 15%–20% of cases as abscesses or granulomas mimicking metastasis.[63,124,133] Poorly formed non-necrotizing granulomas are found in 36% of the patients with hepatic involvement in secondary syphilis. Granulomas are also associated with a hepatic fibroinflammatory mass lesion, which may represent early gumma or granuloma of tertiary syphilis.[61]

Viral infections

Granulomas are occasionally reported in association with hepatotropic viruses like hepatitis A, B, and C.[7,9,12] Transient fibrin-ring granulomas were observed in a patient with acute hepatitis A and disappeared during the recovery phase.[72] Transient epithelioid granulomas were found in 2% of the patients with hepatitis C; the authors had explored the possible association of granulomas with interferon-alpha treatment; however, only 1 patient of the 5 identified had granulomas on posttreatment biopsy and lacking specific features of DILI.[51] Another study reported 2 cases of granulomatous hepatitis likely caused by interferon-alpha treatment, 1 in hepatitis C and another in hepatitis B, which led to treatment cessation in both.[134] The advent of direct-acting antiviral agents for hepatitis C has led to a marked decrease in interferon treatment. Nonhepatotropic viruses like cytomegalovirus and Epstein-Barr may lead to granulomatous hepatitis and fulminant liver failure, particularly in immunocompromised hosts.[74,76] Although the knowledge of hepatic involvement with SARS-CoV-2 is still limited, GLD has not been reported in association with this infection.[135]

Fungal infections

Fungal infections predominantly impact immunocompromised hosts. In the case of invasive candidiasis in acute leukemia, hepatosplenic involvement may be seen in up to 29% of patients. The most common hepatic lesions are granulomas and microabscesses.[69,136] *Histoplasma* and *Coccidioides* enter the host by inhalation of the spores and usually result in asymptomatic pulmonary infection. In approximately half of infected immunocompromised individuals, histoplasmosis may disseminate. Patients with hepatic histoplasmosis present with fever and hepatomegaly, as well as diarrhea and abdominal pain due to gastrointestinal involvement. Granulomas are seen in both portal and lobular areas and are found in 19% of the patients with hepatic histoplasmosis.[65] In a study of 7 patients with hepatic coccidioidomycosis, all presented with febrile illness and had multiple granulomas containing spherules on liver biopsy.[68] Disseminated fungal infections usually lead to fatal outcomes if untreated.

Parasitic infections

Schistosomiasis is a tropical disease that impacts more than 250 million individuals worldwide, with the majority of those infected living in Sub-Saharan Africa. It is caused by Schistosoma species such as *S. mansoni* and *S. japonicum*; the typical source of larvae is contaminated water. The parasites penetrate the skin and reach the liver via hematogenous spread. The eggs induce an immunological cascade in the portal tracts causing granuloma formation and fibrosis, resulting in partial or complete obliteration of portal veins. Early infection presents in an acute form, also called Katayama fever, with fever, pruritic rash, myalgias, and tender hepatosplenomegaly.[67] Untreated infection may progress to advanced fibrosis, complicated by PH and risk for HCC. Schistosomiasis is the main cause of NCPH in endemic-developing countries.[137] Granulomatous disease and complications of PH such as variceal bleeding and encephalopathy are included in a predictive model to estimate 1-year mortality in advanced *S. japonicum* infection.[138]

GLD is reported with fascioliasis, another type of liver fluke, which spreads to the liver after ingestion and penetration of the intestinal wall by immature worms. Untreated acute infection is characterized by right upper quadrant pain, fever, and hepatomegaly, and is followed by a chronic phase with necrotic granulomas and the growth of worms within the biliary tree leading to cholestasis and recurrent cholangitis.[67] The macroscopic appearance of the liver shows scarring and yellow nodules that may mimic metastasis.[82] Helminth infections require systemic treatment; paradoxically,

granulomatous hepatitis has been reported in association with mebendazole and albendazole.[73,83]

The most common protozoal organisms associated with GLD are *Leishmania* species, although rare cases of hepatic granulomas are also reported in toxoplasmosis and giardiasis.[85,139] Leishmaniasis is endemic to Asia, the Middle East, East Africa, and the Mediterranean region. Patients with visceral leishmaniasis present primarily with fever, weight loss, and hepatosplenomegaly. Infection may cause extensive granulomatous hepatitis with fibrin-ring granulomas being the predominant lesions.[87,140]

Workup of fever of unknown etiology

GLD may be found when a liver biopsy is pursued for the workup of FUO. An early study by Simon et al found granulomatous hepatitis in 6.5% of the patients with prolonged fever; a definite diagnosis, Hodgkin's disease, was made in only 1 patient.[141] In the study by Holtz et al, 4 out of 24 liver biopsies done for FUO were diagnostic (16.7%); they found 3 cases of histoplasmosis and 1 case of TB.[142] In another study, the diagnosis was established in 26% of cases of FUO: those patients had *Coxiella* (Q fever), mycobacterial infection, and histoplasmosis.[143]

DIAGNOSIS

Unexplained biochemical liver abnormalities or unexplained systemic symptoms are the 2 commonest scenarios leading to the suspicion of GLD. Liver histology is required for diagnosis, in combination with thorough history taking, physical exam, concurrent laboratory tests, and imaging techniques (Figure 3). Travel history or being born in endemic regions for parasitic infections or TB, family or personal history of autoimmune disease or immunodeficiency, temporal association with medication use—all of these may hint at certain types of GLD. Most common etiologies, such as sarcoidosis or TB should be considered first. The presentation usually depends on the underlying etiology, but the diagnosis may be challenging because of the nonspecificity of the symptoms. Some patients may be asymptomatic, while others may exhibit fatigue, abdominal pain, fever, and pruritus, which are seen in both noninfectious and infectious etiologies.[128,144]

Although there is no specific pattern of liver enzyme abnormalities in GLD, a cholestatic picture with elevation in alkaline phosphatase and gamma-glutamyl transferase (GGT) is the most common, followed by a mixed pattern characterized by elevation of alkaline phosphatase, gamma-glutamyl transferase, as well serum aminotransferases. In hepatic sarcoidosis, most patients have either a cholestatic or a mixed picture of liver enzyme abnormalities.[145] Similar trends are observed in DILI;[39] however, in ICI-related granulomatous hepatitis equal numbers of patients had either cholestatic or hepatocellular injury.[125] Liver enzyme elevation in hepatic sarcoidosis may correlate with the severity of granulomatous inflammation and the degree of fibrosis.[145] Disease-specific tests may point toward certain etiologies: angiotensin-converting enzyme elevation in sarcoidosis, 1,3-β-D-glucan levels, blood/biopsy cultures in fungal infection, viral serologies in viral infections, and autoimmune panel in PBC.

Imaging augments the laboratory workup in the diagnosis of GLD. Cross-sectional methods such as computerized tomography (CT) or MRI are helpful in the evaluation of hepatic lesions and the complications of portal hypertension. While many GLDs present with nonspecific findings, such as increased liver echogenicity on ultrasound, or liver nodularity on cross-sectional imaging, some have pathognomonic features. The presence of calcified septa perpendicular to the capsule on CT in a "turtleback" pattern is a distinct feature of schistosomiasis, which becomes more prominent as the disease advances. In a study by Araki et al, calcifications on CT correlated with the degree of fibrosis in schistosomiasis; calcifications were also found in those who developed HCC.[146] In schistosomiasis, ultrasound is useful to assess the degree of periportal fibrosis and to monitor the response to treatment.[147] Healed mycobacterial or fungal granulomas may also present as calcifications on CT.[148] The contrast-enhanced ultrasound is useful in the diagnosis of infectious granulomas: 93% of lesions present as hypoechoic and irregular in shape, and 60% demonstrate hyperenhancement in the arterial phase.[149] Granulomas can exhibit increased metabolic activity mimicking metastasis on the positron-emission tomography CT.[150,151]

TREATMENT AND FOLLOW-UP

Treatment is guided by the underlying disorder and its severity. Hepatic granulomas in infections should be treated with appropriate antimicrobial, antifungal, antiviral, or antiprotozoal medications. Patients with hepatic TB demonstrate excellent response to anti-TB drug regimens: in a study by Liu et al, all 25 patients who completed treatment had resolution of lesions on the CT and improvement in symptoms.[128] In the case of DILI, the offending medication should be withheld; rechallenge is offered if clinically necessary and only after normalization of liver function. Patients with hepatitis due to DILI may be treated with steroids and ursodeoxycholic acid (UDCA).[110,125,152] UDCA is a first-line therapy for PBC, and it has been shown to improve transplant-free survival.[153] Asymptomatic patients with hepatic sarcoidosis often do not require treatment and

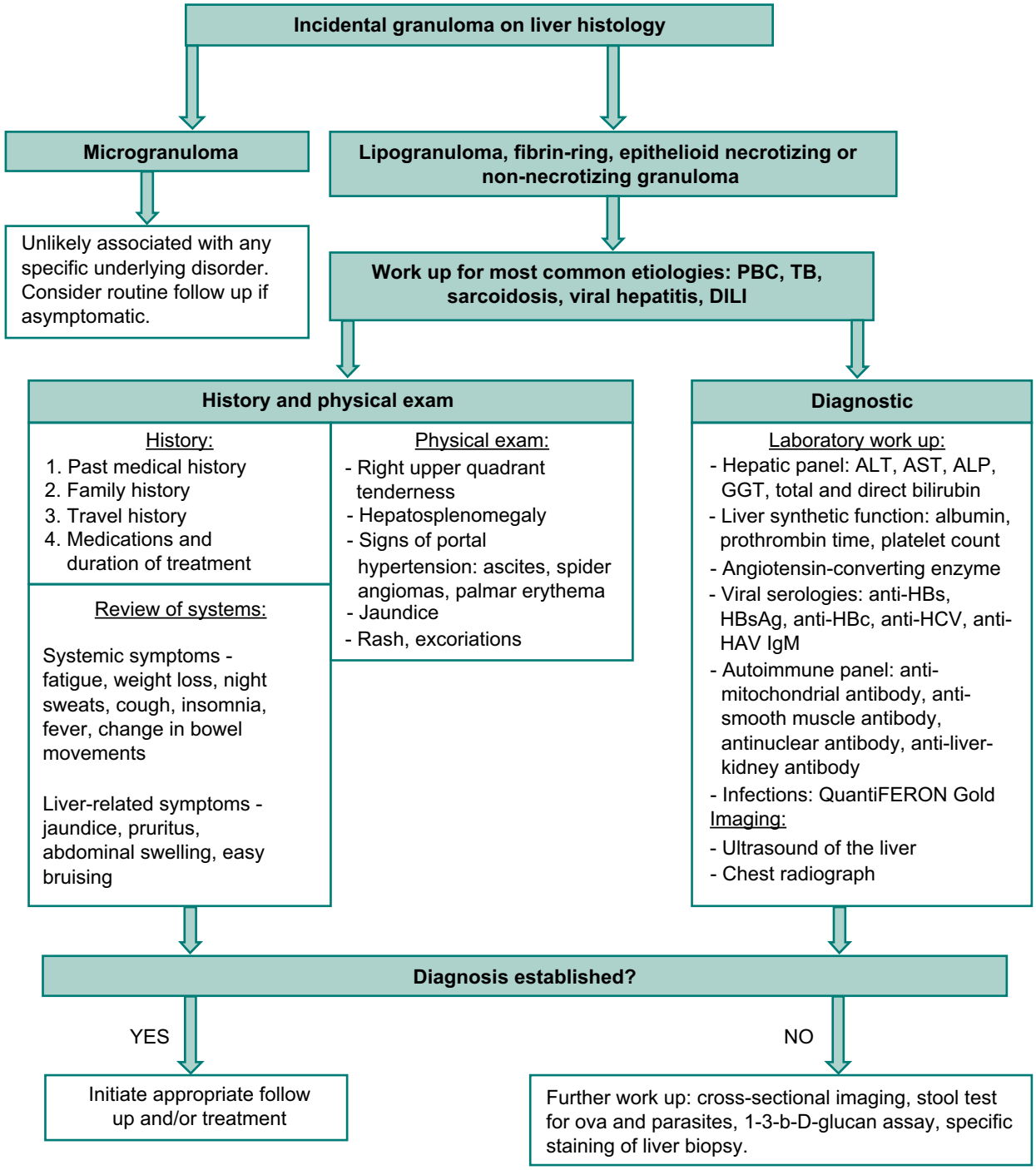

FIGURE 3 Workup of incidental granuloma on the liver biopsy. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; PBC, primary biliary cholangitis; TB, tuberculosis.

the disease may be self-limiting. If cholestatic liver disease or signs of PH develop, prompt treatment with steroids, UDCA, antimetabolites, or anti-TNF medications is indicated.[53,117] In the study by Graf et al, patients with hepatic sarcoidosis demonstrated similar biochemical responses to both steroids and UDCA.[144]

In patients with an incidental finding of granulomas on biopsy, periodic monitoring of liver enzymes and synthetic function every 6–12 months is reasonable. Patients with chronic forms of GLD should be approached as any other patient with chronic liver disease including appropriate vaccination and screening. If the patient progresses to cirrhosis, noninvasive tests to evaluate for PH and imaging every 6 months to screen for HCC are indicated. A liver transplant should be considered in case of decompensated liver

disease. Disease recurrence in the transplanted liver is reported in CVID, sarcoidosis, and PBC.[102,154,155] There is not enough evidence to link the presence of TB granulomas in the pretransplant with the development of TB in the posttransplant period.[156] Patients with inborn errors of immunity should be considered for hematopoietic stem cell transplant before liver disease progresses.[107]

CONCLUSION

Granulomas are commonly found in histological liver specimens. A systematic approach allows for accurate diagnosis and management. The ability to identify histological features, distinguish between granuloma types, and understand the manifestations of GLD and common etiologies of GLD are crucial for proper diagnosis and intervention. GLD is often a part of a systemic process; timely initiation of treatment is essential for the prevention of associated morbidity and mortality.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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