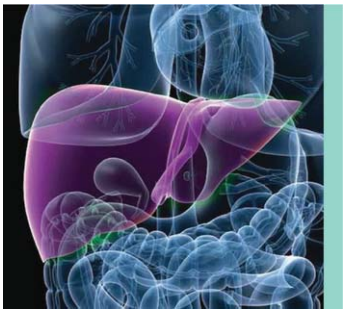

Granulomas of the Liver

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Hepatic granulomas are localized collections of inflammatory cells, which are found in 2% to 10% of patients who undergo a liver biopsy.[1] They can be associated with a variety of systemic conditions or may be an incidental finding on an otherwise normal liver biopsy. Although the granulomas themselves rarely cause structural liver damage, their detection may be the first indication of an underlying systemic disease. Careful assessment for associated clinical symptoms, targeted laboratory and radiological investigations, and characterization of the morphology and localization of granulomas will usually lead to a definitive diagnosis and appropriate treatment.

CAUSES OF HEPATIC GRANULOMAS

Hepatic granulomas are associated with a wide range of disorders (Table 1). The most common causes in the West are sarcoidosis, drug-induced, tuberculosis, neoplastic disease, and primary biliary cholangitis [formerly primary biliary cirrhosis (PBC)].[2] Infectious causes are summarized in Table 2.

Isolated granulomas may also be an incidental finding on a normal liver biopsy or in patients with known liver disease, such as viral hepatitis, with no relationship to the clinical presentation or response to treatment.[3] Indeed, between 10% and 36% of granulomas are reported to have no discoverable cause after extensive evaluation.[4] Granulomatous hepatitis is a syndrome with a prolonged febrile illness, myalgias, hepatosplenomegaly, and arthralgia of unknown cause.

HISTOPATHOLOGY

Granulomas are circumscribed lesions that form as a result of an inflammatory reaction and are characterized by a central accumulation of macrophages, with a surrounding rim consisting of lymphocytes and fibroblasts (Figure 1). There are four main histological variants of hepatic granulomas, which are summarized in Table 3. Noncaseating granulomas are often seen in sarcoidosis, caseating granulomas in tuberculosis, fibrin-ring variants in infections and vasculitis, and lipogranulomas in the context of ingested mineral oil or hepatic steatosis.[5]

Abbreviations: PBC, primary biliary cirrhosis.

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TABLE 1. CAUSES OF HEPATIC GRANULOMA

Autoimmune Disorders
Sarcoidosis
Cholestatic liver disease, e.g., primary biliary cholangitis
Polymyalgia rheumatica
Vasculitides
Granulomatosis with polyangiitis
Polyarteritis nodosa
Churg-Strauss syndrome
Infections
Bacterial, fungal, viral, parasitic (Table 2)
Drugs
Nitrofurantoin, allopurinol, phenytoin (Table 3)
Allopurinol, Bacillus Calmette-Guérin, carbamazepine, chlorpropamide, diltiazem, gold, halothane, hydralazine, interferon-α, mebendazole, methyldopa, nitrofurantoin, phenylbutazone, phenytoin, procainamide, quinidine, sulfa drugs
Malignancy
Hodgkin's lymphoma and non-Hodgkin's lymphoma
Renal cell carcinoma
Hepatic metastases
Inherited
Chronic granulomatous disease
Chronic Gastrointestinal Disease
Crohn's disease
Postoperative Appearance
Jejunoileal bypass
Metal Toxicity
Copper toxicity
Berylliosis
Ingestion of Foreign Materials
Mineral oil, talc, starch
Toxins
Intravesical administration of Bacillus Calmette-Guérin
Idiopathic

TABLE 2. INFECTIOUS CAUSES OF HEPATIC GRANULOMA

Bacterial
Tuberculosis
Brucellosis
Listeriosis
Mycobacterium avium complex
Disseminated Bacillus Calmette-Guérin infection
Rickettsia (typhus fever and Boutonneuse fever)
Coxiella burnetii (Q fever)
Spirochetal (Lyme disease)
Secondary syphilis
Lepromatous leprosy
Yersiniosis
Psittacosis
Tropheryma whipplei (Whipple disease)
Melioidosis
Tularemia
Catch scratch fever
Viral
Cytomegalovirus
Epstein-Barr virus
Hepatitis A, B and C
Fungal
Histoplasmosis
Coccidioidomycosis
Cryptococcus
Candidiasis
Nocardiosis
Parasitic
Schistosomiasis
Toxoplasmosis
Visceral larva migrans
Visceral leishmaniasis

The morphology and location of granulomas can help with a differential diagnosis. Important morphological features include the presence or absence of necrosis, the nature of the infiltrate and surrounding biopsy specimen, and the presence of organisms or foreign material, for example, schistosome eggs or fungal organisms.[6] Although granulomas can be located throughout the hepatic lobule, most occur in the parenchyma. Certain locations are associated with specific disease processes, such as portal granulomas in PBC.

Special stains for microorganisms (acid-fast and fungal staining) and polarizing light microscopy (foreign body talc granulomas) are also invaluable.[7] However, it may be difficult, if not impossible, to determine the significance and cause, based on histology alone.

CLINICAL FEATURES AND INVESTIGATIONS

The observation of granulomata in a liver biopsy specimen warrants thorough workup to identify a possible cause. Clues may be obtained from the medical history,

physical examination, specific blood tests, or radiological studies (Table 4).

Granulomas themselves are typically asymptomatic. Clinical features reflect the underlying systemic disease and its severity. Constitutional symptoms such as fever, night sweats, and weight loss are the most common, especially in tuberculosis, sarcoidosis, and infectious causes. Hepatosplenomegaly may be present in schistosomiasis.[8] Progressive hepatic fibrosis with portal hypertension and cirrhosis is infrequent and is associated with extensive sarcoidosis, primary biliary cholangitis, and schistosomiasis.[9]

From a biochemical perspective, the most common abnormalities are elevations in serum alkaline phosphatase and gamma-glutamyltransferase. However, these are nonspecific and rarely helpful in diagnosis.[10] Hepatocellular dysfunction may also occur when part of a broader inflammatory reaction, for example, a drug reaction. Imaging including plain radiographs, ultrasound, computed tomography, and magnetic resonance imaging may show calcification in chronic granulomas, lymphadenopathy in sarcoidosis (hilar) or lymphoma (generalized), or filling defects, particularly with confluent lesions, but are generally nondiagnostic.[11]

Other tests such as blood cultures, viral serology, skin tests, and tissue specimens from multiple sites are often needed to guide diagnosis (Table 4). Fresh biopsy specimens can be sent for culture, and special stains for acid-fast bacilli, fungi, and other organisms, to increase diagnostic sensitivity for infections in those with constitutional symptoms.

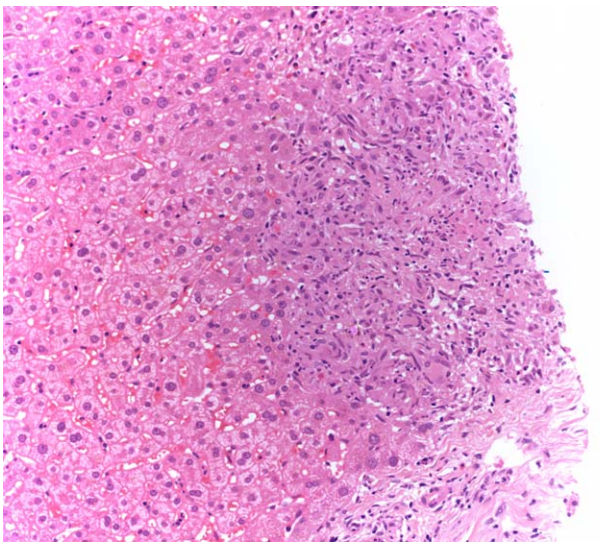

FIG 1 Large, noncaseating granuloma from patient with sarcoid.

TABLE 4. LABORATORY INVESTIGATIONS FOR HEPATIC GRANULOMA

Cause	Investigation
Sarcoidosis and tuberculosis	Chest radiograph
Tuberculosis	Tuberculin skin test
	Acid-fast stains on liver biopsy
Sarcoidosis	Serum angiotensin-converting enzyme
Primary biliary cholangitis	Serum antimitochondrial antibodies and immunoglobulin M
Bacterial, fungal, viral infections	Blood cultures
Fungal	Fungal stains on liver biopsy
Virus	Virology: cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus serology
Parasites	Assess for schistosome eggs
Infection, e.g., *Brucella*, syphilis, *Coxiella*	*Brucella*, syphilis, *Coxiella* serology

TABLE 3. HISTOLOGICAL VARIANTS OF HEPATIC GRANULOMAS

Variant	Description	Causes
1. Noncaseating	Nonnecrotic	Sarcoidosis
2. Caseating	Area of central necrosis	Tuberculosis
		Vasculitis, e.g., GPA
3. Fibrin-ring	Epithelioid cells surround a vacuole within an encircling fibrin ring	Q fever, Hodgkin's lymphoma, Leishmaniasis, cytomegalovirus, hepatitis A, Toxoplasmosis, giant cell arteritis, Q fever, Boutonneuse fever, allopurinol
4. Lipogranulomas	Contain a central lipid vacuole	Ingestion of mineral oil, hepatic steatosis

TREATMENT

Treatment is directed at the underlying disorder. In asymptomatic idiopathic incidental granuloma, treatment is usually withheld and monitoring undertaken with regular clinical assessment and liver function. In patients with symptomatic idiopathic granulomatous hepatitis, immunosuppression with corticosteroids should be considered once tuberculosis has been excluded. Corticosteroids are started with careful evaluation for symptomatic or biochemical response, or both, in the first 3 months.[12] Evaluation of those who do not respond to immunosuppression is important given the differential diagnosis of lymphoma, solid-organ malignancies, and atypical infections.[13]

Because immunosuppression will exacerbate tuberculosis, an empiric course of antituberculous therapy is justified in the presence of fever and other nonspecific symptoms, or if presentation is suggestive of underlying tuberculosis and a specific diagnosis cannot be made.[14] If there is no clinical or radiological response after 1 to 2 months, empiric corticosteroids are considered. In the case of tuberculosis, medications used to treat may themselves be associated with granulomas, such as sulfonamides and isoniazid.

The majority of patients with sarcoidosis are asymptomatic; however, corticosteroids may benefit patients with progressive hepatic sarcoidosis, although whether this prevents hepatic fibrosis is unclear.[15] Ursodeoxycholic acid may be beneficial for pruritus caused by cholestatic jaundice in sarcoidosis and PBC.

Relapse can occur when any treatment is discontinued. Repeat courses of corticosteroids may be required in those responsive to an initial course of immunosuppression. Methotrexate is effective in patients who relapse, are steroid intolerant, or refuse corticosteroid treatment with symptomatic improvement and histological regression in case series.[16]

PROGNOSIS

Hepatic granulomas caused by drugs or infection regress with appropriate treatment. Sarcoid granulomas may disappear spontaneously or persist for years, usually without causing clinically important liver disease. However, progressive fibrosis, portal hypertension, and cirrhosis can rarely develop.[17] In schistosomiasis, progressive portal scarring ''pipestem fibrosis'' is typical; liver function is usually preserved, but marked splenomegaly and variceal hemorrhage can occur.[18]

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