Granulomatous liver disease

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Abstract

Granulomas are circumscribed lesions mainly composed of mononuclear cells that arise in response to poorly degradable antigenic stimuli. They are found in 2-15% of liver biopsies and the meaning of their finding can range from an incidental phenomenon to the manifestation of a systemic disease of infectious, autoimmune or neoplastic origin among other etiologies. The Clinical presentation might lead to the underlying etiology; however, the list of associated conditions is extensive, and differs according to the patient epidemiological history and baseline characteristics. The most useful element for their study is a thorough medical history, with an emphasis on recent trips, exposures and consumption of drugs or raw or exotic foods. A detailed histopathological analysis may help identify the etiology. For example, the presence of epithelioid granulomas with caseous necrosis might indicate tuberculosis and, its absence, sarcoidosis; eosinophil abundance can be associated with drug reactions or parasitic infections; and the presence of foreign bodies can be the cause of granulomatous liver disease (GLD). In this article, we describe the basic clinical-pathological aspects of GLD, and provide a brief summary of the most common etiologies, with an emphasis on the Latin-American region.

KEY WORDS: Granulomatous liver disease. Hepatic granuloma. Hepatic granulomatosis.

Introduction

Hepatic granulomas (HG) are circumscribed lesions mainly composed of mononuclear cells that arise in response to poorly degradable antigens.¹ They are present in 2 to 15 % of liver biopsies, their detection can represent an incidental finding of limited clinical relevance, a manifestation of an established systemic disease, or the finding that will lead to its diagnosis.² Consequently, their discovery in the appropriate clinical context should drive the physician to the search of the underlying cause.³

Pathophysiology

Granulomas are mainly composed of macrophages and T cells. The immune phenotype that triggers them and their histological appearance differ according to

their etiology and to the host immune status.^{1,4,5} For example, exposure to weakly antigenic agents results in the formation of persistent low-turnover granulomas (e.g., sutures), also called foreign-body granulomas (Figure 1). On the other hand, exposure to highly antigenic stimuli (e.g., *Mycobacterium tuberculosis*) results in additional activation of adaptive immune responses and in the formation of more complex granulomas (immune granulomas) (Figure 2).^{1,6} Both, the innate and adaptive immune systems, are involved in their formation and maintenance.⁷ In the case of *Mycobacterium tuberculosis*, its recognition through various macrophage receptors (e.g., complement receptor 4), among others, allows the T-helper cells activation into Th1, Th2, Th17 or regulatory T cells, as well as recruitment of other inflammatory cells (macrophages, neutrophils, B-cells). This results in the formation of the granuloma structure: a center composed

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of macrophages interspersed with neutrophils, surrounded by a ring of B and T lymphocytes.⁸ The balance in the synthesis of various cytokines with pro- (IFN- γ , TNF- α , IL-12) and anti-inflammatory activity (IL-4 and IL-10) in this structure, along with other determinants, defines the characteristics and outcomes of the granuloma.^{9,10} Classically, the predominance of some of these immune phenotypes has been linked to specific etiologies: Th1 with tuberculosis and sarcoidosis and Th2 with parasitic infections such as schistosomiasis.¹¹

Histopathology

Some morphological components may help in the identification of granulomatous liver disease (GLD) etiology, such as its localization within the parenchyma (e.g., portal in primary biliary cholangitis or periportal in sarcoidosis), the type of granuloma, or the presence of some particular components (eosinophils in drug reactions or parasitic infections or foreign bodies such as barium, sutures, talc).^{2,7} However, it is important to emphasize that most these findings are not specific of any cause.^{2,7,12} In broad terms, the following morphological HG classes have been described:⁶⁻¹²

- *Epithelioid granulomas*. These are epithelioid cells whose function is substantially secretory.⁶ Epithelioid granulomas are characterized by well delimited borders of liver parenchyma. They can be associated with several types of necrosis (e.g. caseous), more frequent in granulomas of infectious etiologies, mainly tuberculosis, but also histoplasmosis, candidiasis, among other (Figure 2). They are also found in pathologies such as sarcoidosis or primary biliary cholangitis, with necrosis usually being absent (Figure 1).^{2,6}
- *Suppurative granulomas (granulomas with central micro-abscesses)*. These granulomas are composed of a central abscess surrounded by a ring of epithelioid cells or foam cells. They have been associated with fungal infections (e.g., histoplasmosis, candidiasis), actinomycosis and *Nocardia* spp. infections.⁶
- *Microgranulomas*. Composed of three to seven macrophages mixed with apoptotic hepatocytes and other inflammatory cells.⁶ It is a highly unspecific pattern that can arise in the presence of any chronic liver inflammatory disease, for example, due to adverse drug reactions (beta-lactams, sulfonamides, diazepam, allopurinol, diclofenac).^{6,12,13}

Figure 1. **A)** Epithelioid granuloma without necrosis in lobular location in a patient with primary biliary cholangitis (400x). **B)** Macrophage foam cell lobules in a patient with primary sclerosing cholangitis (400x). **C)** Granulomatous hepatitis with foreign-body-type multinucleated giant cells after surgical procedure (100x). **D)** Granulomatous hepatitis in sarcoidosis; granulomas are small, confluent and without caseous necrosis (100x). The staining employed was hematoxylin-eosin.

Figure 2. **A)** Hepatic granuloma with central caseous necrosis (hematoxylin-eosin 40x). **B)** Hepatic granuloma where macrophages with palisade formation around the caseous necrosis are identified (hematoxylin-eosin 100x). **C)** Ziehl-Neelsen staining was positive for mycobacteria. **D)** Ziehl-Neelsen staining and immunohistochemistry for *Mycobacterium tuberculosis* (1000x).

- *Macrophage foam cell aggregates*. Integrated by foam cells with a poor additional inflammatory response.⁶ These aggregates are especially observed in infectious diseases in immunocompromised patients (human immunodeficiency virus [HIV] carriers). Examples include infections with the *Mycobacterium avium* complex, lepromatous leprosy, histoplasmosis and leishmaniasis (Figure 3).¹²
- *Fibrin ring granulomas*. Their distinguishing features are a central lipid vacuole and a peripheral fibrin ring (Figure 4). They have been mainly described with Q fever; however, there are reports

Figure 3. **A)** Granulomas with macrophage foam cells on the liver parenchyma (hematoxylin-eosin 40x). **B)** Granulomas with macrophage foam cells and abundant mycobacteria (Ziehl-Neelsen 40x). **C)** Macrophage foam cells with abundant mycobacteria (periodic acid Schiff 400x). **D)** Positive immunohistochemistry in mycobacteria within macrophage foam cells (400x).

Figure 4. Fibrin ring granuloma in a patient with Q fever (hematoxylin-eosin 100x).

with various etiologies (cytomegalovirus, leishmaniasis, hepatitis A and C virus [HCV], toxoplasmosis, giant-cell arteritis, allopurinol, lymphomas).^{2,6}

- **Lipogranulomas.** They contain one or multiple central lipid vacuoles surrounded by histiocytes and macrophages.⁶ They are usually found in zone 3, frequently associated with steatosis, mineral oil ingestion or with HCV infection.^{2,6,12,14}

Clinical presentation

HGs are usually indolent; however, between 70 and 80 % of patients exhibit some symptoms secondary to the underlying pathology.^{15,16} Consequently, clinical

characteristics according to the epidemiology their clinical characteristics differ according to the local epidemiology.^{16,17} In studies conducted in developing countries, where the most common cause is tuberculosis, patients often present with fever, weight loss, and fatigue.^{16,18} Conversely, in developed countries, symptoms such as itching and fatigue might be more common due to a higher prevalence of primary biliary cholangitis and sarcoidosis.⁷ Occasionally, GLD *per se* can cause abdominal pain, hepatomegaly, portal hypertension or cholestasis.¹⁶

Up to 63 % of GLD cases may exhibit abnormal liver function tests such as hyperphosphatasia, hyperbilirubinemia and hypertransaminasemia.^{15,16} In patients with sarcoidosis, primary biliary cholangitis and tuberculosis, hyperphosphatasia have predominantly been described. On the other hand, in pathologies associated with less damage of the biliary canaliculi (e.g. HCV) hypertransaminasemia may be more frequently observed.^{2,7,17} Imaging studies can be useful; hepatomegaly or nodular lesions secondary to the presence of HG can be identified.^{2,17}

Differential diagnosis

The list of pathologies associated with GLD is extensive, and the differential diagnosis differs according to the local epidemiology, patient characteristics and history of exposures (Table 1).³ The combination of the clinical presentation features, paraclinical test results and histopathological findings is the best approach for the etiology to be identified. A thorough interrogation and a detailed physical examination are required (with an emphasis on finding out recent trips, risk exposures, drug intake or consumption of raw or exotic foods) and a detailed physical examination (Algorithm 1). Paraclinical tests should be reasonably requested based on clinical judgment. If after this the potential etiology is not evident, an effective strategy might be to search for the most common causes within the studied population.¹⁵ The most commonly reported etiologies in developed countries are sarcoidosis, autoimmune diseases, tuberculosis and idiopathic GLD.^{3,15,19-23} Conversely, the frequency of autoimmune diseases is lower in developing countries (e.g. Saudi Arabia, Iran, India and Turkey), where the main causes are infectious diseases (tuberculosis and schistosomiasis).^{6,16,18,24-26}

In Mexico and in the rest of Latin America, given the absence of GLD epidemiological data, an optional initial approach in patients whose clinical

Table 1. Etiologies associated with granulomatous liver disease

Infectious	Mycobacteria <i>Mycobacterium tuberculosis</i>	<i>Mycobacterium bovis</i>	<i>Mycobacterium avium-intracellulare</i>	<i>Mycobacterium leprae</i>
	Bacteria <i>Brucella</i> spp. <i>Actinomyces</i> spp. <i>Bartonella henselae</i>	<i>Salmonella</i> spp. <i>Coxiella burnetii</i> <i>Rhodococcus equi</i>	<i>Treponema pallidum</i> <i>Rickettsia</i> spp. <i>Francisella tularensis</i>	<i>Chlamydia</i> spp. <i>Listeria monocytogenes</i>
	Parasites <i>Schistosoma</i> spp <i>Strongyloides stercoralis</i> <i>Toxoplasma gondi</i>	<i>Equinococcus</i> spp. <i>Giardia lamblia</i>	<i>Enterobius vermicularis</i> <i>Leishmania</i> sp.	<i>Fasciola hepatica</i> <i>Entamoeba</i> spp.
	Viral Hepatitis B, C	Epstein-Barr Virus		Cytomegalovirus
	Fungal <i>Histoplasma capsulatum</i> <i>Candida</i> spp. <i>Mucor</i> spp.	<i>Coccidioides</i> spp. <i>Cryptococcus</i> spp.	<i>Paracoccidioides brasiliensis</i> <i>Aspergillus</i> spp.	<i>Blastomyces dermatitidis</i> <i>Pneumocystis jiroveci</i>
Autoimmunity	Primary biliary cholangitis	Systemic vasculitis	Systemic lupus erythematosus	
Foreign bodies	Mineral oil	Starch	Silicon	
Neoplasms	Hodgkin's lymphoma	Non-Hodgkin lymphoma		
Other causes	Sarcoidosis	Drug reactions		

presentation is not suggestive of a specific etiology might include a chest X-ray, liver cultures in special media for bacteria, mycobacteria and fungi and a detailed histopathological analysis with the use of special stains (e.g., Fite Faraco, Ziehl-Neelsen, periodic acid Schiff, Grocott, Giemsa). Useful supplementary tests include some serologies (hepatitis B virus, HCV, HIV, syphilis, Q fever, *Brucella* spp, and anti-mitochondrial antibodies), cutaneous tuberculin test, functional interferon gamma release assays and molecular tests such as PCR for the detection of *Mycobacterium tuberculosis*.^{2,15}

Etiology

Despite an exhaustive approach, up to 50 % of cases may remain without an etiological diagnosis (idiopathic GLD);^{7,15} 15 % of these patients may develop symptoms during follow-up, which forces clinical surveillance for sufficient time (12 to 24 months). An important proportion of patients with idiopathic GLD can remain asymptomatic and have a good long-term prognosis.^{3,15,19,21} However, there are case reports of persistent febrile syndromes associated with idiopathic GLD where favorable responses have been documented with glucocorticoids or methotrexate.²⁷ Below, a brief description of their main etiologies is presented.

Autoimmune diseases

PRIMARY BILIARY CHOLANGITIS

Primary biliary cholangitis is an autoimmune liver condition that predominantly affects middle-aged women. It induces the destruction of intrahepatic bile ducts and progressive hepatic fibrosis.²⁸ It is the most common cause of GLD in some countries (Germany, Greece, Ireland, Scotland and Italy) and the second in the United States, responsible for 20 to 68 % and 22 % of cases, respectively.^{3,19} Data in Latin America are restricted to case series.²⁹ It manifests as a cholestatic syndrome with no extrahepatic bile duct obstruction. Its diagnosis requires two of the following three criteria: positive anti-mitochondria antibodies, hyperphosphatasia or histological evidence of primary biliary cholangitis (non-suppurative destructive cholangitis and interlobular bile duct destruction). Its characteristic histopathological image is a florid bile duct lesion (degeneration of the biliary ductal epithelium with focal ductal obliteration and formation of granulomas with predominant portal distribution).^{2,7,30} Currently, the only approved therapy is ursodeoxycholic acid.²⁸

Infectious diseases

Infectious diseases are responsible for 55 to 75 % of cases of GLD in Saudi Arabia, Iran and India.^{16,18,26}

GLD can be the result of a primary liver condition or systemic disease. The most common causes are tuberculosis, some zoonoses (e.g. Q fever, brucellosis), opportunistic infections in HIV-carrier patients (e.g., *Mycobacterium avium*), disseminated fungal infections (e.g., histoplasmosis) and HCV infection.¹² Infectious etiology-characteristic liver granulomas are granulomas with associated necrosis and, therefore, this finding should drive the clinician to the search of an infectious etiology.³¹

TUBERCULOSIS

Tuberculosis is the most common infectious cause of GLD in India (55 %), Saudi Arabia (42.6 %) and Iran (51.4 %).^{16,18,26} In Latin America, there are no data on the prevalence of tuberculosis in GLD; however, the incidence of tuberculosis in this geographical region was reported at 27 cases per 100,000 population in 2017.³² It is usually the result of hematogenous dissemination after acquisition by the pulmonary or gastrointestinal route (50 to 80 %) Compromise limited to the liver is an uncommon manifestation of infection, in which case *Mycobacterium bovis* should be suspected due to its greater involvement in extra-pulmonary sites.^{12,31,33,34} Clinical presentation is dominated by symptoms of extrahepatic compromise, and liver involvement by itself has been associated with nonspecific abdominal pain or pain in the upper right quadrant (65 to 87 % of cases).³³ There are case reports of presentation as acute cholecystitis or cholestatic syndrome.^{33,35} Imaging studies can show hepatomegaly, abscesses, solid focal lesions that resemble liver tumors and even stenosis of the bile ducts.³⁶

Characteristic histopathological findings include multiple foci of epithelioid granulomas with central caseation and fibrinoid necrosis of predominantly peri-portal distribution; however, the absence of necrosis does not rule out this etiology.^{12,33} Granulomas can merge and form tuberculomas, nodules with a diameter of 1 to 4 cm, which in turn may show characteristic calcifications.³³ The diagnosis of liver tuberculosis is based on the demonstration of acid-alcohol-resistant bacilli in smears, cultures or by PCR (sensitivity and specificity of 88 % and 100 %, respectively).^{33,37,38} The treatment of liver tuberculosis does not differ from that required for any extrapulmonary condition associated with tuberculosis.^{33,39}

OPPORTUNISTIC INFECTIONS IN PATIENTS WHO ARE HIV CARRIERS

Opportunistic infections in patients who are HIV carriers show regional variation and differ according to the degree of immune dysfunction. At the beginning of the pandemic, Mexican series reported that most part of opportunistic infections were secondary to *Candida* spp, *Pneumocystis jirovecii*, *Cryptosporidium* spp., *Mycobacterium tuberculosis*, cytomegalovirus, *Histoplasma* spp. and *Mycobacterium avium*.⁴⁰ However, since the advent of antiretroviral therapy (ART), an important reduction in their incidence has been observed. GLD etiologies in these patients have also experienced this epidemiological transition.⁴¹

In a study carried out in the United States in the pre-ART era, the most common causes of liver disease were found to be associated with *Mycobacterium avium/Mycobacterium avium intracellulare* (17.6 %), chronic viral hepatitis (12 %) and tuberculosis (2.6 %).⁴² In Mexico, a 29 % prevalence of GLD was found in liver biopsies. The most common etiologies for liver conditions were *Mycobacterium tuberculosis* (26.6 %), *Histoplasma capsulatum* (20 %), cytomegalovirus (13.3 %) and *Mycobacterium avium/Mycobacterium avium intracellulare* (11 %). However, in the analysis restricted to GLD cases, the most common etiology was *Mycobacterium avium/Mycobacterium avium intracellulare*.⁴³

Regarding the post-ART era, the main causes of liver disease are HCV/HIV, hepatitis B/HIV coinfections and ART-related hepatotoxicity.^{41,44} Given that late diagnosis and ART initiation are still common scenarios in Latin America, the presence of GLD cases is expected to have characteristics of both epidemiological eras (pre and post-ART).⁴⁵ Therefore, assessment of patient immune dysfunction status is paramount when establishing the potential causes of GLD.

ZOONOSIS

Two examples of zoonosis that have been associated with GLD are Q fever and brucellosis, both present in Mexico and other regions of Latin America such as Argentina, Brazil, Colombia, Costa Rica and Ecuador.⁴⁶⁻⁵¹ Q fever is a disease caused by *Coxiella burnetii* (intracellular bacteria); the main risk factor is exposure to farm animals (bovine, ovine or caprine livestock),

through inhalation of stool or urine-contaminated soil aerosols or placentas of infected animals. Frequently, the diagnosis is made in patients without a history of direct contact with this type of animals; it is believed that this may be due to the viability of *Coxiella burnetii* spores and their ability to travel long distances through the wind.⁵² The characteristic granulomas of this disease are those with a fibrin ring (Figure 4).^{12,52} Clinically, it manifests by self-limited episodes of fever, headache, pneumonia and hepatitis, with the development of chronic symptoms in less than 5 % of cases (e.g., infective endocarditis, osteomyelitis, hepatitis). Its diagnosis is based on blood PCR and serology, while the treatment of choice is doxycycline.⁵³

Brucellosis is a granulomatous disease caused by *Brucella* spp.; its route of acquisition is through direct contact with livestock (mainly bovine, caprine or porcine) or by consumption of unpasteurized dairy products.⁵⁴ Brucellosis can affect any organ; clinical presentation varies from an unspecific acute feverish condition (e.g., fever, headache, poly-arthralgia, adenopathies, hepatosplenomegaly) to a predominantly osteoarticular and neuropsychiatric chronic condition.⁵⁴ Liver involvement can occur in up to 50 % of cases; histopathological findings include non-caseating epithelioid granulomas or microgranulomas.⁵⁵ This etiology should be considered in patients with fever with no other evident cause; its diagnosis is established through its isolation in cultures, PCR or serology.^{12,54}

FUNGAL INFECTIONS

Fungal infections are mainly observed as disseminated infections in immunocompromised patients (e.g., neutropenia). Hepatosplenic candidiasis, invasive aspergillosis, cryptococcosis, and some endemic mycoses (histoplasmosis, coccidioidomycosis, paracoccidioidomycosis and blastomycosis) stand out.^{2,56-60} Coccidioidomycosis is highly prevalent in dry regions with elevated temperatures. *Coccidioides immitis* has been predominantly described in the San Joaquin Valley (California) and *Coccidioides posadasii* in Arizona, Texas, Mexico, Central America (Guatemala and Honduras) and South America (Argentina, Colombia, Paraguay and Venezuela).⁶¹ Its most common clinical presentation is lung involvement and in some cases dissemination can be observed.⁶²

Histoplasmosis is the most common endemic mycosis in Central America, also present in Argentina, Brazil, Colombia, Ecuador, Uruguay and Venezuela.⁶¹ Its route of entrance is respiratory, and associated

hepatic granulomas are characterized by lymphohistiocytic infiltrates with Kupffer cell sinusoidal hyperplasia, accompanied by small yeasts (3 to 4 µm in diameter), which are ovoid-shaped, single or in budding, narrow based, detectable by PAS staining.^{12,63-65} Useful diagnostic elements due to their specificity and high negative predictive value in disseminated forms are PCR in blood or tissue and detection of its antigens in urine; the ultimate diagnosis is by its isolation.⁶⁶

HCV infection and hepatitis B have been associated with GLD in the absence of other attributable causes.⁶⁷⁻⁶⁹ In patients with HCV chronic infection undergoing liver biopsy, a prevalence of 1.3 % has been reported, mainly in patients with a history of treatment with interferon.^{67,70} Due to the availability of new non-invasive techniques for fibrosis staging in these patients, as well as to the advent of more effective antiviral treatments, it is expected that these GLD etiologies will be only sporadically found in the future.⁴⁴

In Latin America, the only reported schistosomiasis etiology is *Schistosoma mansoni* (Brazil, Venezuela, Suriname, Puerto Rico and the Caribbean).⁷¹ Cases in Mexico are usually associated with immigrants.^{72,73} The main associated factor is exposure to water contaminated by snails of the genus *Biomphalaria*. It is the main cause of portal hypertension in the world; the parasites invade the mesenteric veins or the portal vein, where they deposit their eggs, which produce a hypersensitivity reaction that results in fibrosis and hepatobiliary obstructive disease. In chronic phases of the disease, a granulomatous reaction usually appears around the eggs, accompanied by areas of fibrosis with abundant eosinophils.¹²

Neoplasms

There are reports of neoplasms such as Hodgkin's and non-Hodgkin lymphoma and clear renal cell carcinoma, whose initial presentation are non-caseating epithelioid HGs.^{2,21,31,74} In tuberculosis endemic areas, such as Mexico, concurrence of both etiologies has been described; therefore, it is recommended for this concurrence to be sought in this group of patients in countries with high tuberculosis endemicity.⁷⁵

Other etiologies

Sarcoidosis is a disease with low incidence in Latin America,^{76,77} however, it represents one of the main causes of GLD in the United States and in

some regions of Europe.^{2,15,19} The frequency of liver involvement varies from 6 % in population-based studies to up to 70 % in studies of autopsies.^{2,17,78} Clinical manifestations (abdominal pain, hepatomegaly) are rare (25 to 40 %), and the most common form of detection is therefore the discovery of altered liver function (hyperphosphatasia, gamma glutamyl transpeptidase elevation and hypertransaminasemia).¹⁷ In turn, anomalies can be observed on imaging studies in 50 % of patients (e.g., hypodense nodular lesions or hepatomegaly).¹⁷ Characteristic granulomas are non-caseating, epithelioid with predominant peri-portal compromise; however, exclusion of other mainly infectious causes is paramount for its diagnosis.⁷⁹ Liver sarcoidosis rarely progresses to cirrhosis (6 to 24 %), and treatment is therefore reserved for patients with serious compromise.^{17,80}

The list of drugs associated with GLD is wide and comprises more than 60 drugs; some antibiotics stand out (e.g., sulfas, isoniazid, nitrofurantoin, norfloxacin), as well as some anticonvulsants (e.g., phenytoin, carbamazepine), allopurinol and paracetamol.^{2,19} GLD caused by drugs can have an acute or chronic onset and, like other etiologies, it can present an indolent evolution only detected by a pattern of hepatocellular or cholestatic damage.⁸¹ Histopathologically, microgranulomas are often found, and occasionally there may be eosinophil infiltration, which points towards this etiology⁸²; their diagnosis is by exclusion of other causes.

Conclusions

GLD clinical spectrum is broad; their finding can range from an incidental finding with little clinical relevance to the manifestation of a systemic disease. Useful elements for diagnosis include a thorough medical examination, a careful review of the histopathology (with a low threshold for special stainings, and microbiological and molecular tests). In Mexico, more studies on GLD are needed in order to know the spectrum of etiologies.

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Algorithm 1. Study of granulomatous liver disease.