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Review

Liver granulomatosis

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SUMMARY

Granulomas of the liver are circumscribed focal lesions (size from 50 to 300 mm) composed of epithelioid cells, varied numbers of mononuclear cells, multinucleated giant cells and other inflammatory cells. They represent a specialized, cell-mediated immune response to a wide variety of etiological antigenic stimulation, infectious and non-infectious or sequestration of a foreign indigestible, inorganic particle within macrophages. The causes of hepatic granulomas are numerous, and their identification can be difficult. The wide variety of etiologic factors includes primary biliary cirrhosis, sarcoidosis, drugs, hepatitis viruses, Hodgkin and non-Hodgkin lymphomas, tuberculosis, and other miscellaneous causes. Sarcoidosis is the main cause. Idiopathic cryptogenic granulomatous hepatitis is a poorly defined term characterized by a febrile illness with systemic signs and symptoms such as fatigue, sweating, shivering, hepatomegaly and/or splenomegaly, and abnormalities in serum liver tests (aminotransferase, alkaline phosphatase). In granulomatous hepatitis, granulomas are found exclusively in the liver and should not be used as an equivalent term for hepatic granulomas. Hepatic granulomas are typically asymptomatic. Constitutional symptoms such as fever, weight loss, anorexia and night sweats are often manifestations of the underlying disease. The recommended evaluation to establish the underlying cause of hepatic granulomas depends on the patient's clinical status, co-existing diseases and exposure history. Liver biopsy provides diagnosis in approximately 15-30% of cases. In almost one third of cases it is impossible to reach aetiological diagnosis on histological criteria alone.

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1. INTRODUCTION

Granulomas have been broadly defined as focal accumulations, size from 50 to 300 mm, of modified macrophages (epithelioid cells), which fuse to form multinucleated giant cells.[1,2] Those large pale-stained epithelioid cells have a surrounding rim of lymphocytes and fibroblasts. Evidence of caseation and perigranulomatous inflammation may also be present.

2. PATHOLOGY

Pathologically, four types of granulomas can be encountered in the liver. The first is the foreign body granuloma, characterized by inclusions of particulate material, such as droplets of indigestible mineral oil, starch, or silicone, in cytoplasmic vacuoles.[3] The second type of hepatic granuloma is called lipoid granuloma or lipogranuloma[4] where macrophages cluster around a vesicle of triglycerides and can be observed in association with any cause of hepatic steatosis. The third type of granuloma, epitheliod granuloma, is characterized by differentiation of the activated macrophages into secretory cells, which synthesize and secrete large amounts of cytokines. Hyperplasia of the endoplasmic reticulum and the absence of inclusions give an homogeneous appearance to the cytoplasm, making them resemble epithelial cells and giving them their characterization. Occasionally, the plasma membranes of contiguous epithelioid cells fuse, producing syncytia, the so-called giant or Langhans' cells. A small number of lymphocytes are usually mixed with macrophages at the center of the granulomas, but lymphocvtes are more numerous at the periphery. Sinusoidal dilatation is commonly associated with granulomatous involvement of the liver and is attributed to the release of inflammatory cytokines by the cells com-

posing the granuloma.[5] Deposition of fibrin strands can occur within the granuloma or at its periphery and characterizes fibrin-ring granuloma. Although fibrin-ring granulomas have been reported mainly in patients with Q fever, they are not specific for this condition. The fourth type of granuloma, lymphohistiocytic granuloma, is clinically and etiologically similar to epithelioid granuloma but differs in that epithelioid cells are not found **in** the focal accumulation of macrophages and lymphocytes.[6] Most granulomas are found near or in the portal tract, but their location is of little help in identifying the causative agent.

Focal accumulation of macrophages can be induced indirectly by antigenic stimulation of the immune system (an example of a delayed-type hypersensitivity reaction) or directly by sequestration of a foreign undigestible, inorganic particle within macrophages, or by both.[7] Immune system stimulation and sequestration are both involved when the foreign organic agent escapes digestion by the macrophages and persists within, as happens with intracellular pathogens such as listeria, leishmania, or mycobacteria. In several infectious disorders in humans, development of well-defined, well-differentiated granulomas is associated with an optimally controlled infection, but the disseminated form of the same infection is associated with ill-defined and poorly differentiated granulomas.[8] Granulomas are commonly found in the liver and the lungs, naturally rich in specialized macrophages, because these two organs are located near two points of entry for foreign agents: the gastrointestinal tract and airways.[6]

The epithelioid and lymphohistiocytic granulomas are characteristic of the involvement of the immune system. There is evidence that the differentiation of monocytes and histiocytes into epithelioid cells depends on the secretion of interferon gamma and tumor necrosis factor beta bv activated Th1 helper T cells or by natural killer lymphocytes.[9-11] Helper CD4+ positive T cells and natural killer lymphocytes are themselves activated by an antigen-presenting cell-secreting tumor necrosis factor alfa and interleukin-12. The $CD4^+$ cells are found in the central part of the granuloma. At the periphery of the granuloma, macrophages are recruited from the circulating monocytes by chemotactic factors. They are also recruited from the resident macrophages by growth factors released by T cells. The lymphocytes that accumulate at the periphery are mostly $CD8^+$ cytotoxic T cells. Their role could be to destroy the macrophages in which the intracellular pathogen persists and thus limit its proliferation.The turnover of the cells that compose the immune granuloma is very high, as compared with the turnover of the cells that make up foreign-body granulomas. The dynamic structure of the immune granuloma explains the different stages of maturation that can be seen in a single biopsy specimen[6].

3. ETIOLOGY

Epithelioid granulomas have been reported in 2-15% of unselected liver biopsies.[1] They are mostly non-specific and require intensive clinical investigation.

The aetiology of hepatic granulomas is broad[6] (Table 1). They can be classified into five categories: systemic diseases, malignant diseases, infectious agents, chemically induced injury, liver diseases and idiopathic/cryptogenic. According to the results from recent research in the United Kingdom, the underlying causes were as follows: primary biliary cirrhosis (23.8%), sarcoidosis (11.1%), idiopathic (11.1%), HCV (9.5%), drug induced (7.9%), autoimmune hepatitis/primary biliary cirrhosis overlap syndrome (6.3%), Hodgkin lymphoma (6.3%), autoimmune hepatitis (4.8%), tuberculosis (4.8%), biliary obstruction (3.2%), other (including NHL, polymyalgia rheumatica, juveline chronic arthritis, graft versus host disease, jejuno-ileal bypass surgery, intravesical BCG) (9.5%).[12] There are considerable geographic variations in the causes of granulomas.[13-17] For example, a series from Turkey[18] revealed that infectious agents including tuberculosis, hydatid disease, brucella and typhoid fever accounted for the cause of over half of their hepatic granuloma. In series from Saudi Arabia[19] Schistosomiasis accounted for over half of the cases. Up to 10% of granulomas remain unclarified even after an intensive search with special staining.[20]

3.1. Sarcoidosis

Sarcoidosis is a disseminated disease defined by the presence of non-caseous granulomas disease of unknown cause that can involve several organs. Sarcoidosis is the main cause of hepatic granulomas, accounting for 12% to 30% of cases,[21] at least in industrial countries where infectious causes are becoming relatively rare. In most patients with sarcoidosis there are no clinical symptoms indicating a hepatic involvement although hepatic granulomas can be identified in approximately two thirds of patients with sarcoidosis, placing the liver behind only the lung and lymph nodes as the primary sites of involvement.[22] When present, clinical presentation includes weight loss, hepatomegaly and abnormal liver function tests.[23] In some patients, there is fever, itching, splenomegaly and abdominal lymphadenopathy.[24] In a few pa-

Table 1. Causes of hepatic granulomas

1. Systemic Diseases	- Listeriosis	- Larva migrans viscerale
- Sarcoidosis	- Actinomycosis	- Toxocariasis
- Common variable immunodeficiency	- Nocardiosis	- Capillariasis
- Chronic granulomatous disease	- Typhoid fever	- Strongyloidiasis
- Wegener's granulomatosis	- Melioidosis	***Fungi***
- Temporal arteritis/Polymyalgia rheumatica	- Cat-scratch disease	- Blastomycosis
	- Whipple's disease	- Cocddioidomycosis
- Erythema nodosum	- Q fever (Coxiella burnetii)	- Histoplasmosis
- Allergic granulomatosis	- Boutonneuse fever	- Cryptococcosis
- Crohn's disease	- Psittacosis	- Candidiasis
- Ulcerative colitis	- Ehlrichiosis	- Aspergillosis
- Jejuno-ileal bypass surgery	***Viruses***	- Mucormycosis
- Systemic lupus erythematosus	- Epstein-Barr virus	**4. Chemicals**
2. Malignant diseases	- Cytomegalovirus	- Beryllium
- Hodgkin's disease	- Coxsackieviruses	- Throrotrast
- Non-Hodgkin's lymphomas	- AIDS	- Copper sulfate
- Carcinoma	- Hepatitis viruses A, C	- Talc and foreign bodies
3. Infections	- Influenza	- Mineral oil
- Tuberculosis, Atypical mycobacteria, Bacillus Calmette Guerin	***Protozoa***	- Hypersensitivity drug reactions
	- Leishmaniasis	**5. Liver Diseases**
- Leprosy	- Toxoplasmosis	- Primary biliary cirrhosis
- Syphilis	- Amebiasis	- Primary sclerosing cholangitis
- Lyme disease	- Malaria	- Extrahepatic biliary obstruction
- Brucellosis	***Metazoa***	- Hypersensitivity cholangitis
- Tularemia	- Schistosomiasis	- Steatosis
- Yersiniosis	- Fascioliasis	**6. Idiopathic/Cryptogenic**

tients, chronic intrahepatic cholestasis, portal hypertension and hepatic failure can complicate the course of the disease.

The number of hepatic granulomas varies considerably from patient to patient. Granulomas predominate around portal tracts but are also present in lobular areas. Old granulomas can present as a dense hyalinized scar. The granulomas are usually at the same stage of development. True caseation necrosis does not occur[25] (Figure 1). Development of hepatic granulomas, especially those located within portal tracts, is associated with injury to septal and interlobular bile ducts, leads to cholestasis, and eventually results in ductopenia and fibrosis mimicking primary biliary cirrhosis.[26] In the portal tracts lacking bile ducts, active or healed granulomas are conspicuous. Other causes of cholestasis are sarcoidosis of the interlobular or/and extrahepatic bile ducts, compression of the common bile duct by enlarged perihilar lymph nodes or/and by sarcoidosis of the pancreas, associated primary biliary cirrhosis or primary sclerosing cholangitis.[6]

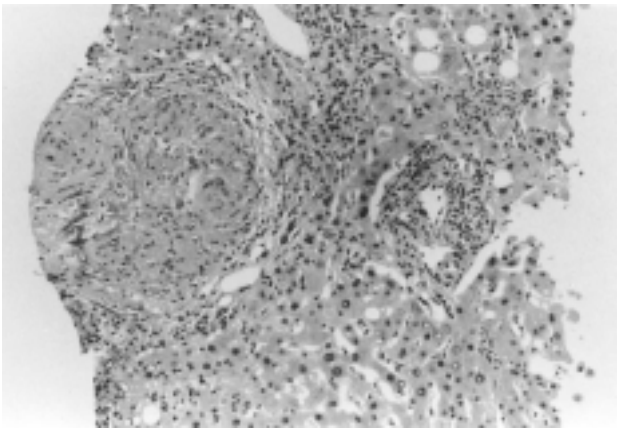

Figure 1. Hepatic granuloma (courtesy of Dr K. Petraki, Histopathologist).

Chronic intrahepatic cholestasis is seen mainly in black Americans and Jamaicans.[27-29] At an early stage, jaundice and histologic features of cholestasis can be absent. The clinical syndrome consists of jaundice and pruritus with liver and spleen enlargement. Marked constitutional symptoms are usually present. Other complications of chronic cholestasis, such as osteomalacia, and skin xanthelasmas and/or xanthomas can occur. Serum alkaline phosphatase and gamma-glutamyl transpeptidase activities are very high. At a later stage, biliary cirrhosis with portal hypertension and ascites can develop. Antimitochondrial antibodies are negative distinguishing sarcoidosis from primary biliary cirrhosis. The course of the disease can be protracted, lasting 10 to 20 years before the end-stage of liver disease is reached.

The diagnosis is frequently difficult based on medical history, laboratory tests and histology[30] Diagnosis of sarcoidosis should be made by first excluding the other causes of hepatic granulomas and then by documenting extrahepatic involvement. In approximately 75% of cases, skin, lymph node, or bronchial tree biopsy is positive. In 15% of cases there is highly suggestive evidence of extrahepatic involvement at a site that cannot be biopsied (e.g., interstitial lung disease, uveitis, or central nervous system involvement). In the few remaining cases, diagnosis is suggested by other, less specific features (e.g., hypercalcemia or serum angiotensin-converting enzyme activity).[6]

Chest radiography reveals paratracheal or hilar lymph node enlargement. Nevertheless, hepatic involvement can be found in association with or without an abnormal chest radiographs.[31]

Liver enlargement is demonstrated in 30% to 50% of the patients by ultrasound (US) scan or computerized tomography (CT) scan,[32] but marked liver enlargement is seen in less than 10% of patients. Abdominal lymph node enlargement is seen in 30% of patients and is better demonstrated by CT scan than by US scan. Echogenicity of the liver is normal in about 50% of patients, is homogeneously increased in 25%, and is heterogeneously increased in 25%. Among patients with heterogeneously increased echogenicity, a few have discretely hypoechoic nodules or nodular contour suggestive of cirrhosis. Scattered calcifications can be seen. CT scan reveals the appearance of multiple small low-attenuation areas in the liver. The appearance on CT scan is usually that of a homogeneous liver, but discrete hepatic nodules can be demonstrated in 5% of patients. These nodules range from 1 to 15 mm in diameter, are diffusely distributed, and have a low attenuation and no enhancement after contrast agent injection.[33] Nodular sarcoidosis of the liver is usually associated with splenic nodules and abdominal lymph node enlargement (Figure 2).[34] There is no relationship between the presence of nodules and the liver or spleen size. In rare cases, nodules may coalesce in the liver and form tumors as large as 40 mm in diameter[35] The nodules detected by CT scan can be further characterized by MR imaging as hypointense lesions, on Tl- and T2-weighted sequences, without enhancement after gadolinium injection. These characteristics allow the nodules to be distinguished from metastases but not from regenerative cirrhotic nodules or from abscesses.

Portal hypertension is uncommon in patients with sarcoidosis. The mechanisms for portal hypertension in patients with sarcoidosis have been attributed to hepatic granulomas (presinusoidal or/and sinusoidal block), to biliary cirrhosis secondary to the destruction of interlobular bile ducts, to compression of the portal vein by enlarged perihilar lymph nodes, to hepatic granulomatous venulitis, to associated primary biliary cirrhosis, or primary sclerosing cholangitis and to thrombosis of the hepatic veins or of the portal vein.[6] The prevalence of increased portal pressure in sarcoidosis of the liver is not known. In approximately 100 patients reported in the literature, portal hypertension has been documented by the presence of esophageal varices or by the results of hemodynamic investigations.[106] Young black patients of either gender and white women older than 40 years of age are usually affected. Generally, there are marked constitutional symptoms, extrahepatic symptoms precede recognition of liver disease in 25% of cases, and, infrequently, thoracic disease. In some patients, the course of sarcoidosis toward terminal hepatic failure mimics that

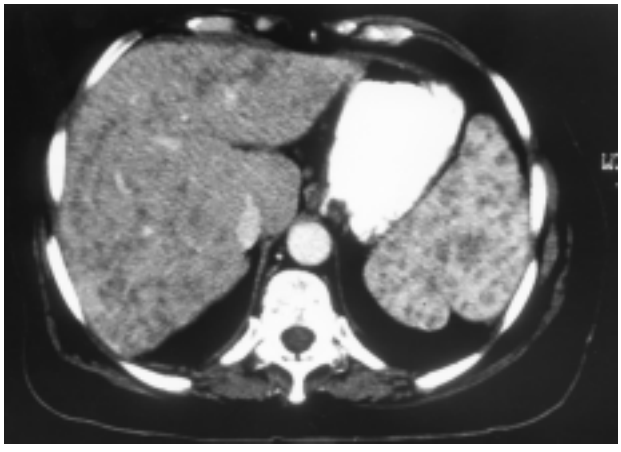

Figure 2. Focal lesions in the liver and spleen in a patient with sarcoidosis.

of active cirrrhosis.

Thrombosis of the hepatic veins is rare in sarcoidosis.[36] Thrombosis has been attributed to the compression of hepatic vein radicles by granulomas. There is a rare condition of granulomatous phlebitis of small hepatic veins with the clinical manifestations of Budd-Chiari syndrome (idiopathic granulomatous venulitis).[37,38] Involvement of the small vessels is a well-known feature of sarcoidosis of lymph nodes or lungs. Treatment with corticosteroids can be successful.[39]

Portal vein thrombosis and isolated granulomatous portal venulitis have been described in association with hepatic sarcoidosis.[40]

There are several reports of hepatic sarcoidosis appearing on the grounds of chronic hepatitis C virus (HCV) infection treated with interferon-alpha (IFN-a).[41] or non-treated, which are attributed to the stimulation of the cellular immune system.[42]

Sarcoidosis can be associated with primary biliary cirrhosis (PBC).[43,44] in less than 1%. Sarcoidosis can precede or follow PBC by several years. The distinction between cholestasis caused by sarcoidosis or PBC is based mainly on the absence of antimitochondrial antibodies in the former.

More rarelly, association of sarcoidosis with primary sclerosing cholangitis has been reported.[45] Sarcoidosis can manifest either before or after the clinical onset of primary sclerosing cholangitis. Sarcoidosis has been described in patients with ulcerative colitis and in patients with Crohn's disease in the absence of primary sclerosing cholangitis.

A systematic study of the effects of corticosteroids on the course and manifestations of uncomplicated hepatic sarcoidosis in a large series of patients is not available. With corticosteroid therapy, constitutional svmptoms are alleviated, liver enlargement regresses, and serum alkaline phosphatase activity decreases. Several patients, although treated at an early stage, later developed chronic intrahepatic cholestasis or portal hypertension Once the clinical features of cholestasis have developed, corticosteroid administration does not stop or slow the progression of the disease and secondary biliary cirrhosis develops. Therefore, liver involvement is not currently considered an indication for treatment with corticosteroids. In chronic intrahepatic cholestasis, the administration of ursodiol (caps Ursdofalkβ 250 mg, 15mg/kg) can be considered. In patients with portal hypertension, without liver failure, recurrent gastrointestinal bleeding can be treated by endoscopic sderotherapy or ligation of esophageal varices. or can be prevented by the long-term administration of propranolol.[46]

Liver transplantation at the terminal stage of chronic intrahepatic cholestasis has been attempted.[47] In a few patients, however, sarcoidosis recurs afterwards.[48] The recurrence can affect lymph nodes, simulating lymphoma or mycobacterial infections, which are common in immunosuppressed patients.

3.2. Wegener's granulomatosis

The classic histopathology in Wegener's granulomatosis is necrotizing granulomatous vasculitis involving small arteries and veins. The clinical manifestation of the disease includes symptoms from the gastrointestinal tract in 15-30% of reported cases.

3.3. Liver Diseases

Primary Biliary Cirrhosis is characterized by granulomatous destruction of septal or interlobular bile ducts.[49] There is an inverse relationship between the stage of the disease and the number of granulomas. Granulomas are absent at the stage of cirrhosis. As pointed out previously, lesions indistinguishable from those of primary biliary cirrhosis can be found in some patients with sarcoidosis.

A study in 2003 revealed that 23.8% of unselected liver biopsies in 1662 patients with liver granulomatosis recognized PBC as the positive underlying etiology. Also PBC may be underestimated because in multiple centers female patients with cholestatic liver profile and positive AMA are not routinely submitted for a liver biopsy.

Granulomas have been encountered in 7% of the patients with **primary sclerosing cholangitis**.[50] Extrahepatic bile duct obstruction can also cause granulomas. It has been documented in the past that hepatic granulomatosis is associated with inflammatory bowel disease and is particularly prevalent in patients with Crohn's disease.[51]

Lipoid granulomas can be encountered in **steatosis**.

Granulomas were reported with a higher-than-expected frequency in patients with **hepatitis C**.[52,53] A cause of granulomas was identified in one half the cases; in the other half, granulomas might have been related to hepatitis C itself.[54] In that survey patient with hepatic granulomas had negative results to tuberculin skin test, Venereal Disease Research Laboratory (VDRL), chest X-ray, computed tomography, and Brucella agglutination tests.

The presence of granuloma seems to predict a favourable response to interferon treatment.

A role for **IFN-a** therapy of hepatitis C in the development of hepatic granulomas has also been suggested though that doesn't seem to be a very common case.[55,56]

Finally an unusual case report of an inflammatory mediated granulomatous reaction in a patient with hepatitis A is documented in the literature.[57]

After **liver transplantation**, granulomas can be found in 5% to 10% of the patients, mostly during the first year. Approximately 30% of these granulomas are of unknown origin and are clinically insignificant. The others are related to recurrent PBC, acute cellular rejection, or infection (e.g., tuberculosis or cytomegalovirus).[58]

3.4 Hodgkin's and non-Hodgkin's lymphoma

It has long been recognized that Hodgkin's disease emerges as a possible cause for the development of liver granulomas. Hepatic granulomas can be found in 5% to 25% of patients with Hodgkin's disease.[59-62] When these granulomas are not associated with Reed-Stemberg cells or atypical mononuclear cells, they have an uncertain significance but no particular prognostic value. They do not indicate hepatic involvement. Hepatic granulomatosis does not seem to affect the outcome or the prognosis of the preexisting Hodgkin disease.

Finally, there are demonstrated cases of hepatic granulomas associated with non Hodgkin lymphoma[63,64] and chemotherapy for acute myeloid leukemia.[65]

3.5 Drug reactions

A variety of therapeutic drugs have been identified as possible causes of hepatotoxity. Individual characteristics, particularly with regard to drug metabolism and immune responses determine the patterns of hepatotoxity. Therapeutic agents are responsible for up to one third of cases of granulomatous hepatitis. Drug-induced granulomas are accompanied by systemic features of hypersensitivity such as fever, anorexia, malaise, rash and eosinophilia indicating a possible immunoallergic mechanism. Most commonly, the clinical manifestation includes mild liver enzyme elevations which refer to a self-limited liver injury.[66] The diagnosis is based on the liver biopsy findings, a reasonable temporal association, and exclusion of other causes of liver dysfunction. Histologically, they are typical non caseating granulomas and another biopsy can reveal granulomas in extra-hepatic places.

Numerous therapeutic agents have been associated with liver granulomatosis, although a cholestatic or viral hepatitis–like hypesensitivity reactions appears to be the classic features Table 2).[67-70] Drug-induced cholangitis can be associated with granulomas, mimicking PBC.[71]

3.6 Beryllium disease

Beryllium disease is an occupational disease mainly affecting the lungs, resulting in the formation of typical non-caseating granulomas also in the liver. It can result from the exposure to beryllium in the aerospace, nuclear, military, automotive, electronics, telecommunication industries, and in alloy applications, such as tubing for oil and gas drilling, tools and dies, jewellery, bicycle frames, and dental appliances. Although the US atomic energy commission has established permissible exposure limits, many studies indicate that even smaller amounts of cumulative beryllium exposure can cause beryllium sensitization and chronic beryllium disease.

According to E Fireman and colleagues, 6% of patients labelled as having sarcoidosis actually had chronic beryllium disease.[72] The development of chronic disease can take more than 30 years but under different circumstances beryllium sensitization can occur within 2 months and chronic granulomatous disease within 3 months of initial exposure. The beryllium-specific T-lymphocyte-proliferation test (BeLPT) screening assists in differentiating chronic beryllium disease from other pneumoconioses, particularly sarcoidosis whose pathological and

Table 2. Reported cases of drug-induced liver granulomas

allopurinol
procainamide
hydralazine
alpha-methyldopa
phenylbutazone
carbamazepine
saridon
rosiglitazone
baclofen
antimicrobial drugs:
- penicillins (ampicillin, flucloxacillin, oxacillin)
- cephalexin
- co-trimoxazone
- norfloxacin, levofloxacine
- nitrofurantoin
- isoniazid
- fansidar
- quinidine

clinical features are often indistinguishable. This test identifies individuals with beryllium sensitization and allows earlier intervention to slow the progression of chronic disease.

3.7 Talc and foreign bodies

Granulomatous reactions caused by foreign bodies have been described in drug abusers, in subjects exposed to occupational pollutants, and more rarely, in association with the use of prosthetic devices.[73] In an unusual presentation, a patient affected by fever of unknown origin for 9 years was diagnosed with cholestasis and acute renal failure with pathological evidence, in parenchyma samples, of granulomatosis of unknown origin. After extensive investigations a correlation was demonstrated between wear debris of porcelain, and cryptogenic granulomatosis.[74] Also a case of a toothpick perforating the stomach, then penetrating the liver, and thereafter forming a liver abscess with granulomatous change has been reported.[75] Finally, incidences of birefringent granules of starch are documented.

3.8 Infectious Agents

A broad spectrum of microorganisms may trigger hepatic granulomas (Table 1). Most of these agents are intracellular pathogens belonging to various genera. Their relative prevalence in a reported series varies according to the background prevalence of the various infectious agents in the geographic area and the ethnic or socioeconomic characteristics of the population. Mycobacteria of the *Mycobacterium tuberculosis* complex are the pathogens most commonly associated with hepatic granulomas in immunocompetent and immunodeficient patients. Certain other infectious disorders, are commonly listed as possible rare causes of granulomatous hepatitis (Table 1).

3.8.1 Brucellosis

Recent infections with *Brucella* species are accompanied by hepatic granulomas in 50% of the cases.[76] *Brucella* can rarely be demonstrated within the liver. Diagnosis relies on isolation of brucella from the blood and on positive serological tests (hemaglutination tests positive at 1/160 titles). The inflammatory reaction induced by the presence of brucella in macrophages results in the calcification of the granulomas. Histology demonstrated central necrosis and a ring of epitheloid cells surrounded by lymphocytes and giant cells arranged as palisades.[77] There are other forms of liver involvement. Nonspecific reactive hepatitis is most frequent. Abscesses are uncommon and may be specifically related to *B. Suis*. The abscesses present as a single heterogeneous tumor with calcification.[78] Clinical manifestation includes fever, sweating, weakness and non-specific pain in the abdomen and can mimic malignant liver tumors or abscesses. Conservative therapy with antibiotics, either alone or combined with percutaneous drainage is usually inadequate and the treatment of choice should be medical-surgical, in order to guarantee excision of the central calcium nucleus responsible for the persistence of the infection.

3.8.2 Tuberculosis

M. tuberculosis is a frequent agent of liver granulomas according to several series. Also, a physician should keep in mind that an effective treatment must be given as early as possible and that a misleading diagnosis of idiopathic granulomatosis and its treatment with steroids risks exacerbating underlying tuberculosis. Therefore caution must be exercised especially in parts of the world with a high incidence of tuberculosis.

Host immunity to mycobacterium infection is dependent on the activation of T lymphocytes and their recruitment with monocytes to form granulomas. These discrete foci of activated macrophages and lymphocytes provide a microenvironment for containing the infection. The cytokine TNF is essential for the formation and maintenance of granulomas. Tuberculosis granulomas are giant cell granulomas with central caseating necrosis and rarely are acid fast bacilli revealed on Ziehl-Neelsen staining. There are several studies highlighting the poor diagnostic yield for tuberculosis on hepatic histology.[6,12]

Hepatic granulomas are common in the miliary form of tuberculosis. Surprisingly, caseating granulomas are rarely seen in liver biopsy in patients with tuberculous peritonitis. Hepatic granulomas are the most common form of liver involvement in tuberculosis. The other forms are tuberculoma, and abscesses. Rarely, compression by tuberculous lymph nodes at the porta hepatis causes biliary tract disease or portal hypertension resulting from obstruction of the portal vein. Features of tuberculous abscess can be schematically contrasted with those of tuberculoma.[6,12] Tuberculous abscesses are very rare, are encountered mainly in immunodeficient patients, and contain pus with numerous acid-fast bacilli, whereas tuberculomas are relatively common, are seen in immunocompetent patients, and consist of coalescent granulomas with few or no acid-fast bacilli. A few cases of fulminant hepatic failure in the absence of underlying liver disease have been described. Diagnosis of tuberculosis in patients with hepatic granulomas may be difficult.

Caseation necrosis may be lacking. Demonstration of acid-fast bacilli by means of the Ziehl-Neelsen stain or culture is obtained in only 25% to 60% of cases. Chest radiographs show a normal aspect in about 25% of the patients. Recently, polymerase chain reaction (PCR) assay was able to detect *M. tuberculosis* with a sensitivity of 88% and a specificity of 100% in a group that included 17 patients with tuberculosis, 8 controls with hepatic granulomas of other origin, and 10 controls with liver disease.[6] These encouraging results need confirmation. When bacteriological documentation is lacking, the absence of other causes, positive Mantoux test, and response to specific therapy could be considered diagnostic criteria.

Mycobacterium mucogenicum, recently characterized, is a rapid-growing mycobacterium rarely seen in human infections.[79]

***Bacillus Calmette Guerin* (BCG)** is an attenuated strain of *M. bovis* which has long been used as a live vaccine against tuberculosis and, more recently, as a local therapy for bladder cancer or melanoma of the skin. Systemic infection with BCG can occur in immunocompromised children following intradermal injection, or in patients with bladder cancer if trauma of the vesical mucosa is associated with instillation into the lumen of the bladder. Systemic BCG infection can present with jaundice caused by hepatic granulomas. Acid-fast stain of the hepatic tissue is usually negative. Tuberculosis presenting as an isolated liver tumour, without active pulmonary or miliary tuberculosis, or other clinical evidence of tuberculosis, is distinctly rare.[80]

3.8.3 Leprosy

Leprosy must be suspected as a possible etiology of liver granulomatosis, mainly in those geographic areas documenting the highest prevalence rates. According to a survey conducted in India in 1987,[81] 9 patients with leprosy, 5 Borderline Lepromatous leprosy and 4 Lepromatous leprosy (LL) who developed jaundice during the course of disease were investigated. Two LL patients developed jaundice during erythema nodosum leprosum reaction. There was slight hepatomegaly and moderate splenomegaly. There were significant alterations in liver enzymes and serum bilirubin. Drugs and virus hepatitis were excluded. The course of prolonged jaundice in leprosy is compared with other diseases which could result in a similar situation.

3.8.4 Q fever

Infection with *Coxiella burnetti* is commonly asymptomatic.[90] Depending on the geographic area, presentation can be predominantly pneumonia or predominantly hepatitis.[82] Diagnosis is based on serology.[83]

Hepatic involvement is characterized by doughnut-shaped epithelioid granulomas.[84,85] Liver granulomas associated with Q fever present a rather characteristic type of inflammation with a fibrinoid ring and fatty necrosis.[85] Fibrin deposition can be interspersed among epithelioid cells. This aspect is highly suggestive of, but not specific for, Q fever.[86]

According to a study from Spain, involvement of the liver alone was documented in 55% of 109 patients with Q fever. In 96% it manifested as a febrile process without focal symptoms and hepatic cytolysis. There were no differences in epidemiologic characteristics between patients with hepatitis and those without.[87] The aim of another study was to describe the clinical and epidemiologic features of Q fever in the southern area of the island of Gran Canaria (Spain). The research revealed that the most frequent clinical presentation was an acute febrile process with elevated liver enzymes (87.5%). Pneumonia was infrequent in the area while Q fever mainly manifested as an acute febrile illness with sub-clinical hepatic involvement. This fact, and the small number of cases with pneumonia and chronic forms, suggest the etiological involvement of *C. burnetii* different strains in various geographic areas.[88]

3.8.5 Treponema

There have been few reports of granulomas in association with secondary syphilis.[6,12] The rarity of the reports and the lack of a direct relationship between treponema and granulomas raise questions concerning any relationship between syphilis and hepatic granulomas.

3.8.6 Whipple's Disease

In Whipple's disease, hepatic involvement is rare, although hepatic granulomas have been reported with and without periodic acid-Schiff (PAS)-positive macrophages.[6,12] Diagnosis is based on PAS stain showing positive macrophages or on the demonstration of *Trophirella whippelii-speciiic* DNA at hepatic or extrahepatic sites of involvement.

3.8.7 Cat-scratch Disease

Infection with *Bartonella henselae* causes cat-scratch disease or bacillary angiomatiosis. In HIV-infected patients, infection with *B. henselae* causes bacillary peliosis hepatitis. Necrotizing hepatic granulomas containing the bacillus have been reported in immunocompetent patients with cat-scratch disease [6,12].

3.8.8 Schistosomiasis

Infection with *Schistosoma japonicum* or *Schistosoma mansoni* results from adult worms laying eggs within the mesenteric venules. Some of these eggs find their way to the intestinal lumen, continuing the parasitic cycle.[89] Other eggs are deposited downstream in the portal venules, which thev block and where they elicit the formation of a granuloma rich in eosinophils and associated with periovular, portal, and perisinusoidal deposition of collagen. The main consequence of schistosomal granulomas and the related fibrosis is portal hypertension.[90] The initiation of granuloma formation is T cell-dependent since granulomas are not formed in their absence (delayed type hypersensitivity reaction).[91]

Thirty-eight cases clinically diagnosed as advanced schistosomiasis were subject to splenectomy in Dongzhi County Special Hospital for Schistosomiasis because of portal hypertension, splenomegaly, and/or hypersplenism.[92] In each case biochemical assay on several indices related to liver damage and fibrosis, ultrasonography and liver biopsy were undertaken. Upon histopathological examination, schistosome eggs were found in 33 out of 38 cases. The main pathological figures were egg granulomas with different degrees of fibrosis and some differences in the pathological changes between schistosomal liver fibrosis and mixed liver cirrhosis (both schistosome and hepatitis in origin) were seen. Advanced schistosomiasis was shown in 18 cases and schistosomiasis associated with hepatitis or cirrhosis was seen in other 20 patients.[92]

3.8.9 Fascioliasis

Tumor-like granulomatous lesions have been described in the liver of patients infected with *Fasciola hepatica* The usual place of residence of the adult worms, following the transhepatic migration of the larvae, is the lumen of the large bile ducts. It has been suggested that the tumour-like lesion results from an ectopic parenchymal location of adult worms.[6,12]

3.9 Cytomegalovirus or Epstein-Barr Virus

Hepatitis caused by recent infection with Cytomegalovirus or Epstein-Barr virus can, rarely, be associated with epithelioid granulomas in immunocompetent patients. Fibrin-ring granulomas were reported in association with each of these viruses.[93]

3.10 Immunodeficiencies

3.10.1 Liver granulomatosis in patients with AIDS

In AIDS patients, infectious disorders, drug reactions, and lymphomas are the main causes of hepatic granulomas. These conditions can usually be diagnosed without the need for liver tissue examinations.[94]

Immunocompromised patients who have AIDS are prone of acquiring opportunistic or not hepatic infections such as hepatitis B, hepatitis C, *M. avium-intracellulare, M.tuberculosis*, coccidioidomycosis, histoplasmosis, toxoplasmosis, cytomegalovirus, herpes simplex, and Ebstein Barr virus. In a documented case of an HIV positive patient, liver biopsy revealed granulomas (acid-fast negative) in the tissue and numerous pathogens (PAS positive) in hepatic sinusoids. Giemsa and GMS staining and electron microscopy all confirmed that the pathogen was *Pneumocystis carinii*.[95] Also, *Bartonella henselae*, the infective agent responsible for cat-scratch disease,[96] is described as a rare cause of hepatic granulomatosis in immunocompetent adults. Fibrin-ring granulomas have been described in patients with visceral leishmaniasis caused by *Leishmania donovani*. Macronodular granulomas can occur in HIV-infected patients.[97]

3.10.2 Common variable immunodeficiency

Common variable immunodeficiency (CVID) is a primary defect that is characterized by impaired antibody production. CVID patients may develop systemic granulomatosis. Patients with primary immunodeficiency are prone to develop Epstein-Barr virus related lymphoproliferative disorders, including lymphomatoid granulomatosis, which most commonly involves the lung, but can also be seen in brain, kidney, liver, and skin.[98] Two CVID patients with systemic granulomatosis who developed B-cell lymphomas, one related to Epstein Barr virus infection, 5 and 12 years after CVID were diagnosed.[99]

3.11 Idiopathic liver granulomatosis

Although granulomas frequently represent a sign of either infectious or non-infectious disease, 20% of the hepatic granulomas lack an identifiable aetiology and no extrahepatic involvement can be found. These cases are defined as idiopathic granulomatous hepatitis. In granulomatous hepatitis, granulomas are found exclusively in the liver. Therefore, granulomatous hepatitis should not be used as an equivalent term for hepatic granulomas. It is uncertain whether idiopathic granulomatous hepatitis should be considered a variant of sarcoidosis of the liver.

According to earlier publications on this subset of patients, those patients with so-called idiopathic granulomas tend to be middle-aged women with cholestatic liver function tests who have an excellent outcome.[6,12]

Granulomatous hepatitis is characterized by a self-limited febrile illness with systemic signs and symptoms such as fatigue, sweating, myalgia, weight loss, weakness, shivering, hepatomegaly and/or splenomegaly, abnormalities in serum liver tests (aminotransferase, alkaline phosphatase), increased erythrocyte sedimentation rate, anaemia, hypergammaglobulinemia and eosinophilia (less than 5%).[100,101] Occasionally endophthalmitis,[102] exanthema,[103] and dry cough may co-exist.

Idiopathic granulomatous hepatitis can be diagnosed only after investigation and exclusion of any other possible cause of granulomatosis, especially infectious, lymphoid or sarcoid diseases. Diagnosis is established by laboratory, radiological (CT), ultrasonographic, histological and follow-up studies of patients.[101]

The outcome of idiopathic granulomatous hepatitis has been favourable, although temporary or prolonged corticosteroid therapy was needed in more than one half of the cases.

In a prospective study of "idiopathic" granulomatous patients, after 5 to 10 years of follow-up, an alternative diagnosis was established in 5 of the 20 patients. Of the remaining 15 patients with fever and idiopathic granulomatosis, 6 were still receiving corticosteroids.[100] Corticosteroid treatment did not result in progression or dissemination of an unrecognized infection. No clinical or laboratory abnormality helped to predict the need for long-term corticosteroid treatment. Also in another case in the literature on non-diagnosed hepatic granulomatosis, it is suggested that HCV infection and polymyalgia rheumatica may emerge as the underlying etiology[12].

4. DIAGNOSIS

Hepatic granulomas are typically asymptomatic. Constitutional symptoms such as fever, weight loss, anorexia and night sweats are often manifestations of the underlying disease and probably relate to the actions of the cytokines released by activated macrophages and lymphocytes[104] Liver enlargement and increased serum alkaline phosphatase activity have each been reported in about 60% of cases. Jaundice is rare except when associated with bile duct injury.

In most cases, granulomas are detected when a liver biopsy is performed during evaluation of an increase in serum alkaline phosphatase and γ-GT. Once hepatic granulomas have been recognized, the cause should be investigated. In each case of liver granulomatosis the aetiological diagnosis often results from a careful consideration of clinical, biological, and histological data.

The evaluation of the asymptomatic patient is usually limited, whereas the patient with constitutional symptoms or signs should be evaluated by obtaining cultures, serological tests and imaging. Drug history, occupational exposure to toxic chemicals, country of origin, and type of lifestyle should be sought. Results from autoantibodies, immunoglobulins, hepatitis serology, and full drug history are evaluated and associated with the histopathology of the liver biopsy. Yet, only rarely do granulomas possess distinct histological features which enable a positive diagnosis. For example a rather characteristic type of inflammation with a fibrinoid ring is characteristic of Q fever, ova of *Schistosoma Mansoni* may be found within the granuloma and caseous necrosis containing acid fast bacilli indicates tuberculosis.[105] Occasionally birefringent granules of starch are identified. Chest radiology, serum angiotensin and calcium measurements are performed to aid the diagnosis of sarcoidosis. Serologic testing (antimitochondrial and antinuclear antibodies, *brucella, coxiella, rickettsia, toxocara, salmonella*, CMV, EBV etc), blood cultures (brucella, salmonella, coxiella, mycobacteria), sputum cultures for mycobacteria, and tuberculin skin test may help to exclude all possible causes associated with liver granulomas. Serologic and bacteriologic studies of blood samples should be considered in the epidemiologic context.

Imaging investigations usually show an enlarged liver with a homogeneous or coarse appearance. Calcifications can be seen on plain radiographs.[106] Focal lesions on imaging studies are unusual but can be seen with coalescence of granulomas. Occasionally, confluence of the granulomas produces multiple small nodules that are detectable by CT scan or ultrasound imaging.[107] Rarely, a tumor can form from the coalescence of granulomas (Figure 2). Certain infectious causes of granulomas are associated with the formation of liver abscesses in immunodeficient patients.

Histology may show mineral oil deposits or foreign body material in the macrophages; schistosomal ova at the center of granuloma; caseating necrosis suggesting tuberculosis; bacteria, mycobacteria or fungi; nonsuppurative cholangitis suggesting PBC; or features of primary sclerosing cholangitis, steatosis or alcoholic liver lesions. In any case of liver histology, histochemistry (Gram stain for bacteria, Ziehl-Neelsen stain for Mycobacteria, PAS stain for Rochalima Whipelii, Whartin-Starry stain for Bartonella Hensella, Grocott-Gomori's methenamine silver stain for fungi), immunohistochemistry, culture of the liver biopsy or specific PCR amplification of the ge-

nome of various pathogens may help to define the cause of granulomas. Liver biopsy provides diagnosis in approximately 15-30% of cases. In almost one third of cases it is impossible to reach aetiological diagnosis on histological criteria alone. In series involving pathologic sources[108] this diagnostic procedure yields a cause in approximately 90% of the cases (40% were primary biliary cirrhosis; 30% were sarcoidosis; 5% were mycobacterial infection, and 15% were miscellaneous pathogens). By comparison, in series from clinical units to which the patients had been referred because no cause could be readily documented, the diagnostic yield was only about 50% (20% were sarcoidosis; 5% were mycobacterial infection; 25% miscellaneous).[6,12]

It is still necessary to ascertain that no extrahepatic site of involvement (e.g., the skin) exists. Investigation for extrahepatic involvement may reveal a specific association (e.g., sarcoidosis), or provide another site that can be sampled for further histologic examination (e.g., enlarged lymph nodes for the diagnosis of Hodgkin's disease or lymphoma) or for further bacteriologic investigation (e.g., lung, skin, or lymph node involvement with mycobacteria).[6,12]

Incindental hepatic granulomas in the absence of a specific underlying cause do not cause progressive liver disease. Unexpected hepatic granulomas can be found at biopsy performed for staging a well-characterized non-granulomatous liver disorder (e.g., alcoholic liver disease or chronic viral hepatitis). In this setting, when all the signs or symptoms can be ascribed to liver disease, and there are no manifestations suggesting an intercurrent illness, investigation can be limited to sarcoidosis and tuberculosis.[6]

In undefied cases, reinvestigation in 3 months, is suggested if there are new or persistent signs or symptoms.

5. CONCLUSIONS

Granulomas of the liver represent a specialized cell-mediated immune response to a wide variety of etiological antigenic stimulation infectious and non-infectious or sequestration of a foreign indigestible, inorganic particle within macrophages. The causes of hepatic granulomas are numerous, and their identification can be difficult. The recommended evaluation to establish the underlying cause of hepatic granulomas depends on the patient's clinical status, co-existing diseases and exposure history. Twenty per cent of the hepatic granulomas lack an identifiable aetiology and no extrahepatic involvement can be found. These cases are described as idiopathic granulomatous hepatitis.

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