Hepatic Granulomas: A Clinician's Perspective

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ABSTRACT

Hepatic granulomas are focal aggregates of transformed epithelioid histiocytes with or without multinucleated giant cells that are cuffed by lymphocytes and plasma cells. They represent delayed-type specialized cell-mediated immunity to a wide-spectrum of antigenic stimuli. Hepatic granulomas are found in up to 10% of liver biopsies and the causes are usually multifactorial. Different antigens like infectious agent, medication, foreign body and malignancy can initiate granuloma formation. Hepatic granulomas *per se* seldom cause architectural changes and often provide a clue to a systemic disease. Most often, to a practicing clinician, it is a combination of clinical presentation, laboratory parameters with information on the typical localization and characterization of the granuloma within the liver by the pathologist that often provides a clue to a definitive diagnosis.

Keywords: Hepatic granulomas, transformed epithelioid histiocytes, multinucleated giant cells, cell-mediated immunity, antigenic stimuli

Granulomas are aggregates of modified macrophages (epithelioid cells) and other inflammatory cells that accumulate after chronic exposure to an antigen and are seen in several systemic diseases. The extent of inflammation associated with formation of granuloma is variable. Bland granulomas have little or no associated inflammation. The term granulomatous hepatitis is used when the inflammation is severe, within or around the granuloma and granulomatoid reaction refers to a poorly delineated granuloma[1]. The presence of a granuloma may be the first harbinger to an ongoing systemic disease.

PREVALENCE OF LIVER GRANULOMAS

The prevalence of granulomas in liver biopsy ranges from 2.4% to 15%[2-9]. Conn et al[10] reported that 66% of their cases of granulomatous reaction were secondary to a systemic disease, 28% to primary liver disorders and 6% were idiopathic. The frequency of granulomas is reportedly high and ranges from 16% to 75% in select groups like patients with fever of unknown origin or those with a human immunodeficiency virus (HIV) infection[11]. In India, granulomas are most often reported in tuberculosis (55%) followed by leprosy, sarcoidosis, histoplasmosis, brucellosis, amebic liver abscess, lymphoma, and malignant granuloma in that order[12].

ETIOLOGICAL CONSIDERATIONS

- Autoimmune: Sarcoidosis, primary biliary cirrhosis.
- Infections:
  - Bacterial- tuberculosis, leprosy, brucellosis, Q fever, rickettsia, listeriosis, Bartonella, *Tropheryma whipplei*
  - Parasites- schistosoma, leishmania
  - Viruses- hepatitis C
  - Fungal- Histoplasma.
- Drugs and chemicals.
- Malignancy.

HISTOPATHOLOGICAL CHARACTERISTICS OF GRANULOMA

A typical granuloma is an inflammatory reaction to a foreign body like microbial organism, drug, etc. It is essentially a compact spherical circumscribed lesion that consists of aggregated epithelioid histiocytes, measuring 50-300 μm. A typical granuloma consists of a central portion of macrophages and is surrounded by lymphocytes and fibroblasts. Differential diagnosis of a granuloma is largely based on its histological characteristics and the location within a hepatic lobule.

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The histological variants include[13-15]:

- **Necrotizing (caseating):** These are large and destroy the adjacent structures with no respect to the liver architecture. Common example is tuberculosis.
- **Noncaseating:** These are seen in sarcoidosis.
- **Granulomatous inflammation:** These are poorly formed granulomas with indistinct edges and consist of mixed inflammatory cells. Examples include drug-induced hepatocellular and/or ductular injury.
- **Lipogranuloma:** This is often seen in steatosis and comprises of aggregates of lipid-containing histiocytes, e.g., mineral oil.
- **Microgranulomas** contain 3-7 cells in cross-section, often admixed with other inflammatory cells and/or apoptotic hepatocytes. This pattern is nonspecific.
- **Foreign body granulomas** consist of inclusions of particulate material like mineral oil, starch and silicone within cytoplasmic vacuoles.
- **Lymphohistiocytic granulomas** are similar to epithelioid granulomas, but unlike the latter, these comprise of accumulations of macrophages and lymphocytes with distinct absence of epithelioid cells.
- **Fibrin ring or epithelioid granuloma:** The fibrin ring or an epithelioid granuloma consists of a central lipid vacuole surrounded by a fibrin ring. The activated macrophages differentiate and aggregate to form giant cells or Langhans cells. These granulomas are seen in infections like cytomegalovirus, hepatitis A, leishmaniasis, toxoplasmosis, Q fever, drugs such as allopurinol and in Hodgkin's disease.

Per se, granulomas can be located in almost all lobules. However, the distinct forms of necrosis as well as location of a granuloma can provide a clue to its origin and this helps in narrowing the differential diagnosis. For example, caseating necrosis is found in tuberculosis, while noncaseating necrosis is common in sarcoid granulomas[16]. The latter are located in the portal and periportal regions. In primary biliary cirrhosis, granulomas are seen near the porta. The drug-induced granulomas are poorly defined and are located anywhere within the hepatic lobules[16].

PATHOGENESIS

The failure of humoral or cellular immune response to eliminate the offending foreign material leads to granuloma formation[17]. Granulomatous reaction is essentially of 2 types, i.e., an immunological reaction to either an inert foreign body or to an active antigen[18]. The response to the agent depends on whether it is located within or outside the cell. For intracellular agents, there is a Th1 response while for extracellular, there is a Th2 immunological response. With the former, several cytokines such as interferon-γ, interleukin (IL)-2 and IL-12 are produced soon after phagocytosis of the agent by the macrophages, which reduce them to small peptides. With the Th2 response, there is secretion of IL-4, 5, 6 and 10. A vicious cycle ensues wherein by positive feedback mechanism the cytokines constantly stimulate the T cells. Thus, the formation and maintenance of liver granulomas is based on cytokine release[16].

With the release of cytokines, clusters of histiocytes and lymphocytes are seen. The histiocytes and macrophages are transformed into epithelioid histiocytes, which conglomerate to a granuloma. The latter have abundant pale cytoplasm. Apart from cytokines, epithelioid cells in particular, within a granuloma secrete proteins like collagenase, lysozyme, and angiotensin-converting enzyme (ACE) (e.g., sarcoidosis)[18]. Elevated ACE levels suggest an active sarcoid.

Typically surrounding the granulomatous reaction is a cuff of lymphocytes, a few plasma cells and eosinophils. Multinucleated giant cells are result of fusion of macrophages. Granulomas when infiltrated by eosinophils are suggestive of either a drug reaction or a parasitic infection. Thus macrophages play a key role in granuloma formation while tissue necrosis (necrotizing granulomas) is largely initiated by epithelioid histiocytes, characteristically seen in infections like tuberculosis.[19]

Accumulation of these effector cells in the portal tract leads to injury of the septal and interlobular bile ducts that can cause cholestasis[16].

CLINICAL PRESENTATION

Majority of the patients are asymptomatic at presentation or have clinical manifestations of underlying systemic disease. Nonspecific symptoms include fever (tuberculosis, sarcoidosis, infectious disease), weight loss, anorexia, and night sweats. Lymphadenopathy may be present in systemic diseases[19-23].

Two-thirds of patients have a hepatomegaly with an elevated alkaline phosphatase and gamma-glutamyl transferase.[21] Jaundice is rare unless there is bile duct injury. Portal hypertension is reported in schistosomiasis (noncirrhotic portal hypertension), sarcoidosis and primary biliary cirrhosis[16]. Final diagnosis is at histology.

DIAGNOSTIC EVALUATION

A comprehensive medical history and physical examination should be pursued along with an extensive medication and travel history. Symptoms and signs are helpful in developing a differential diagnosis. Blood investigations, serological tests and biopsy lead to a definitive diagnosis. Ultrasound can detect a hepatomegaly. Granulomas of 0.5 cm in diameter or greater can be identified on magnetic resonance imaging (MRI) as multiple nodular lesions or, less commonly, isolated hepatic granulomas. Caseating granulomas as in tuberculosis have a high or low signal in T1-weighted MRI, and no enhancement or sometimes peripheral enhancement after gadolinium injection in comparison to noncaseating granulomas in sarcoidosis, which have intermediate signals on T1-weighted images with gadolinium enhancement that may or may not persist on late images[24-26]. However, these findings are operator dependent and difficult to interpret.

In a study[27] on 251 explant livers, we found the prevalence of liver granulomas to be 7.2%. Five patients who had undergone transarterial chemoembolization prior to transplantation, had foreign body granuloma. Five patients were diagnosed to have caseating

Table 1. Salient Features of Important Causes of Hepatic Granulomas

Categories	Causes	Clinical picture	Biochemistry	Granulomas
Autoimmune	Sarcoidosis	Hepatic involvement: 5-15% Asymptomatic, cholestatic liver disease, cirrhosis, PHT, hepatic vein thrombosis	Raised SAP, GGT	Noncaseating epithelioid granuloma Location: Portal tract
	PBC	Cholestatic liver disease	AMA +	Simulates sarcoidosis
Infections: Bacterial, viral, fungal, parasitic, rickettsial, spirochaetal	Tuberculosis	Systemic symptoms: Fever, night sweats, fatigue, anorexia, and weight loss Jaundice rare	Abnormal LFT; raised GGT and SAP	Around portal tract, caseating or noncaseating, AFB ± 90%: military TB 70%: extrapulmonary TB, 25%: isolated liver
	HIV-related: Associated infections e.g., *M. tuberculosis*, *M. avium* intracellulare, *C. neoformans*, CMV, histoplasmosis, toxoplasmosis	Symptoms of primary infection	Abnormal LFT: Raised SAP, GGT, hepatomegaly	Usually similar to infective granulomas
Cirrhosis	HCV, alcohol, HCC, NASH	Features of cirrhosis	Raised SAP, GGT	Often epithelioid granulomas: treatment related (e.g., Interferon or primary disease)
Malignancy	Hodgkin's, non-Hodgkin's lymphoma, renal cell carcinoma	Primary disease	Raised SAP, GGT	Granulomas not considered for staging in lymphomas
	HCC			May be related to primary etiology, e.g., HCV or may be intratumoral
Drugs	Allopurinol, sulfa, chlopropamaide, quinidine	History of drugs		Diffuse, ill-defined
Foreign body	Post-TACE	History	>HCC	Microgranulomas with suppuration
Idiopathic	10-36%	Granulomatous hepatitis: Fever, myalgia, arthralgia, hepatoslenomegaly	Raised ESR	

PHT = Portal hypertension; SAP = Serum alkaline phosphatase; GGT = Gamma-glutamyl transferase; PBC = Primary biliary cirrhosis; AMA = Antimitochondrial antibodies; LFT = Liver function tests; AFB = Acid-fast bacilli; TB = Tuberculosis; HIV = Human immunodeficiency virus; CMV = Cytomegalovirus; HCV = Hepatitis C virus; HCC = Hepatocellular carcinoma; NASH = Nonalcoholic steatohepatitis; TACE = Transarterial chemoembolization; ESR = Erythrocyte sedimentation rate.

granulomas and were started on four drug regimen for tuberculosis - isoniazid, rifabutin, pyrazinamide, and ethambutol. All responded well to treatment. Three patients with hepatitis C virus infection showed portal microgranulomas/granulomas. These were compact, non-necrotizing, epithelioid granulomas of varying sizes observed within portal tracts and lobules. Five cases, where the diagnosis of granulomas remained elusive, isoniazid prophylaxis was given for 9 months to reduce the risk of reactivation of tuberculosis.

The presence of granulomas suggestive of tuberculosis in the explant liver is associated with the development of tuberculosis in the recipients[28]. Granulomas in hepatitis C virus patients could be due to an interferon-mediated stimulation of Th1 immune response or intravenous drug use[29].

The differential diagnosis (Table 1) for hepatic granulomas can be broadly classified as those associated with:

- Infections
- Drugs
- Autoimmune disorders
- Malignancy
- Idiopathic.

CONCLUSIONS

Hepatic granulomas are of multifactorial origin. A definite diagnosis regarding the granulomas can only be made using clinical data and histopathology. In a quarter, the cause for a granuloma remains unknown. In Indian setting, treatment for tuberculosis should be initiated in presence of caseating granulomas and a high index of disease suspicion.

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Temporal Association Between COPD Exacerbations and Cardiovascular Events

Chronic obstructive pulmonary disease (COPD) patients with severe exacerbations are at a high immediate risk of experiencing cardiovascular events, within 1 to 14 days post-exacerbation. Conversely, patients with moderate exacerbations were at highest risk 14 to 30 days following the acute exacerbation event. The risk remained elevated 1 year later irrespective of the severity of exacerbation. These findings from a population-based study from the UK were published April 15, 2024 in the *American Journal of Respiratory and Critical Care Medicine*[1].

This study investigated the temporal relationship between exacerbations of COPD and new-onset nonfatal cardiovascular events. Data for COPD patients in England was sourced from the Clinical Practice Research Datalink Aurum primary care database from 2014 to 2020. Information about various individual and composite cardiovascular events such as acute coronary syndrome, arrhythmia, heart failure, ischemic stroke, and pulmonary hypertension was determined from the linked hospital data. The index date was defined as the occurrence of the first COPD exacerbation; for those without exacerbations, it was defined as the date of eligibility for the trial.

Out of the 2,13,466 patients assessed; 1,46,448 (68.6%) reported at least one exacerbation. Over half (~56%) of these had moderate exacerbations, while ~13% had severe exacerbations. A total of 40,773 cardiovascular events occurred during the course of the study.

Analysis revealed an immediate period of heightened cardiovascular risk within 1 to 14 days after any exacerbation as indicated by the adjusted hazard ratio (aHR) of 3.19. The elevated cardiovascular risk declined progressively but persisted beyond the immediate post-exacerbation period, with an aHR of 1.84 after 1 year.

The risk was highest within 14 days after a severe exacerbation with aHR of 14.5. In patients with moderate exacerbations, the risk was highest after 14 to 30 days with aHR of 1.94.

Patients were nearly 13 times more likely to develop arrhythmia within 2 weeks of a severe exacerbation with aHR of 12.7. The likelihood of HF was also elevated almost ninefold with aHR of 8.31.

To conclude, cardiovascular events after moderate exacerbations occur a little later than after severe exacerbations. By demonstrating the differences in the timing of cardiovascular events following moderate and severe COPD exacerbations, this study highlights significant increases in cardiovascular risk following exacerbations. The extended duration of heightened cardiovascular risk beyond 1 year, regardless of exacerbation severity, underscores the chronic impact of COPD exacerbations on cardiovascular health. This emphasizes the ongoing need for being vigilant and proactively monitor and proactive manage cardiovascular risk in COPD patients, even in the absence of acute exacerbations. The authors also note "*postexacerbation intervention approaches should include the management of cardiopulmonary risk to reduce the risk of COPD and cardiovascular events in the short and long terms*".

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