Granulomas in the Liver, with a Focus on Infectious Causes

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KEYWORDS

• Liver • Granuloma • Infection • Granulomatous inflammation

Key points

- Granulomas in the liver can be generally classified by morphology, which can be helpful in suggesting the cause.
- There are many possible causes of hepatic granulomas, including infectious and noninfectious diseases. Clinical history and other laboratory tests are often helpful in the evaluation of hepatic granulomas.
- A cause of hepatic granulomas cannot be identified for some cases, even following extensive clinical and histologic workup; in some cases, hepatic granulomas are incidental and have no clinical significance.

ABSTRACT

Hepatic granulomas are encountered in approximately 2% to 10% of liver biopsies. There are many potential infectious and noninfectious causes; granulomas can be generally classified by their morphology, which may be helpful in refining the differential diagnosis. This article provides a review of hepatic granulomas with an emphasis on infectious causes.

GENERAL CONSIDERATIONS

Hepatic granulomas have been reported in 2% to 10% of biopsies[1–4] and may be localized to the liver or be a part of a systemic disease. They have been associated with both infectious and noninfectious causes, but in some cases, a cause cannot be identified even after extensive histologic, clinical, and laboratory workup. Granulomas in the liver can also be an incidental finding with no clinical significance or only a minor component of a pathologic process. The histologic features of hepatic granulomas, however, may be suggestive of a cause that can guide further evaluation of patients. This article discusses the causes of hepatic granulomas as they relate to histologic patterns, with an emphasis on infectious diseases.

Granulomas can be roughly classified by their morphology (**Table 1**). *Aggregates of foamy histiocytes* (**Fig. 1**A) are usually infectious in cause and most often occur in immunocompromised patients. Examples include *Mycobacterium avium-intracellulare* (MAI), *Mycobacterium leprae* (leprosy), *Tropheryma whipplei* (Whipple disease), and *Rhodococcus equi* infections.

Epithelioid granulomas are discrete, well-formed collections of epithelioid histiocytes with well-defined borders. Non-necrotizing

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Table 1
Classification of hepatic granulomatous processes by morphology

Granuloma Morphology	Possible Causes
Aggregates of foamy macrophages	Usually infectious: *Rhodococcus equi,* MAI in immunocompromised patients, lepromatous leprosy, Whipple disease
Epithelioid granulomas with or without necrosis	Infectious Tuberculosis (usually with caseating necrosis), MAI in immunocompetent patients, brucellosis, tuberculoid leprosy, syphilis, rarely Whipple disease and viral infections Noninfectious Sarcoidosis, drug reaction, foreign body reaction, common variable immunodeficiency, autoimmune diseases, primary biliary cholangitis, neoplasm-associated, chronic granulomatous disease
Fibrin-ring granulomas	Infectious Q fever, typhoid fever, Epstein-Barr virus, cytomegalovirus, toxoplasmosis, leishmaniasis Noninfectious Drug reaction, lupus, metastases
Granulomatous inflammation associated with prominent suppurative inflammation	Usually infectious: tularemia, listeriosis, melioidosis
Granulomatous inflammation with central stellate microabscess	Infectious Cat-scratch disease, *Nocardia*, tularemia, *Candida*, actinomycosis, other fungi Noninfectious Chronic granulomatous disease
Lipogranulomas	Mineral oil, fatty liver disease, hepatitis C
Microgranulomas	Nonspecific reaction to liver injury

Abbreviation: MAI, mycobacterium avium-intracellulare complex.

epithelioid granulomas can be seen in many conditions (**Fig. 1**B), and the differential is broad. Epithelioid granulomas with caseating necrosis (**Fig. 1**C), however, are highly suggestive of an infectious cause (eg, *Mycobacterium tuberculosis*); these are often randomly distributed throughout the liver with destruction of surrounding architecture.

Fibrin-ring granulomas are composed of epithelioid macrophages with a central fat vacuole surrounded by a ring of fibrin (**Fig. 1**D). They are classically associated with Q fever but have been associated with many infectious causes, including cytomegalovirus, Epstein-Barr virus (EBV), leishmaniasis, and toxoplasmosis,[5] as well as noninfectious causes, such as adverse drug reactions.[5,6]

Granulomatous inflammation, composed of poorly formed granulomas with indistinct borders, is often intermixed with other types of inflammatory cells (**Fig. 1**E). When accompanied by prominent suppurative inflammation, the findings raise suspicion for infectious causes, such as tularemia, listeriosis, and melioidosis. Granulomatous inflammation with associated hepatocellular or bile duct injury raises the possibility of an adverse drug reaction.

Granulomatous inflammation with a central stellate microabscess is usually infectious as well, and examples include *Bartonella* (cat-scratch disease) (**Fig. 1**F) and *Candida* infections and, more rarely, *Nocardia,* tularemia, and actinomycosis.

Lipogranulomas are small collections of macrophages and lipid droplets (**Fig. 1**G). They have been linked to mineral oils in foods and have also been associated with fatty liver disease and hepatitis C virus infection. Lipogranulomas may have associated fibrosis, but they are not thought to