

Brief Report

Causes of Hepatic Granuloma: A 12-Year Single Center Experience from Southern Iran

Bitá Geramizadeh MD¹, Reza Jahangiri MD¹, Elham Moradi MD¹

Abstract

Background: Hepatic granuloma is reported in 2 – 15% of liver biopsy specimens. It is relatively easy for the pathologist to diagnose, but sometimes arriving at a specific etiology is quite difficult. Until now, there are few published studies about the etiology of hepatic granuloma in Iran. In this study, we attempt to determine the causes of hepatic granuloma from one of the largest referral centers in this country.

Methods: In a retrospective study over 12 years, a hepatopathologist reviewed all liver biopsies with granuloma. The medical records, including clinical findings, autoantibodies, viral markers, imaging studies, drug histories, and all other specialized tests, such as molecular studies, were reviewed to reach a definite diagnosis.

Results: During 12 years, there were 72 cases diagnosed with liver granuloma. The most common cause of hepatic granuloma was infectious, with *Mycobacterium tuberculosis* (52.8%). The second most common cause was visceral leishmaniasis in 8.3% of biopsies. Other less common causes were fungal infections, visceral larva migrans, primary biliary cirrhosis, and hepatitis C, each in 4.2% of cases. Autoimmune hepatitis was diagnosed in 2.8% of patients. Lymphoma, drug induced, disseminated BCGitis, CMV infection, foreign body reaction and sarcoidosis, were each found in 1.4% of the liver biopsies. After all investigations, there were 12.5% idiopathic hepatic granulomas.

Conclusion: According to this study, the most common cause of hepatic granuloma in Iran is tuberculosis. This finding is completely different from western countries and very similar to the results of countries such as Saudi Arabia.

Keywords: etiology, hepatic granuloma, Iran, liver biopsy

Introduction

Granuloma is the focal aggregate of epithelioid histiocytes with and without multinucleated giant cells that are usually surrounded by lymphocytes.¹

Many diseases that produce granulomas can involve the liver. Some are intrinsic hepatic diseases, whereas others are disseminated systemic diseases that involve the liver and other organs.²

Hepatic granulomas have been reported in 2 – 15% of liver biopsies,³ the etiology of which differs in various geographic areas of the world.

To the best of our knowledge, there is no published study about the incidence and etiology of hepatic granuloma in all age groups from Iran. Therefore, we performed this study to determine the etiology of liver granuloma in our center, which is one of the largest referral centers in this country.

Materials and Methods

We performed a retrospective review on all cases found to have hepatic granuloma via liver biopsies over a 12-year period, from January 1996 to December 2008, in affiliated hospitals of Shiraz University of Medical Sciences.

Excluded from the study were biopsies with the diagnosis of lipogranuloma. Pathology slides of all remaining cases were retrieved from the archives of the Pathology Department and reviewed by a

hepatopathologist.

The patients' medical records were reviewed for diagnostic investigations that included medical histories, clinical findings, autoantibodies, immunoglobulins, viral markers, imaging studies, drug histories, and all other specialized tests, such as molecular studies.

According to the pathological findings, medical charts and all laboratory characteristics, attempts were made to find a particular etiology in each case.

Results

Over 12 years (1996 – 2008) there were approximately 3142 liver biopsies, of which 72 cases were reported to have granulomas (2.3%).

Of the 72 cases, there were 33 females (45.8%) and 39 males (54.2%). The age range was 10 days to 75 years (mean 24±22 years).

After reviews of all histopathologic, laboratory, and clinical investigations, a definite final diagnosis was made in 63 cases whereas 9 (12.5%) cases remained without a final diagnosis and were labeled as idiopathic.

Overall, 37 cases (51.4%) were positive for *Mycobacterium tuberculosis* as diagnosed by either PCR (21 cases) or histopathologic slides and acid fast staining (16 cases). Of these, there were 20 males and 17 females with an age range of 10 days to 50 years. Less common causes of hepatic granuloma in our center were: visceral leishmaniasis (6 cases, 8.3%); visceral larva migrans (3 cases, 4.2%); hepatitis C infection (3 cases, 4.2%); primary biliary cirrhosis (PBC) in 3 cases (4.2%); fungal infection (aspergillosis and zygomycosis) in 3 cases (4.2%); autoimmune hepatitis (AIH) in 2 cases (2.8%); and non-hodgkin's lymphoma (NHL), drug-induced, BCGitis, CMV infection, sarcoidosis, and foreign body

Authors' affiliation: ¹Transplant Research Center, Pathology Department, Shiraz University of Medical Sciences, Shiraz, Iran.

Corresponding author and reprints: Bitá Geramizadeh MD, Transplant Research Center, Pathology Department, Shiraz University of Medical Sciences, P.O. Box 71345-1864, Shiraz, Iran. Tel: +98-711-647-4331, Fax: +98-711-647-4331, E-mail: geramib@sums.ac.ir

Accepted for publication: 20 October 2010

reaction, each in 1 case (1.4%).

Table 1 shows the final diagnosis in 72 cases of hepatic granuloma based on clinical, laboratory, and histological data.

Table 1. Final diagnosis in 72 cases of hepatic granuloma based on clinical, laboratory, and histological data.

Diagnosis	Number of cases	Percentage
Tuberculosis	37	51.4%
Visceral leishmaniasis	6	8.3%
Visceral larva migrans	3	4.2%
Fungal infection	3	4.2%
Hepatitis C	3	4.2%
Primary biliary cirrhosis	3	4.2%
Autoimmune hepatitis	2	2.8%
Drug-induced	1	1.4%
Foreign body	1	1.4%
Sarcoidosis	1	1.4%
Neoplasm	1	1.4%
Disseminated BCGitis	1	1.4%
CMV	1	1.4%
Idiopathic	9	12.5%
Total	72	100%

CMV=Cytomegalovirus.

Discussion

Hepatic granuloma has a wide range of varied etiologies worldwide.⁴ In reports from western countries, the most common causes of hepatic granuloma have been noninfectious, such as sarcoidosis or biliary diseases, particularly PBC.^{3,5}

In our 72 cases, there was only one documented case of sarcoidosis (1.4%). On the other hand, in countries such as Saudi Arabia,⁶ infectious causes (mainly mycobacterial infections) are the most common causes of liver granuloma in 42.6% of patients. The vast majority of granulomas from our center were mycobacterial infections (51.4%). Of these, 43.2% (16 cases) were diagnosed by acid fast staining and 56.8% (21 patients) were diagnosed by molecular studies and PCR.

One recent study from a children's hospital at another center in Iran⁷ has shown similar results, with mycobacterial infections at the top of the list (45.5%). There are other studies from countries such as Turkey⁸ that have shown infectious and noninfectious causes with relatively equal frequencies. PBC was present in 23% of cases, with mycobacterial infection and sarcoidosis each present in 15% of cases diagnosed with hepatic granuloma.

The second most common cause of hepatic granuloma in our center was visceral leishmaniasis, which was diagnosed in 6 cases; 50% were detected by routine histopathologic slides and 50% by PCR in the liver tissue. With the exception of Greece (1 case), there were no reported cases of liver granuloma worldwide due to leishmaniasis. However, in these studies, PCR for leishmaniasis was not performed.^{1,6,7} Hepatitis C is a common cause of liver granuloma.⁹ In the majority of studies from different geographic regions of the world, a few cases have been reported.^{1,3,6-8}

Although brucellosis is endemic in some parts of Iran, no hepatic granuloma was caused by brucellosis in our study. Of note, we

performed PCR for the most common strains of brucellosis in the liver tissues of idiopathic cases, but none were positive. In a recent study from Saudi Arabia⁶ only one case (1.6%) was produced by brucellosis. In this study there were three cases with histologic evidence of VLM that showed severe eosinophilic infiltration and many Charcot-laden crystals. These cases were confirmed by immunologic tests. A study from Brazil¹⁰ reported VLM as a common cause of hepatic granuloma, however, no other countries noted VLM as an etiologic agent.

Another cause of hepatic granuloma was disseminated BCGitis in a neonate, who was later shown to be immune deficient. Disseminated BCGitis, as a cause of hepatic granuloma, has been recently reported from Turkey.⁸

Fungal infection, another rare cause of hepatic granuloma, was diagnosed in 3 patients. One was immunodeficient and found to have aspergillosis; the two other immunocompetent cases had gastrointestinal zygomycosis with liver involvement. This infection has rarely been reported as a cause of hepatic granuloma.²

Despite thorough investigations, 9 (12.5%) cases were idiopathic. In recent studies, there is a trend toward a decreased incidence of idiopathic hepatic granuloma, secondary to advances in immunologic tests, molecular studies, and imaging modalities.¹

According to this study, in countries such as Iran, the most common cause of liver granuloma is *Mycobacterium tuberculosis*. In cases of liver granuloma, ancillary studies should exclude *Mycobacterium tuberculosis* before labeling the granuloma as idiopathic.

References

1. Dourakis SP, Saramadou R, Alexopoulou A, Kafiri G, Deutsh M, Koskinas J, et al. Hepatic granuloma: A 6-year experience in a single center in Greece. *Europ J Gastroenterol Hepatol*. 2007; **19**: 101 – 104.
2. Lamps L. Hepatic granuloma, with an emphasis on infectious causes. *Adv Anat Pathol* 2008; **15**: 309 – 318.
3. Gaya DR, Thorburn D, Oien KA, Morris AJ, Stanley AJ. Hepatic granulomas: a 10-year single experience. *J Clin Pathol*. 2003; **56**: 850 – 853.
4. Al Mofleh IA, Al Rashed RS, Ayoola EA, Al Faleh FZ, Al Amri SM, Al Rikabi AC, et al. Hepatic granuloma in Arab population. A retrospective study from a teaching hospital in Riyadh. *The Saudi J Gastroenterol*. 2000; **6**: 41 – 46.
5. Mert A, Ozaras R, Bilir M, Tahan V, Cetinkaya A, Sibel Y, et al. The etiology of hepatic granuloma. *J Clin Gastroenterol*. 2001; **32**: 275 – 276.
6. Sanai F, Ashraf S, Ayman A, Sato MB, Batwa F, Al-Husseini H, et al. Hepatic granuloma: decreasing trend in a high incidence area. *Liver International*. 2008; **28**: 1402 – 1407.
7. Monajemzadeh M, Choopani M, Mahjub F, Mamishi S, Khodadad A, Sina AH, et al. Granulomatous hepatitis: a 10-years study in Iranian children. *Res J Biol Sci*. 2009; **4**: 503 – 505.
8. Onal IK, Ersoy O, Aydinli M, Yonem O, Harmanci O, Sokmenseur S, et al. Hepatic granuloma in Turkish adults. A report of 13 cases. *Eur J of Intern Med*. 2008; **19**: 527 – 301 – 12.
9. Snyder N, Martinez JG, Xiao SY. Chronic hepatitis C with hepatic granulomas. *World J Gastroenterol*. 2008; **14**: 6366 – 6369.
10. Musso C, Castello JS, Tsanaclis AMC, Pereira FEL. Prevalence of Toxocara-induced liver granuloma, detected by immunohistochemistry, in a series of autopsies at a children's reference hospital in Vitoria, ES, Brazil. *Virchows Arch*. 2007; **450**: 411 – 417.