Turk J Gastroenterol *2014; 25: 524-8*

Hepatic granulomas in Turkey: A 6-year clinicopathological study of 35 cases

LIVER

Memduh Şahin, Güldal Yılmaz, Mehmet Arhan, İlker Sen

Department of Gastroenterology, Gazi University Faculty of Medicine, Ankara, Turkey

Original Article

ABSTRACT

Background/Aims: Granulomas are focal aggregates of modified macrophages that are surrounded by a rim of lymphocytes and fibroblasts. The present study aimed to evaluate the prevalence and etiology of hepatic granulomas (HGs) in the Department of Gastroenterology with a wider population.

Materials and Methods: We performed a retrospective study on 2662 liver biopsy specimens analyzed between 2005 and 2011 at Gazi University Department of Gastroenterology to determine the presence of HGs.

Results: There were 16 cases with primary biliary cirrhosis, of whom 14 without any other causative etiology. There were 6 cases of sarcoidosis, 2 cases of Fasciola hepatica infection, 2 cases of hepatitis C, and 2 cases of hepatitis B. One case had both tuberculosis and rheumatoid arthritis and one case had both tuberculosis and brucellosis. There was also one case each of leishmaniasis and Hodgkin's lymphoma. The diagnosis of autoimmune hepatitis was found in two cases. One case had immune cholangiopathy.

Conclusion: The leading causative etiology of HGs was primary biliary cirrhosis, followed by sarcoidosis. As a study performed in a center that accepts patient profiles throughout Turkey, tuberculosis took a minor part in HG etiology. A drug-affected or toxic case of HG was not observed.

Keywords: Hepatic granuloma, primary biliary cirrhosis, biopsy, tuberculosis, sarcoidosis

INTRODUCTION

Granulomas are focal aggregates of modified macrophages that are surrounded by a rim of lymphocytes and fibroblasts. They occur as a result of a delayed immune response mediated by cell reactions (1). The incidence of hepatic granulomas (HGs) ranges from 2% to 15% in the world (2-5). The types of etiologies have different characteristics in accordance with the geographical locations and patient population (3-5). Some frequent causes of HGs include infections, neoplasms, drugs, and autoimmune diseases. Primary biliary cirrhosis (PBC) has been reported as one of the most common causes of HGs in Western populations (2,3). On the other hand, the dominant worldwide cause of HGs is mycobacterial infections and sarcoidosis (6-11). Hepatitis C Virus (HCV) has been recognized as a common cause of HGs for a few years (12). Additionally, hepatitis B virus (HBV) has been accepted as a rare cause of HG formation with unknown clinicopathological significance (13).

The present study aimed to evaluate the prevalence and etiology of HGs in the Department of Gastroenterology of our University Hospital.

MATERIALS AND METHODS

We performed a retrospective study on 2662 liver biopsy specimens analyzed between 2005 and 2011 at Gazi University Department of Gastroenterology. The patients providing specimens were from different parts of Turkey. Biopsies revealing lipogranulomas or mineral oil granulomas were excluded from this study.

Laboratory information was collected from the hospital computer database, including biochemical tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, and albumin], HCV antibody level, Brucella agglutination tests, and tuberculin skin test. Diagnostic clues provided by medical history, physical examination, and pre-

Address for Correspondence: Memduh Şahin, Department of Gastroenterology, Gazi University Faculty of Medicine, Ankara, Turkey
E-mail: memduhsahin@gazi.edu.tr
Received: 1.5.2013 **Accepted:** 20.10.2013

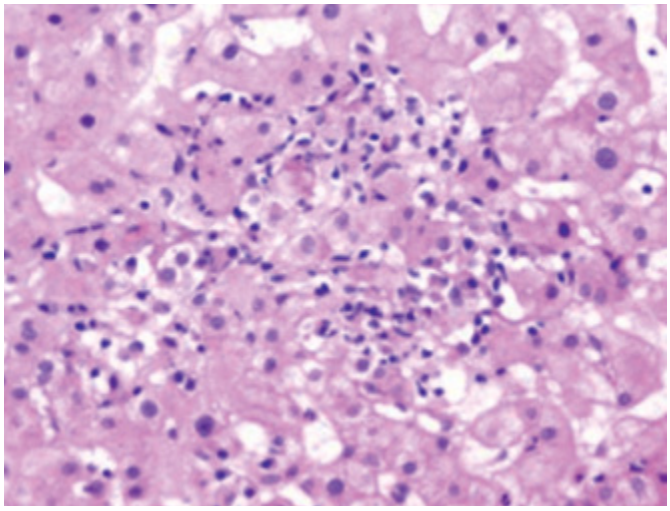

Figure 1. Kupffer cell aggregates in a liver biopsy sample (hematoxylin and eosin staining x400).

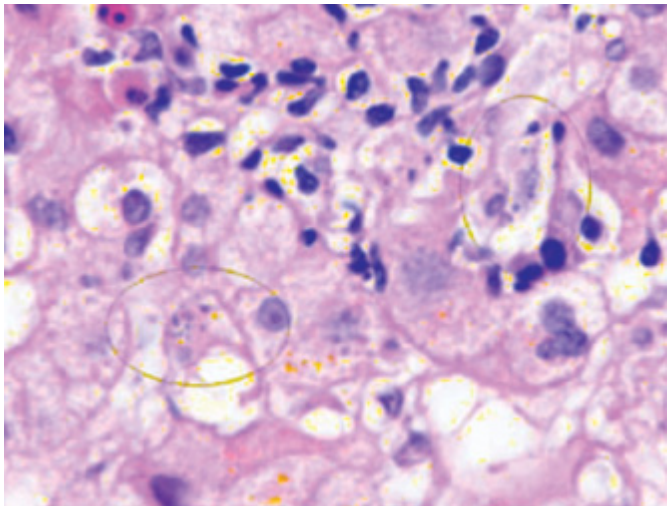

Figure 2. The case of figure 1 with leishmania amastigotes (hematoxylin and eosin staining x1000).

liminary laboratory data were verified by thoracic computed tomography, ultrasonography, organ biopsy, antimitochondrial antibody, presence of hepatitis B surface antigens, and venereal disease research laboratory test. Liver biopsy during the study period (2005-2011) was performed on all patients using a 16-gauge tru-cut biopsy needle.

In addition to the liver biopsy specimens, clinical symptoms were studied. Diagnosis of PBC was performed with antimitochondrial antibody M2. Bacille Calmette-Guérin (BCG) tests were performed for all patients. The diagnosis of sarcoidosis and tuberculosis were performed with chest tomography assistance. Data regarding immunoglobulins, hepatitis A, B, C, and D serology, HBV DNA for chronic hepatitis B, HCV RNA for chronic hepatitis C, imaging studies, drug history, endoscopy, and further specialized tests were obtained through the hospital database. Tuberculosis was diagnosed based on presence of acid-fast bacilli and caseation necrosis. Noncaseating granuloma without a fungal or bacterial agent was accepted as sarcoidosis. Leishmaniasis was diagnosed with bone marrow and other typical body specimens and serology (Figures 1, 2). In all patients, liver function tests (ALT, arginine aminotransferase, gammaglutamyl transferase, ALP) were performed before sample collection.

A statistical analysis was performed to show differences between the sarcoidosis and PBC cases in laboratory findings. Since the number of cases with hepatitis C and B, and other diagnoses was low, these patients were not included in the analysis. The statistical analysis was performed using non-parametric Mann-Whitney U test to explore the differences in AST, ALT, and hemoglobin levels and lymphocyte count between the sarcoidosis and PBC cases with HG. One case (case no. 16) who had both sarcoidosis and PBC was included in the sarcoidosis group.

RESULTS

Among 2662 biopsy samples, HGs were found in 35 (1.31%) cases (27 females and 8 males). The mean age of the cases was 51.6 years (range, 28-82 years). The etiology of HGs was analyzed. Sixteen cases had PBC, of whom 14 without any other causative etiology, 1 had also sarcoidosis, and 1 had also hepatitis C. There was also one case each of leishmaniasis and Hodgkin's lymphoma. One case had both tuberculosis and rheumatoid arthritis and one case had both tuberculosis and brucellosis. The diagnosis of autoimmune hepatitis was found in two cases. One case had immune cholangiopathy.

Some of the liver function tests and hematological values with pathologic subtypes of all PBC patients are summarized in Table 1. Ten (62.5%) cases were classified as Scheuer stage 2. The second highest proportion of the HG cases was diagnosed as sarcoidosis. Diagnosis of 6 cases was pure sarcoidosis and one case had a diagnosis of sarcoidosis and PBC (Table 2).

There were also patients with other diagnoses that were hepatitis C, autoimmune hepatitis, tuberculosis, brucellosis, leishmaniasis, hepatitis B, and cholangiopathy. The findings of hematologic, biochemical, and pathological evaluations in these patients are presented in Table 3. The liver granulomas of the brucellosis patient with concurrent tuberculosis are shown in Figure 3.

There was no significant difference between the PBC and sarcoidosis cases in terms of the mean hemoglobin value (12.69 mg/dL vs. 12.58 mg/dL; p=0.871). No significant differences were also found between the PBC and sarcoidosis cases in terms of AST and ALT levels and lymphocyte count (53.26 mg/dL vs. 33.3 mg/dL, p=0.447 for AST; 49.7 mg/dL vs. 45.6 mg/dL, p=0.731 for ALT; and 34.4% and 24.1%, p=0.161 for lymphocyte count).

DISCUSSION

Granulomas are composed of modified macrophages mixed with other inflammatory cells that accumulate after chronic exposure to antigens. HGs can be accompanied by severe in-

Table 1. Hematologic, pathologic and liver function values and age/gender data of primary biliary cirrhosis cases

Case no	Age/gender	Hemoglobin g/dL	Scheuer stage	NLR	AST/ALT U/L	ALP/GGT U/L
1	62 years/F	12.6	2	53/37.3	294/240	910/1617
2*	51 years/F	13.1	2	72.3/18.8	35/38	117/109
3	38 years /F	11.82	3	221/88	31/31	60.39/24.02
4	56 years /F	12.8	2	56.9/34.3	34/27	190/114
5	33 years/M	13.6	2	64.8/30.2	28/38	91/42
6	58 years/F	10.9	2	39/46	25/19	102/69
7	64 years/M	14.5	2	50.7/35.8	108/117	542/681
8	41 years /F	13.42	3	48.95/39.55	33/29	200/179
9	43 years/F	12.8	1	84.5/11.7	30/22	75/18
10	82 years/M	13.3	2	54.4/30.9	24/14	112/56
11	49 years/F	12	2	61.2/27.8	29/29	190/260
12	66 years/F	13.1	1	52.7/36.5	18/13	134/26
13	46 years/F	12.6	2	62.99/22.67	39/39	126/131
14	37 years/F	13.8	1	50.6 /29.5	34/33	179/199
15	47 years/F	12.5	1	57.52/29.22	37/56	54/33
16**	62 years/F	10.2	2	82.8/8.02	52/36	1099/891

NLR: neutrophil-to-lymphocyte ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gammaglutamyl transferase; M: male; F: female
*Case 2 had also hepatitis C.
**Case 16 had also sarcoidosis.

Table 2. Laboratory findings and age/gender data of sarcoidosis cases

Case no	Age/gender	Hemoglobin g/dL	Calcium mmol/L	Sedimentation	NLR	AST/ALT (U/L)	ALP/GGT (U/L)
16*	62 years/F	10.2	9.2	9	82.8/8.02	52/36	1099/891
17	62 years/M	14.3	9.2	15	63.3/24.1	34/64	214/555
18	66 years/F	13.1	9.1	77	71.4/15	20/26	233/159
19	40 years/F	11.4	8.9	13	63/20	20/12	154/85
20	59 years/M	13	No data	17	54.9/37.1	21/26	152/391
21	36 years/M	15.9	9.85	6	57.8/37.4	58/135	96/158
22	58 years/M	10.2	13.3	62	61.4/26.9	28/20	197/403

NLR: neutrophil-to-lymphocyte ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gammaglutamyl transferase; M: male; F: female
*Case 16 had also PBC

flammation within or surrounding granulomatous materials, which is identified as granulomatous hepatitis. The symptoms of granulomatous liver disease depend on the underlying disease. Patients are frequently asymptomatic and may not have laboratory evidence of hepatic dysfunction (14).

In the present study, the prevalent causative etiology of HGs was PBC; this is consistent with earlier studies performed in eastern countries. On the other hand, in some studies performed in eastern countries, the most prevalent cause of HGs is tuberculosis. To the best of our knowledge, there are 2 studies targeted to find the causative factors in Turkey. Turhan et al. (11) analyzed 86 liver granulomas with a leading causative pathology of PBC and found most specimens to be in an advanced stage of PBC. In that particular study, out of all PBC specimens, the rate of those that were causative of HGs was 70.37%; this rate was higher than that of the present study. In our study, microgranuloma specimens were excluded; consequently, there were 16 (45.7%) PBC cases; two of them had also other causative factors. Most of our patients were in the stage 2 subgroup. The rate of cases diagnosed with sarcoidosis was 20% in the present study, which was higher that (4.7%) reported in the study by Turhan et al. (11). In another study conducted in Turkey, Onal et al. (15) reported HGs in 13 subjects out of 592 patients (2.2%). The leading cause of

Table 3. Other causes of hepatic granuloma with characteristic laboratory and pathological values

Case no	Age/gender	Diagnosis	AST/ALT	Sedimentation	Pathologic specificity
23	61 years/F	Hepatitis C	23/22	14	Fibrosis:1/6, NIA:6
24	73 years/F	Hepatitis C	54/43	11	Fibrosis:3/6, NIA:5
25	28 years/F	Autoimmune hepatitis	251/339	5	Fibrosis: 1 and portal localized granulomas
26	39 years/F	Immune cholangiopathy	22/23	No data	HG
27	64 years/F	Autoimmune hepatitis	37/45	36	HG
28	28 years /F	Hepatitis B	29/35		NIA:9, Fibrosis:1
29	28 years/F	Leishmaniasis	32/42	86	HG
30	44 years/F	Hodgkin's lymphoma	15/34	No data	HG
31	52 years/F	Fasciola hepatica	34/42	No data	Necrotizing Eosinophilic Granulomatosis
32	59 years/F	Fasciola hepatica	14/17	No data	Necrotizing Eosinophilic Granulomatosis
33	25 years/F	Tuberculosis + rheumatoid arthritis	35/21	62	Necrotizing Granulomatosis
34	39 years/M	Hepatitis B	31/73	6	NIA:4, Fibrosis 2/6
35	77 years/M	Brucellosis + tuberculosis	47/26	55	Fibrosis:2/6

AST: aspartate aminotransferase; ALT: alanine aminotransferase; HG: Hepatic Granulomas; NIA: necroinflammatory activity; M: male; F: female

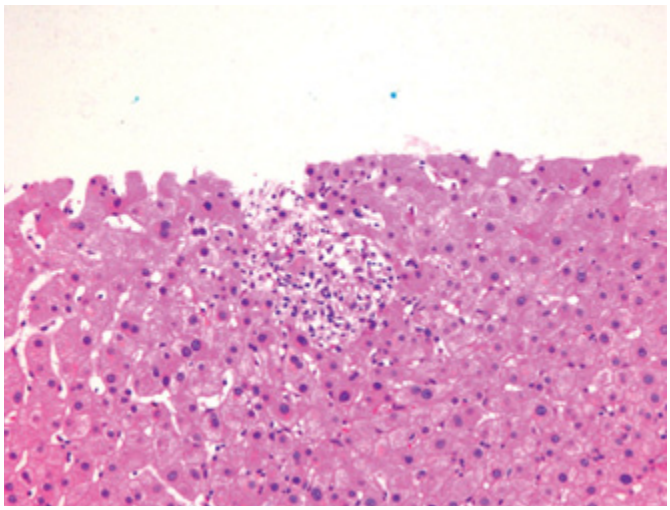

Figure 3. Granuloma formation in the liver (hematoxylin and eosin staining x200).

HGs was also PBC in that study. In the study by Onal et al. (15), an interesting case of BCGitis was focused. As seen in the studies by Turhan et al. (11) and Onal et al. (15), the cases of PBC took great part in the etiology of HG. In the present study, the cases of tuberculosis were rarely diagnosed; one case with concurrent brucellosis and another with concurrent rheumatoid arthritis constituted a minority of all patients. Indeed, these results are not expected for Turkey where tuberculosis is endemic. This can be attributed to the fact that such tuberculosis patients might be treated in primary health care centers and thus only cases of HG requiring differential diagnosis might present to our tertiary health care center.

In Iran, Geramizadeh et al. (16) diagnosed 72 cases with liver granuloma in a 12-year period and reported tuberculosis (52.8%) as the leading cause of HG, followed by visceral leishmaniasis (8.3%). In that particular study, the rate of leishmaniasis was notable. In our study, one case had the diagnosis of leishmaniasis. After a long examination period, the final diagnosis was based on histopathologic evaluation. The difference in leishmaniasis rates in our study and in the study by Geramizadeh et al. (16) is an interesting finding given similar geographical location.

Hepatitis C is not a common cause of HGs. One study in Turkey explored the rate of HGs in hepatitis C patients and the prevalence of HGs in patients with chronic hepatitis C was 1.3% (8 of 605) in reference to the patient population (12). As we only studied cases with HGs, the rate of hepatitis C was 8.7% (3 out of 35 cases). One of these patients had also a concurrent diagnosis of PBC with elevated ALP and GGT values and antimitochondrial antibody positivity (Case No. 16).

Brucellosis is a common cause of HG in endemic countries, like Turkey. In the present study, one patient had brucellosis and treated before acceptance to our department, because of the diagnostic polymerase chain reaction agglutination values. After the acceptance, we obtained a sample of vertebrae in addition to a liver sample, which showed caseation necrosis. In a study in Greece, it was reported that HG in all 14 brucellosis patients and concluded that different histologic patterns could be observed in liver involvement in brucellosis, the most common being granuloma formation (17).

In the present study, there were no significant differences between the sarcoidosis and PBC cases in terms of hemoglobin, AST, and ALT levels. However, this finding was obtained using non-parametric tests due to the low number of cases; thus, further studies with larger sample sizes should be performed

using also other laboratory data and stronger parametric tests. In conclusion, the leading cause of HGs in the present study was PBC, followed by sarcoidosis. Moreover, infectious etiology should be sought with wide clinical and laboratory research procedures. Specifically, hepatitis C was the leading infectious reason of HGs in our expertise. In this study, being a study performed in a center that accepts patient profiles throughout Turkey, tuberculosis took a minor part in HG etiology. A drug-affected or toxic case of HG was not observed.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.Ş., İ.S.; Design - M.Ş.; Supervision - M.Ş., İ.S., M.A.; Resource - G.Y.; Materials - M.Ş.; Data Collection&/or Processing - M.Ş.; Analysis&/or Interpretation - M.Ş.; Literature Search - M.Ş., G.Y.; Writing - M.Ş.; Critical Reviews - M.Ş., G.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Lefkowitch JH. Hepatic granulomas. J Hepatol 1999; 30 (Suppl 1): S40-5.
2. Gaya DR, Thorburn D, Oien KA, Morris AJ, Stanley AJ. Hepatic granulomas: A 10 year single centre experience. J Clin Pathol 2003; 56: 850-3. [CrossRef]
3. McCluggage WG, Sloan JM. Hepatic granulomas in Northern Ireland: a thirteen year review. Histopathology 1994; 25: 219-28. [CrossRef]
4. Sartin JS, Walker RC. Granulomatous hepatitis: A retrospective review of 88 cases at the Mayo Clinic. Mayo Clin Proc 1991; 66: 914-8. [CrossRef]
5. Satti MB, al-Freihi H, Ibrahim EM, et al. Hepatic granuloma in Saudi Arabia: A clinicopathological study of 59 cases. Am J Gastroenterol 1990; 85: 669-74.
6. Guckian JC, Perry JE. Granulomatous hepatitis. An analysis of 63 cases and review of the literature. Ann Intern Med 1966; 65: 1081-100. [CrossRef]
7. Wagoner GP, Anton AT, Gall EA, Schiff L. Needle biopsy of the liver. VIII. Experiences with hepatic granulomas. Gastroenterology 1953; 25: 487-94.
8. Cunnigham D, Mills PR, Quigley EM, et al. Hepatic granulomas: Experience over a 10-year period in the West of Scotland. Q J Med 1982; 51: 162-70.
9. Mir-Madjlessi SH, Farmer RG, Hawk WA. Granulomatous hepatitis. A review of 50 cases. Am J Gastroenterol 1973; 60: 122-34.
10. Hughes M, Fox H. A histological analysis of granulomatous hepatitis. J Clin Pathol 1972; 25: 817-20. [CrossRef]
11. Turhan N, Kurt M, Ozderin YO, Kurt OK. Hepatic granulomas: a clinicopathologic analysis of 86 cases. Pathol Res Pract 2011; 207: 359-65. [CrossRef]
12. Ozaras R, Tahan V, Mert A, et al. The prevalence of hepatic granulomas in chronic hepatitis C. J Clin Gastroenterol 2004; 38: 449-52. [CrossRef]
13. Tahan V, Ozaras R, Lacevic N, et al. Prevalence of hepatic granulomas in chronic hepatitis B. Dig Dis Sci 2004; 49: 1575-7. [CrossRef]
14. Coash M, Forouhar F, Wu CH, Wu GY. Granulomatous liver diseases: A review. J Formos Med Assoc 2012; 111: 3-13. [CrossRef]
15. Onal IK, Ersoy O, Aydinli M, et al. Hepatic granuloma in Turkish adults: a report of 13 cases. Eur J Intern Med 2008; 19: 527-30. [CrossRef]
16. Geramizadeh B, Jahangiri R, Moradi E. Causes of hepatic granuloma: a 12-year single center experience from southern Iran. Arch Iran Med 2011; 14: 288-9.
17. Akritidis N, Tzivras M, Delladetsima I, Stefanaki S, Moutsopoulos HM, Pappas G. The liver in brucellosis. Clin Gastroenterol Hepatol 2007; 5: 1109-12. [CrossRef]