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

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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-
liminary laboratory data were verified by thoracic computed
tomography, ultrasonography, organ biopsy, antimitochon-
drial antibody, presence of hepatitis B surface antigens, and ve-
nereal 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 antimito-
chondrial antibody M2. Bacille Calmette-Guérin (BCG) tests were
performed for all patients. The diagnosis of sarcoidosis and tuber-
culosis 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 special-
ized 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 be-
tween 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 he-
moglobin 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 hepa-
titis C, autoimmune hepatitis, tuberculosis, brucellosis, leish-
maniasis, hepatitis B, and cholangiopathy. The findings of he-
matologic, 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.

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-
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 than (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>
<thead>
<tr>
<th>Case no</th>
<th>Age/gender</th>
<th>Hemoglobin g/dL</th>
<th>Calcium mmol/L</th>
<th>Sedimentation</th>
<th>NLR</th>
<th>AST/ALT U/L</th>
<th>ALP/GGT U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62 years/F</td>
<td>12.6</td>
<td>9.2</td>
<td>9</td>
<td>82.8/8.02</td>
<td>52/36</td>
<td>1099/891</td>
</tr>
<tr>
<td>16*</td>
<td>62 years/F</td>
<td>10.2</td>
<td>9.2</td>
<td>9</td>
<td>82.8/8.02</td>
<td>52/36</td>
<td>1099/891</td>
</tr>
</tbody>
</table>

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
HG 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.

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

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

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REFERENCES