

Granulomatous Hepatitis: A 10 Years Study in Iranian Children

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Abstract: Hepatic granulomas have been reported in 2-15% of unselected liver biopsies, with a wide clinical profile responsible for their presence. To date, no series concerning the prevalence and the etiology of granulomas from Iran has been reported. To evaluate the current prevalence and etiologic factors of granulomatous hepatitis in Iranian children. A retrospective review of patient pathology report between 1996 and 2005; all patients who had a liver biopsy at Children's Medical Center revealing granulomatous hepatitis had their case notes and liver biopsies reviewed and a standard proforma completed. Hepatic granulomas were found in 33 patients. Of those identified, 54.5% were female, with a mean age of 3.1 years (SD = 4.8). In 19 cases (57.6%) a definite clinical diagnosis was established. Underlying etiologies were as follows: mycobacterial infection (45.5%), sarcoidosis (6.1%), HCV infection (3.0%) and kala-azar (3.0%). About 42.4% of cases remained undiagnosed. Our series showed that mycobacterial infection is an important cause of granulomatous hepatitis in this population. A rather large number of idiopathic cases were recorded.

Key words: Granulomatous hepatitis, children, hepatic granuloma

INTRODUCTION

The liver may react to different infectious and non-infectious agents, developing granulomatous lesions which make granulomatous hepatitis. Granulomas of the liver are circumscribed lesions (size from 50-300 mm) composed of epithelioid cells, varied numbers of mononuclear cells and/or multinucleated giant cells. They represent a specialized cell-mediated immune response to a wide variety of endogenous or exogenous factors (Pasquale, 2003).

Granulomatous hepatitis is usually characterized by a febrile illness with systemic signs and symptoms such as fatigue, sweating, shivering, hepatomegaly and/or splenomegaly, abnormalities in serum liver tests (aminotransferase, alkaline phosphatase) (Pasquale, 2003).

Underlying etiologies of hepatic granuloma, according to Gaya (2003) experience, were as follows: Primary Biliary Cirrhosis (PBC; 23.8%), sarcoidosis (11.1%), idiopathic (11.1%), drug induced (9.5%), HCV

(9.5%), PBC/Autoimmune Hepatitis (AIH) overlap (6.3%), Hodgkin lymphoma (6.3%), AIH (4.8%), tuberculosis (4.8%), resolving biliary obstruction (3.2%) and other single miscellaneous causes (9.5%) (Gaya, 2003). But it varies in different parts of world. To date, no series about its prevalence and etiology from Iran has been reported. Thus, we undertook an analysis of all liver biopsies revealing hepatic granulomas over a 10 year period, to evaluate the current prevalence and etiologies of granulomatous hepatitis in Iranian children.

MATERIALS AND METHODS

A retrospective review was performed on all patients found to have granulomatous hepatitis on liver biopsy performed between April 1996 and March 2005 at Children's Medical Center (CMC). In addition to being a referral tertiary care centre, CMC is the major pediatric teaching hospital of Tehran University of Medical Sciences. It admits patients from all regions of Iran, representing a wide spectrum of socioeconomic levels.

A list of all biopsies reporting granulomas was generated from the pathology department file. All biopsies were stained for mycobacteria and fungi (Ziehl Neelsen and PAS, respectively) and also hematoxylin and eosin and were reviewed by our pathologist.

Etiology was determined by results from clinical findings, immunoglobulin levels, hepatitis serology and full drug history. The above results and clinical assessment were recorded in a standard proforma, as were liver function tests at the time of biopsy.

Statistical analysis: The statistical analysis was performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA).

RESULTS

Granulomas were detected in 33 patients. Of those identified, 54.5% were female, with a mean age of 3.1 years (SD = 4.8). The etiologic factors of 19 cases (57.6%) of granulomatous hepatitis were identified by pathologic examination and also, review of their clinical and laboratory data.

Table 1 shows the frequency of patients with granulomatous hepatitis according to age groups. About 60.6% of the patients were between 1 month and 1 year old.

Table 2 shows the various etiologies of liver biopsies revealing epithelioid granulomas.

Fifteen cases were attributed to mycobacterial infection and of these, 66.7% had caseous necrosis.

Sarcoidosis accounted for 2 of the 33 cases. Two patients in our series were deemed to have Hepatitis C virus infection and kala-azar, respectively. The definite cause of fourteen cases remained undiagnosed by our tools, although all of them used antibiotics which are known cause of granuloma formation, however we could not prove their etiologic role.

Table 1: Frequency of patients with granulomatous hepatitis according to age groups

Age groups	Number of cases	Percentage of cases
>1 month	1	3.0
1 month-1 year	20	60.6
1 year-6 years	3	9.1
<6 years	9	27.3

Table 2: Underlying diagnosis of patients diagnosed with epithelioid hepatic granulomas between April 1996 and March 2005 at Children's Medical Center

Underlying diagnosis	Number of cases	Percentage of cases
Mycobacterial infection	15	45.5
Undiagnosed	14	42.4
Sarcoidosis	2	6.1
HCV infection	1	3.0
Kala-azar	1	3.0

Clinically, 48.5% of patients presented with hepatosplenomegaly, 36.4% with pyrexia, 30.3% with jaundice and 9.1% with anemia, 9.1% with pneumonia, 6.1% with lymphadenopathy, 6.1% with weight loss, 3% with skin lesions and 3% with fatigue. About 18.2% showed elevated levels of liver enzymes and elevated levels of bilirubin, 12.1% elevated alkaline phosphatase levels and 9.1% raised ESR, 9.1% positive PPD, 3% pancytopenia, 3% leukocytosis and 3% thrombocytopenia.

The 11 patient having mycobacterial infection had immunodeficiency states.

DISCUSSION

Granulomas are defined as focal accumulations of modified macrophages (epithelioid cells), which may fuse to form multinucleated giant cells and typically have a surrounding rim of lymphocytes and fibroblasts. They are an example of a delayed-type hypersensitivity reaction in response to some form of antigens (Pasquale, 2003). Cases of granulomatous hepatitis are well characterized in terms of their infective and idiopathic etiology and association with drugs and HIV co-infection ((Ishak, 1988; Ryan, 1998; Murthy, 1997). Etiologically, granulomas may be infective or non-infective. The infective causes include bacteria, fungi, mycobacteria and viruses. In the non-infective types, the causes may be sarcoidosis, drugs or idiopathic (Pichardo-Bahena, 2002).

Hepatic granulomas are not uncommon, seen in up to 30% of routine liver biopsy specimens and can result from a number of infective and non-infective conditions. Of these, tuberculosis and sarcoidosis together account for 50-65% of cases. Total 26-50% of cases remain undiagnosed despite extensive investigations (Sartin, 1991; Zoutman, 1991).

We found 33 cases of granulomatous hepatitis over a 10 years experience. Mycobacterial infection was seen to be an important cause of granulomatous hepatitis in our study (45.5% of cases). Sarcoidosis, Hepatitis C virus infection and kala-azar were the other known causes. Patients aged 1 month 1 year were found to be particularly affected; impaired immunity in this age group could be responsible for the presence of infection.

In our series, similar to that reported by Shabharwal (1995) infections accounted for a large proportion of cases. Mycobacterial infection was the commonest cause seen in 55% of cases in their study. Other causes included leprosy, sarcoidosis, histoplasmosis, brucellosis and amoebic liver abscess (Sabharwal, 1995). Also, a series from Turkey revealed that infectious agents including mycobacterial infection, hydatid disease, brucella and

typhoid fever accounted for over half of their hepatic granuloma cases (Mert, 2001). In addition, in a series from Saudi Arabia, schistosomiasis accounted for over half of the cases, with mycobacterial infection the next most common cause (Satti, 1990). This is in sharp contrast to other parts of the world. The most common clinical diagnoses study were primary biliary cirrhosis which accounted for 90 cases (55%) and sarcoidosis which accounted for 30 cases (18%). Other less common conditions associated with hepatic granulomas included tuberculosis, Crohn's disease, chronic active hepatitis, drug hypersensitivity and extra-hepatic biliary obstruction (McCluggage, 1994). In addition, the study showed that autoimmune liver diseases including primary biliary cirrhosis, overlap syndrome and autoimmune hepatitis accounted for the majority of cases (68%), followed by sarcoidosis, chronic hepatitis B virus and hepatitis C virus infection, idiopathic, drugs and other miscellaneous causes (Saramadou, 2007).

Liver biopsy provides diagnostic information in approximately 15-30% of cases, identifying directly the microbial agent with special microbial stains and polymerase chain reaction or finding distinctive microscopic features, suggestive of specific microorganisms. Unfortunately, in one third of cases is impossible to reach etiological diagnosis on histological criteria alone (Pasquale, 2003). We identified the etiologic factors in 57.6% of our cases by pathologic examinations and the exact cause of 42.4% of cases remained undiagnosed. The type of mycobacterium was not clear for us because no sample for mycobacterial culture was taken in most of cases but according to clinical data it seems that most of them had disseminated BCG infection and had proven underlying cell mediated immunodeficiency.

CONCLUSION

Our series showed that mycobacterial infection is an important cause of granulomatous hepatitis in Iranian children. Unfortunately there are a few published data concerning the prevalence and etiologic factors of granulomatous hepatitis in children, so we can hardly investigate whether there has been an alteration in distribution of diagnoses in our series compared with those published so far in the literature. Finally, despite extensive investigations, 42.4% of our patients had no etiology identified and were thus, labelled idiopathic.

RECOMMENDATIONS

We recommend that for cases with mycobacterial infection, differentiation with molecular methods, available for formalin-fixed paraffin embedded tissues and for cases with no organism molecular methods that can show any small amount of organisms be done especially in developing countries to estimate their role in disease formation.

REFERENCES

- Gaya, D.R., 2003. Hepatic granulomas: A 10 year single centre experience. *J. Clin. Pathol.*, 56 (11): 850-853.
- Ishak, K.G., 1988. Drug-induced and toxic granulomatous hepatitis. *Baillieres. Clin. Gastroenterol.*, 2: 463-480.
- McCluggage, W.G., 1994. Hepatic granulomas in Northern Ireland: A 13 year review. *Histopathology*, 25 (3): 219-228.
- Mert, A., 2001. The aetiology of hepatic granulomas. *J. Clin. Gastroenterol.*, 32: 275-276.
- Murthy, B.V.R., 1997. A 1990s perspective of hepatitis C, human immunodeficiency virus and tuberculosis infections in dialysis patients. *Semin. Nephrol.*, 17: 346-363.
- Pasquale, G., 2003. Bacterial granulomatous hepatitis. *Infez Med.*, 11 (2): 69-74.
- Pichardo-Bahena, R., 2002. Epithelioid granulomas in a patient with hepatitis C virus. *Ann. Hepatol.*, 1 (2): 91-93.
- Ryan, B.M., 1998. The development of hepatic granulomas following interferon-alpha 2b therapy for chronic hepatitis C infection. *Eur. J. Gastroenterol. Hepatol.*, 10: 349-351.
- Sabharwal, B.D., 1995. Granulomatous hepatitis: A retrospective study. *Indian. J. Pathol. Microbiol.*, 38 (4): 413-416.
- Saramadou, R., 2007. Hepatic granulomas: A 6 years experience in a single center in Greece. *Eur. J. Gastroenterol. Hepatol.*, 19 (2): 101-104.
- Sartin, J.S., 1991. Granulomatous Hepatitis: A retrospective review of 88 cases at the Mayo Clinic. *Mayo Clin. Proc.*, 66: 914-918.
- Satti, M.B., 1990. Hepatic granuloma in Saudi Arabia: A clinicopathological study of 59 cases. *Am. J. Gastroenterol.*, 85: 669-674.
- Zoutman, D.E., 1991. Granulomatous hepatitis and fever of unknown origin. *J. Clin. Gastroenterol.*, 13: 69-75.