HEPATIC GRANULOMAS - AN EXPERIENCE OVER THE LAST 8 YEARS

R S E Chong, H S Ng, L B Teh, J M S Ho

ABSTRACT

Twenty cases of hepatic granulomas seen in the Department of Medicine over the period of 8 years from 1981 - 1988 were reviewed. Prolonged fever and jaundice were the commoner presentations. While the aetiology was varied, patients with tuberculosis and idiopathic causes formed the major groups. There were also 2 rare causes, one due to cytomegalovirus infection and the other a result of allopurinol hypersensitivity. The idiopathic group of cases fared well but those with tuberculosis did badly and 2 out of 6 died. The absence of pulmonary involvement and the high incidence of jaundice and liver dysfunction in the patients with tuberculosis were the other striking features.

Keywords: Hepatic Granulomas, idiopathic, tuberculosis.

SINGAPORE MED J 1990; Vol 31: 422 - 426

INTRODUCTION

The liver is an organ through which a large proportion of the blood flows through. It is very much akin to a filter or sieve through which bacteria, toxins, drugs or any other substance that is absorbed through the gut and circulating in the body will have to pass through.

Granulomas in the liver are the inflammatory response of such foreign substances in the liver. Taking into account the multiple aetiologies, a finding of hepatic granulomas can only serve as a useful diagnostic tool if other investigations and the clinical situation are taken into consideration. With the exception of tuberculosis, this finding has very little prognostic implication on liver function. The commonly used term "granulomatous hepatitis" is really a misnomer as there is no true hepatitis from the histological point of view and the majority of patients do not suffer from gross liver dysfunction. In this study of 20 consecutive cases with hepatic granulomas, we looked at their clinical presentations, investigations and the final diagnoses reached. The principal aims were to identify the commoner causes of granulomas in Singapore, to look for any diagnostic clues from investigations and to study the course of disease of the different causes.

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MATERIALS AND METHODS

Over the last 8 years (1981-1988), 20 patients with hepatic granulomas were seen in the Department of Medicine III, Singapore General Hospital. These patients had been investigated for various problems ranging from abnormal liver function tests to prolonged fever and had liver biopsies as part of the diagnostic workup.

We looked at a) their presentation, b) biochemical abnormalities including liver function tests, peripheral blood counts c) bacteriological tests including cultures and various serological tests to agents like cytomegalovirus and brucella, d) course of disease and eventual outcome e) the final diagonsis reached.

RESULT

Diagnoses

After investigations, a definite diagnosis was made in only 14 patients, the other 6 where aetiology was unknown were classified as idiopathic (see Table I). Tuberculosis was the commonest cause followed by the idiopathic group.

Clinical Presentation

Fever was the commonest presention and was seen in 11 patients including the 6 cases with an idiopathic cause (Table II). Eight patients presented with jaundice and of these 4 had tuberculosis, 2 had primary biliary cirrhosis and 2 had drug induced causes (1-oral

Table I
Aetiological Diagnoses Reached in the Patients

Aetiology	No.
Tuberculosis	7
Idiopathic	6
Primary biliary cirrhosis	3
Non Hodgkin's lymphoma	1
Cytomegaloviral infection	1
Oral contraceptives	1
Allopurinol	1
Total	20

Table II
Presenting Symptoms in All the Patients

Symptoms	No.
Fever	11
Jaundice	8
Incidental finding	1
Total	20

Table III
Presenting Symptoms in Tuberculosis

Symptoms	No.
Jaundice	4
Fever with anorexia, weight loss	2
Incidental finding	1
Total	7
Associated Signs	
Gross Ascites	1
Multiple nodules on CT scan of the abdomen*	1
Chest Roentogenograms	
a) Normal	4
b) Abnormal	3 (localised disease 1, miliary disease 2)

* This patient, No. 12 in Table IV, was later found to have tuberculomas on laparotomy.

contraceptives, 1 allopurinol). The remaining patient was found to have granulomas on liver biopsy for alcoholic liver disease. He had a history of contact with tuberculosis and was treated with a course of anti-tuberculous chemotherapy. Looking at tuberculosis as a group, other than the asymptomatic patient, the presenting symptoms of the other 6 patients were jaundice in 4, anorexia, weight loss and fever in 2. One patient also had gross ascites associated with jaundice (Table III). It is also interesting to note that 1 of the patients presenting with jaundice had on CT scan of the abdomen multiple nodules in the liver which turned out to be tuberculomas on laparotomy.

Biochemical Tests
Liver function tests showed elevated alkaline phosphatase in all cases but their range was variable, being highest in patients with primary biliary cirrhosis. Transaminases (SGPT/SGOT) were variably affected with 6 in the normal range. A high globulin level was noted in some patients with idiopathic disease, tuberculosis and primary biliary cirrhosis but it was of no value in predicting outcome or prognosis. Eosinophilia was present in the blood and liver of the patient with allopurinol induced hepatitis.

Bacteriological Tests.
All patients with idiopathic and tuberculous aetiologies had their liver biopsies cultured for acid-fast bacilli. None of these had positive cultures despite the presence of acid-fast bacilli demonstrated on Ziehl-Neelsen stain in 3 patients. Serology to cytomegalovirus (IgM CMV) was positive in patient no. 19 (see Table IV) and the virus was also cultured in the urine.

Course of Illness and Outcome
All the patients were followed up regularly by the gastroenterologist concerned. Periodic liver function tests were done but there were no repeat liver biopsies. Eventual outcome was based on clinical and biochemical rather than histological parameters. From Table IV, it can be noted that patients with idiopathic causes fared relatively better than those due to tuberculosis.

Idiopathic group
The overall prognosis for this group was good. Spontaneous recovery was observed in 4 of 6 patients after 2-4 weeks. One patient responded to prednisolone after a failed trial of anti-tuberculous chemotherapy. The other absconded follow-up.

Tuberculosis: Both deaths in this series had tuberculosis, 1 of whom had miliary shadows on chest roentgenogram and the other a rather prolonged illness of one month before any treatment. It is also interesting to note that both deaths were from the 3 patients with acid-fast bacilli demonstrated on Ziehl-Neelsen stain of liver tissue. The other 5 patients responded well to anti-tuberculous chemotherapy.

Primary biliary cirrhosis: Despite the presence of granulomas, all 3 patients though alive have shown considerable deterioration both clinically and in liver function tests.

Drug induced causes: 1 patient with allopurinol induced disease recovered after cessation of the drug and a course of steroids. The other patient with a history of oral contraception ingestion was unfortunately lost to follow-up.

Cytomegalovirus: The patient had a spontaneous recovery after 3 weeks.

Non Hodgkin's Lymphoma: This was an Indian patient who after diagnosis returned to India and was lost to follow-up.

Table IV
Diagnosis, Relevant Investigation and Course of Illnesses

Diagnosis	Case	TP g/dl	Alb g/dl	Liver Function Tests SGOT iu	SGPT iu	SAP iu	Bil mg/dl	Investigations (relevant)	Course of illness
Idio-pathic	1	9.0	2.7	43	34	221	0.2	All investigations – negative	Recovered
	2	6.9	4.1	195	187	120	0.5		Recovered
	3	5.9	3.2	89	164	466	0.8		Recovered
	4	6.4	3.9	125	271	147	1.1		Recovered
	5	6.0	3.8	125	205	130	1.1		Absconded F.U.
	6	6.0	3.8	125	205	130	1.1		Is well on prednisolone
Tuber-culosis	7	5.8	3.7	409	284	310	6.1	CXR miliary TB ZN +ve	Died
	8	5.8	3.3	656	408	375	3.9	CXR-nad ZN -ve	Recovered
	9	5.4	3.3	656	408	375	3.9	CXR-nad ZN -ve	Recovered
	10	5.7	3.3	26	25	300	2.0	CXR-TB(R) apex ZN +ve	Died
	11	8.3	3.5	30	18	195	1.5	CXR-miliary TB ZN -ve	Recovered
	12	7.9	3.1	30	32	101	0.4	CXR-NAD ZN -ve	Recovered
	13	7.7	4.3	43	57	103	2.2	CXR-NAD ZN +ve	Recovered
PBC	14	7.4	3.2	120	210	990	6.7	Antimitochondrial (AMA) ab -ve	Deteriorated
	15	7.3	3.1	65	70	600	1.7	AMA +ve	Deteriorated
	16	7.5	3.1	60	70	800	5.3	AMA +ve	Deteriorated
DNG (oral contraceptives)	17	7.3	3.6	52	52	401	36.4	AMA +ve	Absconded
Allopurinol	18	6.8	3.0	96	174	350	2.8	Eosinophilia 39% (TW 19x10^9/L)	Recovered
Cytomegalo virus infection	19	7.5	4.0	110	123	108	0.8	IgM CMV +ve Urine for CMV +ve	Recovered
Non-Hodgkin's lymphoma (large cell)	20	7.5	3.3	24	32	104	0.3	Lymph node biopsy proven	Absconded

SGOT – Aspartate transaminase
SGPT – Alanine transaminase
SAP – Alkaline phosphatase
TP – Total protein
Bil – Serum bilirubin
Alb – Serum albumin

DISCUSSION

Hepatic granuloma is a pathological reaction to a variety of stimuli including drugs, infection, toxins and others[1]. This histological finding is in the majority of cases non-specific unless the history and other investigations are taken into consideration. Liver biopsies with granulomas are found usually in patients with difficult diagnostic problems and it is not suprising that prolonged fever, complex cases of jaundice and hepatomegaly with abnormal function tests are the commoner presentations in our series. The high incidence of idiopathic causes, about 30% in our series is similar to that in others[2,3]. This probably reflects the difficult situations when liver biopsies are done. The absence of sarcoidosis but the high incidence of tuberculosis probably reflects the low incidence of the former and the high prevelance of the latter, tuberculosis being a condition endemic in our country. This differs from other series where sarcoidosis is a very common diagnosis[2-5].

Tuberculosis of the liver per se is uncommon and the majority of the patients are asymptomatic and rarely present with any severe liver dysfunction. The presence of pulmonary tuberculosis does not imply concomitant involvement of the liver[6, 7] and in a study by Cruise[6] only 7 patients out of 1748 patients with pulmonary tuberculosis had jaundice. This is also seen in our series where only one patient had localised pulmonary tuberculosis, 2 had miliary shadows indicating a systemic disease rather than localised disease and 4 patients had no changes on chest roentgenograms (Table III). This condition which is sometimes also known as primary tuberculosis of the liver[8, 9] is thought to be due to extensive involvement of the liver and though ascites and splenomegaly are common, the absence of extra abdominal involvement is characteristic. It is an important entity to recognise as a high mortality is associated with late treatment.

Other than extensive involvement of the liver, tuberculosis has also been described involving primarily the biliary tract resulting in a form of cholangitis[6]. The presence of huge tuberculomas has also been reported[9] albeit rare. This was seen in patient no. 12 who had numerous filling defects on CT scan which on laparotomy turned out to be tuberculomas. Our series, like in

others[8,9] has reported a relatively high mortality in patients with tuberculosis of the liver and probably reflects the extensive hepatic involvement by the time significant symptoms and signs appear. Nevertheless, response to treatment is encouraging and it should be started based on histological findings rather than culture results which are usually negative. In our series, the diagnosis was based primarily on the finding of caseous necrosis and the loss of reticulin helped occasionally by the presence of acid-fast bacilli on Ziehl-Neelsen staining.

Though the diagnosis of idiopathic granulomatous hepatitis is made by excluding all other known causes, this condition is now thought to represent a distinct entity[10-14]. All patients present with fever but based on the course of disease, 2 distinct groups are thought to exist. The first group has a self limiting course as in patients 1 to 4 where resolution is to be expected in 2-4 weeks[10]. This has been thought to be due to an atypical form of infectious mononucleosis. The other group has a protracted course with persistent fever and only responds to steroids which are usually given after a course of anti-tuberculous chemotherapy[12-14]. Our patient (no. 6) responded well and continues to do well on steroids. Unfortunately, our series like in others has been unable to predict when steroids are needed and how long they should be kept on. In view of this, we felt it would be prudent to keep our patient on the smallest possible dose of steroids indefinitely.

The 3 patients with primary biliary cirrhosis deteriorated despite the presence of granulomas, a finding initially thought to predict a better prognosis[15]. This finding has since been refuted by other studies[16]. The prognosis in primary biliary cirrhosis is now thought to be dependent on other factors like serum bilirubin, albumin levels and prothrombin times[16-19] rather than histological staging. Though granulomas are seen in early primary biliary cirrhosis, they are unlikely to offer a good prognosis. Infection with cytomegalovirus virtually always involves the liver but hepatic granulomas are rare[20,21], being first described by Reller in 1973[20]. This finding does not alter the prognosis of the disease and, like all other forms of cytomegaloviral involvement of the liver, is usually self limiting. Similarly, allopurinol induced hepatic injury is also uncommon and just over 20 cases have been reported in the literature[22,23]. The mechanism is thought to be a hypersensitive one and as seen in our patient (no. 18), is usually associated with the development of fever, rash, peripheral as well as tissue eosinophilia. Deaths have been reported from massive hepatic necrosis and treatment is withdrawl of the drug, steroids having no proven value.

On looking at all our cases, the most common causes were tuberculosis and idiopathic. While in western countries, a trial of steroids would be useful where the diagnosis was unclear, it would differ here due to the high incidence of tuberculosis. This problem being very similar to that often seen in terminal ileal disease where the differentiation of Crohns disease from tuberculosis is often difficult. A good one to two-month trial of anti-tuberculous treatment should be considered in all our patients with hepatic granulomas of unknown aetiology before the use of steroids.

CONCLUSION

In this study of 20 patients, the most common causes of hepatic granulomas were patients with idiopathic and tuberculous aetiologies. The majority of the cases in the idiopathic group fared well and had self limiting courses with only 1 case having to be put on long-term steroids. This contrasted with the patients with tuberculosis, 2 of whom died. The group was characterised by a) the relative absence of pulmonary and extra-abdominal involvement b) the high incidence of jaundice. It is important to start early treatment based on clinical suspicion taking into consideration the endemicity of the condition here rather than relying on positive liver tissue culture for mycobacterium tubercle, which is usually negative.

ACKNOWLEDGEMENT

We are grateful to Ms Jamalia Ali for her invaluable help in typing the manuscript.

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