DUPLEX DOPPLER ULTRASOUND OF HEPATIC SCHISTOSOMIASIS JAPONICA: A STUDY OF 47 PATIENTS


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Abstract. This study describes the ultrasound (US) appearances of the liver with hepatic schistosomiasis japonica (HSJ), and studies the portal hemodynamics in 47 patients with HSJ using duplex Doppler US over a period of 15 years. All patients but two were Chinese war veterans seen in Taiwan about 35–55 years after their presumed infection in Mainland China. The US presentations were reviewed. The data from Doppler portal flow studies were available for 39 patients with HSJ, and compared to data from Doppler portal flow studies in 40 normal healthy volunteers and to this data in 40 patients with postnecrotic cirrhosis. A typical “coarse reticular pattern” due to fibrosis in the whole liver was noted in 40 patients (85%). Other findings included periportal fibrosis (15%), septum-like fibrous bands extending to the liver capsule (32%), and an apparent nodular liver surface (19%). Splenomegaly was noted in seven patients. While coexisting hepatocellular carcinomas (HCC) were evident in three patients, and esophageal varices were found in three others, yet both conditions were found only in patients with positive hepatitis-B-surface antigen (HBsAg). HSJ can be confidently diagnosed in patients with hepatic fibrosis when the hepatic pathology is presented as the coarse reticular pattern. The portal hemodynamics in HSJ patients who have been isolated from the infection site (for more than 35 years) are significantly different from portal hemodynamics in cirrhotic patients and are similar to those in healthy volunteers.

INTRODUCTION

Schistosomiasis is one of the most common parasitic infec-
tions in humans. There are five species of Schistosoma which can cause severe disease in man, namely: S. haematobium, S. mansoni, S. japonicum and the recently recognized S. mekongi and S. intercalatum. It has been estimated to affect about 200 million people in more than 71 countries worldwide. S. japonicum is still one of the major public health problems in Mainland China, the Philippines, Japan, and Indochina, with more than 10 million people infected in Mainland China alone. No primarily infected cases have been reported in Taiwan, but it may be encountered there in the immigrants from Mainland China. Hepatic schistosomiasis japonica (HSJ) has received little attention and splenoportal hemodynamics has not been studied. Here, the ultrasound (US) features were reviewed and Doppler portal flow studies were done in 47 patients of pathologically proved HSJ who were presumed to have obtained the infection in Mainland China and had been isolated from the active infection site for some 40 years. To the best of our knowledge, this is the largest such report in the English literature. The differences of US presentations between HSJ and hepatic schistosomiasis mansoni (HSM), the two major hepatic forms of schistosomiasis, are also emphasized.

MATERIALS AND METHODS

Over a period of 15 years, duplex Doppler US examinations of the liver and portal venous system were done in 47 patients who were, for the purpose of ruling out the possibility of metastatic or hepatic tumor, tested and subsequently proved to have HSJ by either percutaneous needle biopsy (21 patients) (Figure 1) or intraoperative wedge biopsy or segmentectomy (26 patients). All patients were enrolled in this study in accordance with a protocol approved by the institutional review board of the medical ethics committee. Informed consents were obtained when percutaneous liver biopsy was indicated. None of these patients had active infection at the time of the investigation since none had ova in their feces. All patients but two were male army veterans who had immigrated from the Yangtze River basin of Mainland China (age at immigration: 16–39 years). While their ages at the time of the study (1984–1998) ranged from 53 to 85 with a mean age of 68.4, all presumably had been infected with schistosoma japonica over 35–55 years earlier in Mainland China. The major symptoms and causes suggesting use of abdominal US were upper abdominal pain in 17 and general malaise in 11; the other 19 presented with symptoms of underlying pulmonary or chronic renal diseases, abnormal liver function tests or necessitated work-up for known malignancy.

All subjects abstained from eating the night before the US study, while medications had been stopped at least 3 days before the study of Doppler portal flow measurement. Healthy subjects and cirrhotic patients without ascites consumed food freely. While the US scanners we used were DRF 400 (Diasonics, Milpitas, CA, USA), ATL UM8 (Advanced Technology Laboratory, Bothell, WA, USA), RT 3600 (GE Medical System, Milwaukee, WI, USA), XP 10 (Acuson, MountainView, CA, USA), Spectra Master Series and VST (Diasonics, Milpitas, CA, USA), and HDI 3000 (Advanced Technology Laboratory, Bothell, WA, USA), all were equipped with 3.0- or 3.5-, and 5.0-MHz transducers and duplex (or triplex) Doppler function. All patients were examined before eating in the morning. The liver, spleen, portal venous system were assessed using real-time image first, followed by Doppler spectral analysis of the portal vein.

With the pulsed Doppler US, the spectrum of the main
portal vein in its mid-portion was obtained. The axial size of the sample volume was adjusted to encompass the portal vein lumen in its entirely middle third. The angle between the Doppler beam and the long axis of the vessel was measured as less than 60°. Measurements of time average maximum velocity (TAMV) of the portal flows were done at least twice for each site and the averages were used for further studies (Figure 2). The portal flow rate (ml/min) was calculated from the diameter, was assumed to be circular.

The available Doppler portal flowmetry data were reviewed for 39 patients. The study was carried out by comparing the portal blood flow measurement of these 39 patients with HSJ (Group A, mean age: 68.4 ± 5.7 years) with those of 60 patients with cirrhosis (Group B, mean age: 55.2 ± 8.1 years) and those of 40 healthy adult volunteers (Group C, mean age: 59.5 ± 6.3 years).

RESULTS

US features of HSJ in these 47 patients included: (a) In 40 patients (85%), a coarse reticular pattern, mostly diffuse, was found; and 11 of these were predominantly in the right lobe (Figure 3). While the thickness of reticulum was mostly > 2 mm, the size of nodules within the reticulum was mostly from 5 to 30 mm, and the reticula were often associated with a portal vein radicle in the center (Figure 4). Six of these 40 patients were accompanied by minimal periportal fibrosis (represented by “bird’s-claw” pattern)12 (Figure 5); (b) Periportal fibrosis as the only finding was noted in seven patients (15%); (c) In 15 patients (32%), thick, septum-like fibrotic band in extending to the liver capsule were found (Figure 6); (d) In 9 patients (19%), liver surface nodularity secondary to the deep fibrotic furrows on the surface was found, which

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was always associated with underlying thick fibrotic bands (Figures 3, 6). In this instance, occasional larger reticula could be found (13%) (Figure 6); (e) in 3 patients (6%) hepatic tumors (hepatocellular carcinoma, HCC) were found; and (f) in 40 patients (85%) there was a small liver size in 40 (85%) (Table 1).

The most common associated finding was splenomegaly (i.e. > 12 cm in axial length), being noticed in 10 patients (21%); among those, dilated portal vein (> 1.3 cm) was noted in six patients (13%), splenoportal vein thrombosis with calcification was noted in two patients (4%), while esophageal varices were noted in three patients (6%). Six of the 10 patients with splenomegaly were associated with a positive HBsAg immunoassay (60%). In the other 37 patients without splenomegaly, only 22% (8/37) showed positive HBsAg. No one was demonstrated to have a significant patent paraumbilical vein. The results of measurements of portal blood flow in 39 patients with HSJ, in 40 patients with cirrhosis (Group B) and in 40 healthy adult volunteers (Group C) are shown in Table 2. There was no statistically significant difference in blood flow velocity and blood flow volume between group A and group C. On the other hand, blood flow velocity and flow volume were significantly decreased in Group B as compared with the control group (Group C). The portal flow tended to decrease in cirrhotic patients but not in these 39 patients with HSJ (Table 2).

**DISCUSSION**

*Schistosomiasis japonicum* in man chiefly affects the tissue of the intestine and the liver. After the schistosomal ova reach the liver through the portal vein and incite a chronic granulomatous reaction, presenting as pipestem and periportal fibrosis,1–5 the terminal portal vein branches become occluded, leading to presinusoidal portal hypertension, splenomegaly, varices, and ascites.2,3 Diagnosis of hepatic schistosomiasis is mainly based on the discovery of eggs from stools, needle biopsy or intraoperative wedge biopsy of the liver, and by peritoneoscopy.

However, as the output of schistosomal eggs per day may

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Ultrasoundographic features of liver and other associated findings (47 cases)</th>
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<tbody>
<tr>
<td>Findings</td>
<td>Case number</td>
</tr>
<tr>
<td>Liver:</td>
<td></td>
</tr>
<tr>
<td>a. Coarse reticular pattern</td>
<td>40</td>
</tr>
<tr>
<td>• thickness of reticulum &gt; 2 mm</td>
<td>(34)</td>
</tr>
<tr>
<td>• thickness of reticulum ≤ 2 mm</td>
<td>(6)</td>
</tr>
<tr>
<td>• size of nodules 10–30 mm</td>
<td>40</td>
</tr>
<tr>
<td>b. with minimal periportal fibrosis</td>
<td>7</td>
</tr>
<tr>
<td>c. periportal fibrosis only (minimal)</td>
<td>7</td>
</tr>
<tr>
<td>d. thick septum-like fibrotic band</td>
<td>15</td>
</tr>
<tr>
<td>e. liver surface nodularity associated with</td>
<td></td>
</tr>
<tr>
<td>subcapsular furrows</td>
<td>9</td>
</tr>
<tr>
<td>f. small liver size (&lt; 12 cm)</td>
<td>40</td>
</tr>
<tr>
<td>Spleen:</td>
<td></td>
</tr>
<tr>
<td>a. splenomegaly (&gt; 12 cm in the greatest diameter)</td>
<td>10</td>
</tr>
<tr>
<td>b. splenic echopattern change</td>
<td>0</td>
</tr>
<tr>
<td>Portal vessels:</td>
<td></td>
</tr>
<tr>
<td>a. dilated portal vein (&gt; 1.3 cm)</td>
<td>6</td>
</tr>
<tr>
<td>b. splenoportal vein thrombosis with calcification</td>
<td>2</td>
</tr>
<tr>
<td>c. esophageal varices</td>
<td>3</td>
</tr>
</tbody>
</table>
be very low, and the eggs are sometimes difficult to find within the fibrotic bands from needle or wedge biopsy; these diagnostic methods may not be conclusive.\textsuperscript{11-15} Imaging modalities, such as computed tomography (CT) and US have been used in the diagnosis of schistosomiasis of the liver or the intestine.\textsuperscript{6-10,12-21} The CT and US features of the liver in Schistosomiasis mansoni are well documented.\textsuperscript{11-12} The CT and US manifestations of Schistosomiasis japonicum were most frequently reported in articles from Japan and Taiwan.\textsuperscript{6-9,19-21} While there have been several reports on the US presentation of HSM.\textsuperscript{12,14,16}

The characteristic features of “schistosomal periportal fibrosis” are dense echogenic bands along the long axis of the intrahepatic portal vein radicles. This would show a “bird claw” pattern at the bifurcation points of the widened echogenic portal tracts, and round or oval echogenic foci when scanned across their long axes.\textsuperscript{12,14,15} Widening of the portal vein and splenic vein and hypertrophy of the left hepatic lobe are also common findings in HSM.\textsuperscript{15} Homeida et al graded the periportal fibrosis as grades 1 to 3, depending on the degree of thickened walls and degree of narrowing of portal vein radicles. In the study with US in two villages in the Geriza Region of Sudan, they concluded that the prevalence and degree of splenomegaly as well as the portal and splenic vein diameters increased with grade. Splenomegaly was noted in 35-40% of patients with periportal fibrosis.\textsuperscript{15} In most individuals with hepatosplenitic schistosomiasis the spleen is increased in size. However, hepatosplenic schistosomiasis can occur without splenomegaly.\textsuperscript{22} Patients with periportal fibrosis have a prevalence of esophageal varies of 54\% to 67\%.\textsuperscript{23} In the review of 103 patients with hepatosplenic schistosomiasis mansoni,\textsuperscript{14} Cerri found that there were high incidences of prominent periportal fibrosis (73\%), left lobe hypertrophy (81\%), splenomegaly (100\%), and portal vein dilatation (73\%).

However, the above described findings are rarely encountered in HSJ in our series (Table 1). The characteristic US feature of HSJ is chiefly a “coarse reticular pattern”, which may be associated with minimal periportal fibrosis occurring only in the region of the hepatic hilum without extending to the subsegmental zones. These may produce more diffuse and more peripheral changes of the hepatic fibrosis, and therefore form a “coarse reticular pattern”. The coarse reticular pattern, also known as network pattern first described by Nakayama et al,\textsuperscript{24} has been reported to be characteristic US finding of the liver infected with S. Japonicum. The echogenic reticular bands of fibrosis are connected to the liver capsule and appear to be augmentation of interlobar and interlobular septa; they encircled blocks of parenchyma that often contain a central portal branch.\textsuperscript{25} The reticular bands have been identified histologically as dense fibrous tissue contain ova.\textsuperscript{26} This has also been demonstrated in our series. None of the 103 HSM cases reported by Cerri et al had coarse reticular pattern. The reasons for that are probably because the eggs of S. japonicum are of smaller size (one half those of S. mansoni) and S. japonicum produces more eggs (approximately ten times more) than S. mansoni.\textsuperscript{19,27-28} In our experience, needle biopsy from the reticulum can yield more positive results in the histological study.

There is no convincing evidence that schistosomiasis may predispose to HCC.\textsuperscript{15,27} While it is well known that hepatitis B infection and schistosomiasis japonica share the same endemic areas, and the hepatotropic viruses play a pathogenetic role in the development of HCC,\textsuperscript{29-31} Nakashima et al found that of 227 cases of HCC, only 24 patients (10.6\%) were associated with HSJ. However, 16 of these 24 patients (67\%) exhibited evidence of post-necrotic cirrhosis as well, suggesting that viral hepatitis rather than HSJ infection is the predominant etiologic factor involved in carcinogenesis.\textsuperscript{29} All HCCs occurred in our series were also associated with positive HBsAg, confirming the relationship of hepatitis B infection and HCC.

Dopplex ultrasound, by combining real-time ultrasound imaging and Doppler spectrum analysis of the blood flow in the region of interest, has been used for measurement of portal vein hemodynamics for years.\textsuperscript{32-35} The portal venous flow is isolated from the systemic circulation by the capillary plexus of the bowel and the liver sinusoids. Flow is normally at a slow steady velocity towards the liver.\textsuperscript{36} The portal venous flow is known to be influenced by factors such as age, sex, body texture, posture, respiration and food ingestion.\textsuperscript{37-40}

Several authors have noticed a decrease in the velocity of portal venous flow in patients with cirrhosis.\textsuperscript{32,33} The liver involved by chronic infection with schistosomiasis will present with collagen deposition within the portal tracts, which will result in presinusoidal portal hypertension.\textsuperscript{3}

The portal blood flow should also be theoretically decreased as it was in the group of patients with cirrhosis. However, our study showed that there was no significant difference in portal venous flow velocity and volume between the group of patients with HSJ and the control group. There are several possible reasons for these results: 1. elimination of active infection source (in the present series of patients, immigration to Taiwan) results in a prompt decrease in the collagen synthetic rate without any change in collagenolysis, causing slow reversal of fibrosis\textsuperscript{41}; 2. while in the early stage of noncirrhotic portal fibrosis (including schistosomiasis), the portal venous velocity may decrease, however, because of the relatively dilated portal vein, the portal venous flow rate increases, this has been demonstrated by Doppler flowmetry in some workers.\textsuperscript{42-44} and 3. in the present study, 40 of these 47 patients (85\%) presented with coarse reticular pattern (7 were also associated with minimal periportal fibrosis), and 7 presented with minimal periportal fibrosis only (15\%). According to Kardorf et al, severe periportal fibrosis indicated a risk of portal hypertension, and reticular pattern apparently did not.\textsuperscript{45} This may explain why the portal venous flow velocity in our series was not significantly reduced. No patient was demonstrated to have a dilated paraumbilical vein in this series. This also suggested that these patients could be in the early stage of portal hypertension. Results obtained by US study

### Table 2

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Portal vein blood flow velocity (cm/sec)</th>
<th>Blood flow (ml/min)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>A: HSJ (n = 39)</td>
<td>15.62 ± 4.73</td>
</tr>
<tr>
<td></td>
<td>B: Cirrhosis (n = 40)</td>
<td>10.68 ± 3.46</td>
</tr>
<tr>
<td></td>
<td>C: Control (n = 40)</td>
<td>16.29 ± 4.07</td>
</tr>
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\*P<0.005 (95% confidence interval: 53.26-284.41); P<0.0023 (95% confidence interval: −283.49-21.24); P<0.05, not significant.
showed that the prevalence of patent paraumbilical vein ranged from 18% (patients with cirrhosis) to 82% (patients with portal hypertension). Yet the patients in our study were a unique group, having immigrated to Taiwan from Mainland China some 40 years ago where they had no chance of treatment for their HJS infection with drugs. They also had no documented or known history of medical treatment for HJS in Taiwan. In addition, they had benefited from being isolated from the original infection site for 40 years.

Although Oncomelania snails (the intermediate host of *S. japonicum*) have been found in some endemic areas in Taiwan, the *S. japonicum* in Taiwan is only a zoophilic strain and has not been found to infect man. None of the patients described here was infected in Taiwan; all patients but one are immigrants from Mainland China. Most of them moved to Taiwan after World War II during their adolescence or young adulthood (from 16 to 39 years old). None of them was found to have Schistosome ova in their feces. In the four patients who had undergone segmental or hemi-colon resection for adulthood (from 16 to 39 years old). None of them was found to have Schistosome ova in their feces. In the four patients who had undergone segmental or hemi-colon resection for adenocarcinoma, the surgical specimens of the resected colon also showed chronic inflammation with multiple calcified schistosome ova, fibrosis and infiltration of plasma cells and lymphocytes.

In recent years, international tourists, travelling businessmen, and immigrants have apparently increased in number, particularly in Asia. Radiologists and gastroenterologists in both nonendemic and endemic countries should be familiar with the US features of HJS since US is usually the imaging modality-of-choice in the developing countries.

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