Hepatocellular Carcinoma—A study of 200 cases

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Abstract
During a 7 year period 200 patients with histologically documented hepatocellular carcinoma were studied. The highest age specific rates were found between 30 and 60 years of age. More than 90% of patients came to medical attention because of abdominal pain, right hypochondrial mass, anorexia or weight loss. Hepatitis B virus markers, studied by CIEP and ELISA techniques, were positive in 25 of 98 patients studied. Alpha-fetoprotein was detected in 72 percent of patients studied. Aflatoxin was absent in the serum of the 14 cases studied for it. Cirrhosis was detected in 19 percent of patients only, the low incidence being partly accounted for by the fact that tissue was obtained by needle biopsy. Treatment was supportive.

Key Words: Hepatocellular carcinoma, alpha-fetoprotein, HBsAg, aflatoxin.

Introduction
The incidence of hepatocellular carcinoma (HCC) is low in most developed countries. By contrast it is common in sub-Saharan Africa and the Far East. We are reporting our findings in 200 cases of histologically proven HCC that we have seen in the department of Gastroenterology, Osmania General Hospital, Hyderabad, AP, during 1978-1985.

Material and Methods
Patients with suspected diagnosis of HCC were referred to our department for assessment and management.

The workup included a detailed clinical assessment, hemogram, liver function tests, roentgenogram of the chest, barium series, hepatic seotography, alpha-fetoprotein, aflatoxin and HBsAg estimation. Confirmation of diagnosis was obtained by liver biopsy in all cases. Those cases in whom diagnosis was probable but pathologic confirmation could not be obtained were excluded from the study.

In the initial 50 cases, HBsAg was estimated by immunodiffusion and CIEP (counter immunoelectrophoresis) techniques; later ELISA (enzyme linked immunosorbant assay) and RPHA (reverse passive haemagglutination) techniques were employed in 46 cases.

Alpha-fetoprotein (AFP) was estimated by CIEP in 53 cases. In the last 17 cases AFP was measured quantitatively by ELISA also. Aflatoxin was assayed in the serum of the last 14 cases of HCC by ELISA and TLC (thin layer chromatography). Hepatic scintigraphy was carried out in 121 cases using 131I in one case and 99Tc. Ultrasound examination was done in 22 cases.

Results
The age of the 161 male and 39 female (4:1) patients ranged from 14 to 80 years, with peak incidence in the 4th (18.5%) and 5th (42.7%) decades of life.

The presenting symptoms were mass in the abdomen (92.5%), pain in the abdomen (94%), loss of appetite (98%) and weight (80%), jaundice (15.5%) and hematemesis melan (10%). The duration of complaints varied from less than 2 weeks to one year, being less than 3 months in 25.8% of cases; 8-8% were admitted within 15 days following the onset of symptoms.

Hepatomegaly was detected in 192 (96%) cases. In 69% the liver varied in size from 4 cm to 10 cm below the costal margin. The liver was tender in 84% and its surface nodular in 55% of cases. All of them were hard on palpation. Clinical jaundice was noticed in 32% of cases, and 18% each had ascites and pedal edema. A bruit was heard over the liver in only 10% of cases. Splenomegaly was noted in 48 (24%) cases.

Laboratory findings: Serum bilirubin was normal in 67% of cases (Table). In four patients a picture of obstructive jaundice was seen, with bilirubin levels ranging from 1.5 to 5.8 mg/dl.

Table 1: Liver function tests in 200 cases of hepatoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>1.5</td>
<td>0.2–6.5</td>
</tr>
<tr>
<td>SGPT (&lt;5 U/ml)</td>
<td>98.4</td>
<td>25–500</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (K.A units)</td>
<td>52.7</td>
<td>6–150</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>2.7</td>
<td>1.3–5.5</td>
</tr>
<tr>
<td>Serum globulin (mg/dl)</td>
<td>3.6</td>
<td>2.4–5.8</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>19.1</td>
<td>14–39</td>
</tr>
</tbody>
</table>

more than 8 mg/dl and alkaline phosphatase more than 30 KA units. Alkaline phosphatase was elevated in 96.7% and serum transaminates in 47.5% of cases. The albumin levels were depressed in 149 cases.

Radiology: Twelve cases showed an elevated right hemidiaphragm. Right sided pleural effusion was observed in 4 cases. Ultrasonography of the liver showed a single or multiple space occupying lesions in 18 of 22 cases. Hepatic scan showed a cold area in the right lobe in 82 (67.7%) cases and in the left lobe in 21 (17.4%) cases. Eighteen (14.9%) cases showed diffuse patchy uptake.

Alpha-fetoprotein was positive in 40 of 55 cases (72%) in whom it was estimated by CIEP. By ELISA (normal level up to 25 ng/ml), 9 (53%) of 17 cases showed increased AFP levels, with a mean of 421 ng/ml; 4 (23.5%) cases showed slight increase (mean 31 ng/ml) and another 4 (23.5%) cases showed normal levels (mean 12 ng/ml). HBsAg was positive in 4 (8%) of 50 cases tested by CIEP and 21 (45.8%) of 46 cases tested by ELISA. Aflatoxin was not detected in any of 14 consecutive cases.

Histopathology: Of 200 cases 67.5% showed typical trabecular pattern. The trabeculae varied in thick-
ness, comprising of 2-8 cell thick plates. Pleomorphic variant of HCC was the second most common variety (8.5%), followed by adenocarcinoma (6.9%), clear cell carcinoma (1.8%), and papillary carcinoma (1.7%). Associated cirrhosis was observed in 38 cases (19%). Regenerative nodules were seen encircled by thick bands of fibrous tissue. Morphologically, the commonest type of cirrhosis observed was the macro nodular type.

Discussion

As seen from the present study, hepatocellular carcinoma is not an uncommon disease in this part of India. Our figure is likely to be underestimated as only biopsy-proven cases were included. However, HCC is common in sub-Saharan Africa, South East Asia, Japan and the Pacific islands. The incidence of HCC in our country is perhaps midway between that in these countries and in most western countries.

Male predominance (4:1) in our series is in accordance with most published reports. The peak incidence was in the 5th decade of life. The age of onset varies with the geographic location. In sub-Saharan Africa, the tumor develops at a relatively younger age, with a peak incidence in the third, fourth and fifth decades of life. In the Far East, most cases occur in the fifth and sixth decades of life. In populations with a low incidence, the peak occurrence is in the sixth to eighth decades of life.

At least one of the common biochemical parameters of liver function was abnormal in almost all our patients. These findings are similar to those of other investigators, who found serum alkaline phosphatase and SGOT to be abnormal in more than 80% of their patients, whereas serum bilirubin was less often elevated.

The diagnostic value of alpha-fetoprotein is widely confirmed. A positive result obtained by the relatively insensitive CIEP technique almost always indicates the presence of HCC. With relatively sensitive techniques, between 28 and 87 percent of patients with HCC will have demonstrable alpha-fetoprotein in the serum. However false positive rates are higher with these techniques. False positive rates are substantially reduced if higher values, eg, above 500 ng/ml, are taken as significant. Our finding of positivity in 72% of cases is compatible with published results.

There is overwhelming evidence that hepatitis B virus causes HCC. It appears to be responsible for at least 80% of the cases worldwide, although the percentage varies geographically. In our series HBsAg was detected in 25 of the 96 cases in which this marker was looked for, and in 2 of these 96 patients anti-HBs was detected in their sera. Since less sensitive tests like CIEP were employed for detection of these markers in the initial phase of the study and since only two markers (HBsAg and anti-HBs) were looked for, these figures almost certainly are an underestimate.

There is a significant increase in the risk of HCC in patients with cirrhosis, especially macro nodular cirrhosis. The proportion of carcinoma in cirrhotics ranges from 15 to 55%, being higher in populations with a high incidence of HCC. Conversely, cirrhosis, mainly macro nodular, is present in the non-neoplastic liver tissue of 0 to 30% of patients with HCC.

In our patients the diagnosis of cirrhosis was made in only 19% of patients with HCC. This is because we relied solely on needle biopsy for histopathologic studies. In one institution, the frequency of associated cirrhosis increased dramatically when peritoneoscopy supplemented liver biopsy for diagnostic purposes.

The only effective treatment of liver cancer is surgical resection. Yet the number of tumors amenable to surgical extirpation has been abysmally poor in places where the incidence is highest. Encouragingly, however, some centres are now obtaining 5 years survival rates as high as 20%.

References