Hepatocellular Carcinoma Sub-types in North-Central Nigeria: A Histological Review of Liver Biopsies


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Authors' contributions

This work was carried out in collaboration between all authors. Author RAV was responsible for the research concept, design and protocol. Authors JAN, BAO and OOJ critiqued the draft manuscript. The histological classification of each case was independently cross-checked by authors ANM, MDA and BMM. All authors read and approved the final manuscript.

ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide and a greater burden of this disease is born by the hepatitis B virus (HBV) endemic and resource deficient sub-Saharan Africa. This investigation was carried out to determine the pattern of hepatocellular carcinoma sub-types in north-central Nigeria.

Materials and Methods: Archival formalin fixed and paraffin embedded 374 liver biopsy specimen blocks were obtained, sectioned, re-stained and examined histologically. Classification of primary liver cancers was done according to standard World Health Organisation criteria.

Results: Chronic HBV infection was found in 219 (58.6%) and cirrhosis in 29 (7.8%) cases. HCC

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occurred in 76 (20.3%) cases with background cirrhosis in 18 (23.7%) of the HCC. The HCC subtypes found were the trabecular 54 (71.1%), acinar 10 (13.2%) and mixed trabecular and acinar 6 (7.9%), clear cell 5 (6.6%) and fibrolamellar 1 (1.3%) respectively.

**Conclusion:** HCC is the most common histologically diagnosed primary liver cell carcinoma with the trabecular subtype as the predominant variant in Nigeria, followed by the pseudoglandular and the mixed types.

**Keywords:** Liver; liver biopsy; hepatocellular carcinoma; hepatocellular carcinoma sub-types.

**1. INTRODUCTION**

Hepatocellular carcinoma (HCC) is the most common form of primary liver cell carcinoma and the 6th most common cancer worldwide [1]. The highest burden of this disease is born by the resource–constrained regions of the world with the highest occurrence in South East Asia and sub-Sahara Africa [2-4].

The first report of the high incidence of this disease in black Africans was published in 1921 by Pirie [5]. Since then, several authors have equally reported high Figures in several countries in sub-Saharan Africa [6-8]. This high incidence largely parallels the endemicity of hepatitis B virus infection [9,10]. Other aetiological factors implicated in pathogenesis of hepatocellular carcinoma include hepatitis C virus infection, aflatoxin B1 contamination, dietary iron overload, non–alcoholic steatohepatitis and chronic alcoholism [11-13]. Liver cirrhosis is the common end point of most liver diseases and may co-exist with HCC [14,15].

Inadequate health facilities, lack of access of patients to these facilities where available, poverty, superstitious beliefs, etc, have bedevilled the development of reliable cancer registries in most resource-constrained regions and, therefore, data on HCC from these regions have been largely incomplete or inaccurate and not faithfully reflect the true picture of the disease burden [16].

Whereas most previous published papers on HCC in Nigeria have provided insight into the frequency of histologically confirmed cases, this study aimed to document the occurrence of the morphological sub-types of hepatocellular carcinoma in Jos, north-central Nigeria.

**2. MATERIALS AND METHODS**

This retrospective study encompassed 374 liver biopsy tissue specimens accessioned in Jos University Teaching Hospital from January 2000 to December, 2009 inclusive. Archival records and paraffin embedded tissue blocks were retrieved re-sectioned and stained. Excluded from this evaluation were specimen blocks with missing or incomplete records, inadequately fixed or processed specimens and fine needle aspiration cytology specimens. Needle core tissue biopsy specimens which were too small or inadequate for evaluation were also excluded. Special stains such as Masson’s trichrome, Gordon and Sweet’s silver impregnation and Perls’ Prussian blue were also employed. Socio-demographic data, clinical information and hepatitis B surface antigen screening results available on the laboratory request forms were retrieved. Tumors were classified histologically according to the World Health Organization criteria and hepatocellular carcinoma cases were further grouped into morphological sub-types as trabecular, pseudoglandular, compact, fibrolamellar, or scirrhous [17]. Ethical clearance was obtained from the Ethical Committee of Jos University Teaching Hospital. Statistical computation was done using the 2007 version of Microsoft Excel.

**3. RESULTS**

Chronic hepatitis was found in 228 (61%) of the 374 specimens. Chronic hepatitis B virus infection accounted for 219 (58.6%) specimens, all serologically positive for hepatitis B virus surface antigen (HBsAg). Peak occurrence was in the 31-40 years age bracket. There were 29 (7.8%) cases of liver cirrhosis with peak occurrence within the 31-40 years age group.

Liver cancers constituted 88 (23.5%) of the total liver biopsy specimens diagnosed during the study period. Eighty three (94.3%) of these were primary cancers. HCC constituted 76 (91%) of the primary cancers and 20.3% of the total liver biopsy specimens (Fig. 1).

Fifty male and 26 female had HCC with a male to female ratio of 1.9:1. These had an average age of 46.2±13.9 years and peak frequency (30.03%) within the 41-50 years age bracket. Eighteen
(23.7%) of the HCC cases occurred on the background of cirrhosis.

Other primary cancer types diagnosed included cholangiocarcinoma (2.4%), hepatoblastoma (4.8%) and haemangioendothelioma (1.2%). Metastatic cancers constituted only 5.7% of all the cancers and were all adenocarcinomas (Fig. 1).

The distribution of the morphological variants of HCC presented on Fig. 2 shows that the trabecular subtype of hepatocellular carcinoma was the most common making up 54 (71.1%), followed by the acinar 10 (13.2%) and the mixed trabecular and acinar 6 (7.9%) patterns. The less common variants were the clear cell 5 (6.6%) and one fibrolamellar (1.3%) sub-type.

More than half (37, 68.5%) of those with the trabecular sub-type of hepatocellular carcinoma were males while a smaller proportion (17, 31.5%) were females giving a male:female ratio of 2.2:1. In males, this sub-type were found in the age range of 21-80 years and the largest number (12, 32.4%) of these male cases occurred within the 41-50 years age group. In female, this sub-type was found to be most common in the 31-40 years age group which is a decade earlier the commonest age group in males (Table 1).
Table 1. The frequency of occurrence of HCC sub-types in different age brackets

<table>
<thead>
<tr>
<th>Age</th>
<th>Trabecular M</th>
<th>Trabecular F</th>
<th>Acinar M</th>
<th>Acinar F</th>
<th>Mixed M</th>
<th>Mixed F</th>
<th>Clear Cell M</th>
<th>Clear Cell F</th>
<th>Fibrolamellar M</th>
<th>Fibrolamellar F</th>
<th>Total Sum</th>
<th>%</th>
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<td>0</td>
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<tr>
<td>11-20</td>
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<td>0</td>
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</tr>
<tr>
<td>21-30</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>11</td>
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<tr>
<td>31-40</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>18.4</td>
</tr>
<tr>
<td>41-50</td>
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<td>2</td>
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<td>1</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>23</td>
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<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>22.4</td>
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<tr>
<td>61-70</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>7.9</td>
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<tr>
<td>71-80</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
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</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>76</td>
<td>100</td>
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</table>

Similarly, the acinar sub-type of HCC was found to be more common in males (8, 80%) than in females (2, 20%). And in both genders, this disease occurred mainly between the ages of 31 and 50 years. However, the combined trabecular and acinar patterns showed a preponderance of females (4, 66.7%) than males (2, 33.3%) and the greatest proportion occurred in the 51-60 years age group. The clear cell pattern was also more common in females. Only one case of fibrolamellar hepatocellular carcinoma occurred (Table 1).

4. DISCUSSION

Chronic hepatitis B virus infection, the major risk factor for HCC in Nigeria, constituted 219 (58.6%) of the 374 histologically diagnosed liver biopsy specimens. The HBsAg status of the histologically diagnosed HCC cases was not ascertained in this study. However, the sero-prevalence of HBsAg in the general population has been reported to be between 10 – 15%, and HBsAg positivity has also been shown to be as high as 86.8% in Nigeria [18,19]. A small proportion (7.8%) had cirrhosis and this peaked within the same age bracket (31 – 40 years) like chronic hepatitis, just a decade earlier than HCC. The high incidence of HCC and peak within the working class age group (40 – 50 years) represents a source of economic loss to the countries in sub-Sahara Africa.

Hepatocellular carcinoma occurred on a background of cirrhosis in 18 (23.7%) of the cases observed. This is comparable with the report from Bangladesh (18.8%) but much lower than the Figures from Tanzania (66.2%), Malaysia (73.5%) and Yemen (74.5%) [20-23].

A large proportion, 58 (76.3%), of HCC cases appears to have skipped the cirrhotic stage. Hepatitis B virus infection endemicity and synergism with aflatoxin B1 have been implicated for rapid progression to malignancy and occurrence at an earlier age in this region [11,24]. The proportional contribution of aflatoxin, another very important risk factor for HCC, has not been widely studied in Nigeria. However, 6 (7.6%) out of 79 cases of HCC at Ibadan were found to have p53 codon 249 mutations in one study [24]. This mycotoxin produced by Aspergillus flavus and Aspergillus parasiticus, has been reported to contaminate most staple food items such as yams, maize and peanuts consumed in the region. Poor agricultural practices by peasant farmers and lack of distinct policies on handling of food items or implementation of such policies where they exist are some of the causes of the high content of aflatoxin B1 in some poorly preserved food items in this region [25,26]. Persistent exposure in an individual may lead to formation of DNA adducts and GC – TA transversion mutation at the third position of codon 249 of p53 gene. The effects of this mutation, when combined with HBx protein inhibition of the expression of p53 in an individual infected with HBV, promote carcinogenesis and rapid progression to HCC [27].

Seventy six cases of HCC found in this study constituted 20.3% of the total. This proportion is less than previous observations reported in Jos (31.3%), Kano (27%), Lagos (33%), and Enugu (24.6%) [28-31]. This present work provides data on the frequency of the histological sub-types of this tumour. In decreasing order of relative frequency, the histological subtype of HCC found in this research were trabecular (71.1%), acinar (13%), mixed (7.9%), clear cell (6.6%), fibrolamellar (1.3%) (Figs. 2-4). Seleye-Fubara and colleagues reported a similar predominance of the trabecular sub-type (49.3% of 75 HCC
cases) followed by the acinar/pseudoglandular in Port Harcourt, southern Nigeria [32]. In contrast, over 50% of the HCC cases in Lagos were reported to be pseudoglandular [33].

In terms of relative frequency, our findings are similar to reports from Tanzania with the trabecular (47.9%), pseudoglandular (24.6%), compact (17.6%), clear cell (6.3%),

Fig. 3. Photomicrograph of hepatocellular carcinoma, trabecular pattern. The malignant polygonal cells are arranged in thick irregular cord (H & E, X 20)

Fig. 4. Photomicrograph of hepatocellular carcinoma, acinar/pseudoglandular (H & E, x 40 objective)
similar evaluation in Malaysia found the trabecular (73.1%), acinar (11%), clear cell (7.7%), solid (5.8%) and sclerosing (1.9%) subtypes, in descending order of occurrence [22]. Our results are also in keeping with those of Chedid and colleagues in the United States of America in which trabecular HCC (43%) was more frequent than the pseudoglandular (13%) in a series [34] but differs from Nzeako and colleagues in the same country with the trabecular (61%), compact (18.1%), mixed (10.6%), and the pseudoglandular pattern ranking fourth (4.6%) [14]. Bralet et al. [15] in France also reported the trabecular (70%) being more common than pseudoglandular HCC (3%). In contrast to our findings, a predominance of the acinar/pseudoglandular sub-type (45.3%), followed by the trabecular (39.6%) and solid (7.8%) was reported in Bangladesh 20. The trabecular sub-type is the commonest sub-type in most geographical locations but there is significant diversity in the frequency of the other patterns except for the fibrolamellar which is consistently rare.

Fibrolamellar HCC is a very rare variant and only one case was seen in our series. It has the peculiar characteristic of having a good prognosis and predilection for adolescents and young adults. However, the one seen in this study occurred in a male patient in the fifth decade. Recent data suggest that fibrolamellar HCC has a poorer prognosis and high recurrence rate after surgery than initially thought [35].

The trend towards a comprehensive molecular classification of HCC has stirred up studies on both morphological and molecular intra-tumour heterogeneity. Perhaps, a future study will clearly delineate the molecular characteristics of each of the sub-types or explain why a particular morphological subtype develops in an individual [36].

5. CONCLUSION

This study recorded a high incidence of hepatocellular carcinoma in resource – constrained sub-Sahara African region many of those affected being mainly individuals within the working population. The trabecular variant of the tumour is the most predominant morphological subtype in north-central Nigeria. The fibrolamellar variant is rare. The findings of this study underscore a persisting need to effectively control the aetiological risk factors, particularly infection with hepatitis B virus and contamination with aflatoxin B1. The scourge of this cancer will be reduced with re-appraisal of current preventive measures and perhaps, institutionalisation of newer therapeutic modalities.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


Available: http://dx.doi.org/10.4236/jct.2014.514132