

Clinicoradiologic and Sonographic Patterns of Metastasis in Hepatocellular Carcinoma

Jesse A. Otegbayo, MBBS, MSc, FWACP; Omolola M. Atalabi, MBBS, FWACS, FMCS; and Abdulmumini Yakubu, MBBS, FWACP

Ibadan, Nigeria

Hepatocellular carcinoma (HCC) is usually diagnosed at an advanced stage, when little remedy could be offered. There is a need for relatively affordable, available and non-invasive tests for diagnosis, staging and detection of metastasis among individuals at risk.

A clinical, chest radiographic (CXR) and abdominal ultrasonographic examination was carried out to detect and evaluate the pattern of metastasis among 53 untreated patients. One patient had clinical paraparesis with no outward evidence of metastasis. CXR revealed lung metastasis in 11 (20.8%), with multifocal deposits and bilateral involvement in 10 (18.8%), and unilateral single deposit in one. Two (3.8%) patients had perihilar lymphadenopathy and consolidation, respectively, while 18 (34%) patients had elevated right hemidiaphragm and four (7.5%) had pleural effusion. One had right basal pneumonitis, multiple cavitary lesions in the lung fields and soft-tissue wasting. No abnormality was seen in 17 (32.1%) cases.

Abdominal ultrasonograph showed probe tenderness in 22 (41.5%), hepatomegaly in 49 (92.5%), with 33 (62.3%) of these having nodularities of varying sizes. The spleen was enlarged in 10 (18.9%) cases, with four (7.5%) showing irregular outline. There were eight (15.1%) cases with para-aortic lymphadenopathy. Portal hepatic lymphadenopathy was demonstrated in two (3.8%) cases, while pleural effusion was detected in seven (13.2%).

Metastasis is common in HCC at presentation, the lung is the commonest site of spread. Clinically visible metastasis appears uncommon in HCC.

Key words: hepatocellular carcinoma ■ metastasis ■ pattern

© 2006. From the Liver Unit, Departments of Medicine (Otegbayo, Yakubu) and Radiology (Atalabi), University of Ibadan/University College Hospital, Ibadan, Nigeria. Send correspondence and reprint requests for *J Natl Med Assoc.* 2006;98:1620-1622 to: Dr. Jesse A Otegbayo, Department of Medicine, University College Hospital, PMB 5116, Ibadan, Nigeria; fax: +234-2-241 3545; e-mail: otegbayoa@comui.edu.ng

INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked as the fifth commonest cause of cancer worldwide and one of the leading causes of cancer deaths.¹ In the United States, where health services are adequate, an increase in the incidence of HCC has been documented recently, ostensibly due to the increasing scourge of hepatitis-C virus (HCV).²

HCC is usually advanced at time of diagnosis and alpha-fetoprotein (AFP), used as a tumor marker for HCC, has a low sensitivity and reliability.³ Furthermore, other screening markers, such as alpha-L-fucosidase, des-gamma carboxyprothrombin and the recently discovered squamous cell carcinoma antigen,⁴ are not readily available even in developed countries. A consensus conference of the European Association for the Study of the Liver (EASL) has recommended the use of AFP and abdominal ultrasonography for screening individuals at risk of development of HCC.⁵ A recent study among our patients revealed a poor quality of life in patients with HCC.⁶ In light of this, it is important to study every possible presentation of the disease—in particular, to know the other organs usually affected by this tumor using relatively simple and affordable methods, especially in resource-poor environments.

The objective of this study was to study the clinical, radiologic and ultrasonographic pattern of metastasis in HCC among untreated patients at the University College Hospital, Ibadan, Nigeria. It was expected that the study would reveal the usual area of metastasis for evaluation whenever this tumor was suspected, especially in patients with chronic liver disease and hepatitis-B and -C infections. This would also assist in staging of disease at diagnosis and aiding the management plan.

MATERIALS AND METHODS

This prospective cross-sectional study evaluated 53 hospital patients with histological diagnosis of HCC. Demographic data as well as height and weight were measured to calculate the body mass index (BMI). Clinical history, a thorough physical examination, searching

for swellings and areas of undue tenderness were performed. A plain posterior-anterior x-ray examination and abdominal ultrasonography were carried out on all the patients using the Aloka SSD-1700 USS machine-5 MHz probe.

SPSS version 11 statistical package was used to determine relative ratio frequency, mean and standard deviation using Students' t test. Statistical significance was specified at $p < 0.05$.

RESULTS

Demographic Features

There were 37 men and 16 women with a male:female ratio of 2.3:1. Age and sex distribution showed the peak age range as 40–49 (37.8%) for men, while the corresponding value for women was 60–69 (31.3%). The mean age for men was approximately 45.9 years, 11.3 (mean ± SD), while that of women was approximately 52.5 ± 17.3 (mean ± SD). There was no significant difference in the mean ages of men compared with women ($P=0.11$). Age range for men was 23–75 years, while that of women was 20–82 years.

Most of the patients were of the Yoruba (southwestern Nigeria) extraction constituting 75.5%, followed by Igbo (eastern Nigeria) at 7.5%. Traders made up 39.6%, while 24.5% and 15.1% were artisans and civil servants, respectively.

Significant alcohol consumption (defined as 80g/day for five years or 40g/day for 10 years) was found in 35.8%, while 18.9% smoked tobacco.

Clinical Features

Five (9.4%) were previously diagnosed as cirrhotics, while one patient had concomitant pulmonary tuberculosis. Hard and nodular hepatomegaly was present in 48 (90.6%) of the patients, while one patient developed paraparesis, with no clinically appreciable swelling or tenderness on the spine. Other presenting clinical features are as shown in Table 1.

Some clinical features occurring with a frequency of

1 or 2 were pruritus, early satiety, palmar erythema, digital clubbing, pallor, leukonychia, fluffy hair, palmo-plantar hyperpigmentation, paraparesis, right axillary adenopathy, cough and chest pain.

Chest X-Ray

There were secondary metastatic deposits in the lungs in 11 (20.8%) patients with multifocal deposits (Figure 1), and bilateral involvement in 10 (18.8%) cases, and unilateral single deposit in one patient. Two (3.8%) patients each had perihilar lymphadenopathy and consolidation, respectively, while 18 (34%) patients had elevated right diaphragm and four (7.5%) had pleural effusion. One had right-sided basal pneumonitis and another had multiple cavitary lesions in the lung fields. Soft-tissue wasting accounted for one case, while no radiological abnormality was seen in 17 (32.1%) cases.

Abdominal Ultrasound

Probe tenderness in the right upper quadrant was found in 22 (41.5%) patients, while the liver was enlarged in 49 (92.5%) cases. Thirty-three (62.3%) had hepatic nodules of varying sizes, representing intrahepatic metastasis in both hepatic lobes. There was splenomegaly in 10 (18.9%) cases, with four (7.5%) showing irregular outline, but no definite mass was found. There were eight (15.1%) cases with para-aortic lymphadenopathy, and portal hepatic lymphadenopathy was demonstrated in two cases (3.8%). Pleural effusion was detected in seven (13.2%).

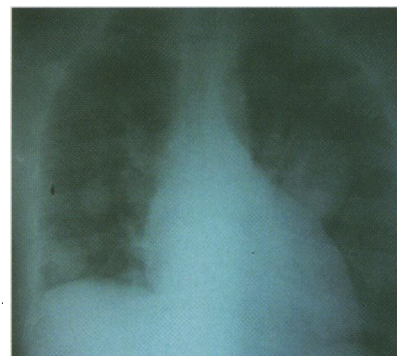
DISCUSSION

The finding of only 9.4% of the 53 HCC subjects suggests that clinically diagnosed liver cirrhosis was a rare presentation in our cohort of patients with HCC in Nigeria, in spite of the well-known fact that that cirrhosis is a premalignant condition and HCC focus is found in 80% of patients with liver cirrhosis.⁷ This may be due to the aggression of the disease in populations where hepatitis B is strongly associated with HCC, as previ-

Table 1. Presenting clinical features in HCC patients

Clinical Feature	Number	Percentage
Weight loss	50	94.3
Abdominal swelling	48	90.6
Hard/nodular hepatomegaly	48	90.6
Abdominal pain	47	88.7
Ascites	37	69.8
Jaundice	30	56.6
Anorexia	30	56.6
Pedal edema	25	47.2
Dilated abdominal veins	13	24.5
Prior cirrhosis	5	9.4

Figure 1. Chest radiograph showing bilateral cannon-ball metastasis in the lung fields



ously reported by Colombo and his colleagues.⁸ It may also be due to late presentation at a healthcare facility in our environment, where alternative herbal medical practitioners are usually first consulted and only resort to orthodox medicine when herbal medicine fails. Nodal metastasis, found in the right axilla, para-aortic and portal hepatic area in some of our patients, is known to be well associated with the spread of HCC.⁹ It is, however, difficult to attribute the lymphadenopathies to metastatic spread, as this may be reactive lymph node hyperplasia that may be found in association with cancer. A biopsy of the lymph nodes may clarify this. However, the splenomegaly found in 18.9% of the cohort may be in favor of reactivity in the reticuloendothelial system. The significance of the irregularity of outline of the spleen found in four (7.5%) of the patients is difficult to explain at this stage.

Pulmonary tuberculosis is a common wasting disease and may be confused with other wasting diseases, especially in the presence of respiratory symptoms, which may or may not be of infective origin. The finding of coexistence of clinical and radiological evidence of pulmonary tuberculosis with HCC in two of our patients is an eye opener and calls for a thorough clinical examination in patients with seemingly infective respiratory problem. Where in doubt, abdominal ultrasonography should be carried out in cases of disseminated tuberculosis presenting with hepatomegaly. Lymphangitic carcinomatosis, bony metastasis and miliary lesions as reported by Tsai et al.¹⁰ were not seen in our patients. The possibility of coexistence of pulmonary tuberculosis should, however, be considered in cases presenting with miliary shadows on chest radiograph.

Intrahepatic metastasis appears to be the most dominant mode of spread in our patients, with abdominal ultrasonography appearing to be more likely to pick hard nodular hepatomegaly than clinical examination (92.5% vs. 90.6%). The difference in sensitivity, however did not attain statistical significance ($p > 0.05$). Bilobar affection of the liver was found in about two-thirds of the patients [33 (62.3%)] with nodularities of varying sizes. This type of presentation precludes interventional modalities such as liver transplantation and radiofrequency ablation among other therapeutic measures for HCC. An intense surveillance program with ultrasonography or alpha-fetoprotein has been shown to improve detection rate in patients at risk of HCC.¹¹ These noninvasive tests may further enhance early detection of HCC in at-risk individuals.

By far, the commonest radiological finding in the chest x-ray was elevated right hemidiaphragm (34%), but abdominal ultrasonograph appeared to be more sensitive in detecting pleural effusion than chest x-ray [seven (13.2%) vs. four (7.5%)]. This finding is remarkable, as pleural effusion may signify pleural metastasis.¹² It would be suggested that abdominal ultrasonograph be

preferred over CXR to exclude pleural effusion as a marker of pleural spread. The patient who developed paraparesis did not show any vertebral tenderness—bony invasion with cord compression is unlikely the cause, but a spinal radiograph was not done. A similar case of paraparesis in which only the MRI picked an intracordal mass was reported by Cho et al.¹³ A paramalignant syndrome may, however, be responsible.

In conclusion, intrahepatic and pulmonary metastases are common in HCC at presentation among our patients. Clinically visible metastasis appears to be uncommon in HCC. Regular CXR and abdominal ultrasonograph are highly recommended in patients with or at risk of HCC, and are much cheaper in our practice than SCCA and liver-specific microbubbles (as suggested for occult HCC).^{4,14}

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