

Cutaneous features seen in primary liver cell (Hepatocellular) carcinoma patients at a University Teaching Hospital in Nigeria

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SUMMARY

Primary liver cell carcinoma (PLCC), predominantly hepatocellular carcinoma is a killer. In the southwestern region of Nigeria it occupies the second position, behind prostate cancer in males. Females account for about a third of diagnosed cases. Children are not spared. Over 80 % of PLCC cases present to the hospital at an advanced stage in Nigeria and some die within weeks of admission to the wards. A prospective hospital based study was carried out to determine muco-cutaneous features associated with the entity as a possible aid to diagnosis cutaneous features being considered a cheap tool that can help diagnosis in a developing country-at an affordable cost. 80 of 84 patients seen during the study period had data that were adequate for analysis. The age range was 18-76 years with a mean of 56.2 years. The male female ratio was 17:3 indicating that males remain the more affected gender. No skin feature was found to be specific to PLCC. Jaundice (63.75 %), pallor 43.75 %), peripheral oedema (32.50 %), palmoplantar macular hyperpigmentation (47.5 %/25.0% - plantar /palmar) however were the common features documented in the study. Moderate to severe pityriasis versicolor was found in 18.75 % of cases. 61.25 % had core temperature less than 36⁰ C. Amongst non-cutaneous features found on examination, right sided upper abdominal pain/discomfort and swelling were common. While none of the features documented in this study are specific to PLCC (and most are likely related to underlying liver cirrhosis) it may be helpful to realize that Jaundice and marked palmoplantar macular pigmentation, the complaint of pain /mass, and the presence of a tender nodular mass in the right hypochondrium should make one to consider the localization of the disease to the liver. Pain/tenderness in the right hypochondrium suggest rapid growth of the liver from increased mitosis in the hepatocytes and a stretching of the liver capsule. Metastasis to the liver accounts for a very small percentage in Nigerians. A nodular liver is thus likely to be from a primary liver pathology.

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Introduction

It strikes all age groups and both genders and has no regard for the social class. By the time of its diagnosis in Nigeria it is often at an advanced stage. The maximum productive period of life between ages 18 and 50 years is often affected. Primary liver cell carcinoma is a relentless killer. Carcinoma arising within the liver may be of liver cell (hepatocellular), bile duct cells (cholangiocellular) or mixed origin. Primary liver cell carcinoma accounts for 80-90 % of liver carcinoma. Edington and Maclean [1] first published a cancer rate survey from Ibadan, Nigeria in 1963. The study reported that the most common cancers in Ibadan cancer registry in descending order

were cancer of the reticuloendothelial system, carcinoma of the cervix, Burkitt's tumour, primary liver cell cancer (PLCC) and cancer of the breast and of the stomach. In 1981 Abioye published more figures from the Ibadan cancer registry [2]. His survey highlighted the fact that PLCC predominated in the adult males while cervical cancer predominated amongst females. Between 1989 and 1996 PLCC shifted in position to the second position, behind prostate cancer in males [3]. Considering that about a third of females are still currently diagnosed as PLCC, primary liver cell cancer is still a contender for the first position in both genders. Children are not spared, although it accounted for less than 1 % of all

abdominal malignancies in children ≤ 14 years of age [4]. Over 80 % of PLCC cases present to the hospital at an advanced stage in Nigeria and at the University College Hospital, Ibadan, Nigeria over 25 % of cases die within 3 weeks of admission to the wards [5]. It was decided to conduct a prospective hospital based study to determine cutaneous features associated with PLCC as a possible aid to diagnosis – cutaneous features being a cheap tool that can help diagnosis in a developing country at an affordable cost [6].

Material and Methods

All consecutive adult patients diagnosed to have PLCC and who were admitted to the Gastrointestinal /Liver (GIT) unit in the department of Medicine of the University College Hospital (UCH) Ibadan, Nigeria formed the population sample. The study period spanned 14 months, December 2002 to February 2004. Diagnosis was both clinical and laboratory based -abdominal ultrasonography, liver biopsy /fine needle aspiration, tumor markers –alpha-fetoprotein, carcinoembryonic antigen, ascitic fluid cytology and other relevant liver function tests. The study was conducted jointly by the GIT and Dermatology units of the department of medicine of UCH. The dermatologists recorded the cutaneous findings while the gastroenterologists confirmed the diagnosis of PLCC. Information on age, gender, and symptoms, past medical history and routine drug usage were collected. To ensure data were not

missed, the body was divided into the following anatomical regions – (a) Face/scalp/neck, (b) Mouth (c) Back (d) Chest/abdomen, (e) upper limbs/axillae/hands, (f) lower limb/feet. Core temperature was recorded instead of skin temperature because of marked cachexia in some of the patients, the age of some of the patients and the coldness of the third floor ward where the GIT unit is sited.

Results

Patients were seen in the study period. 80 had data that were adequate for analysis. The age range was 18 – 76 years with a mean of 56.2 years. The male female ratio was 17:3 indicating that males remain the more affected gender. The age groupings are shown in table 1 indicating that PLCC spreads across young adults to elderly people with the peak between age group 31 to 62. The cutaneous, mucosal and relevant features associated with PLCC in the study are documented in tables 2 and 3. No skin feature was specific to PLCC. Jaundice (63.75 %), pallor 43.75 %), peripheral oedema (32.50 %), palmoplantar macular hyper pigmentation (47.5/25.0% - plantar /palmar) however were the common features documented in the study. Moderate to severe pityriasis versicolor was found in 18.75 % of cases. 61.25 % had core temperature less than 36⁰ C. Amongst non-cutaneous features right-sided upper abdominal pain/discomfort and swelling was common.

Table 1: Age groupings of PLCC patients in the study

Age in years	No of patients	Percentage
11 –30	7	8.75
31-50	26	32.50
51-70	43	53.75
71-90	4	5.00
	80	100.00

Discussion

Carcinoma arising within the liver may be of liver cell (hepatocellular), bile duct cells (cholangiocellular) or mixed origin. Hepatocellular carcinoma, Primary liver cell carcinoma accounts for 80-90 % of liver carcinoma. There is however little practical purpose in distinguishing between the two types since both may be found in different parts of the same tumor and the clinical course are similar. Skin features documented with PLCC include cutaneous porphyria [7, 8], pityriasis rotunda [9,10], papules and nodules to the skin from metastasis [11, 12]. Some features found in this study point to possible underlying or background liver cirrhosis

(LC) before the transformation to malignancy. This seems to be the trend in Africa and it is in agreement with documented finding from UCH Ibadan [5] with an incidence of 63 % for underlying cirrhosis of the liver in PLCC and in other parts of Africa with incidence of underlying cirrhosis varying from 60 % to over 90 % [13, 14]. Some of the features found in these PLCC patients like peripheral oedema (ankle /leg) and ascites and palmoplantar macular hyper pigmentation and low core temperature have been documented from UCH, Ibadan the same hospital in liver cirrhosis patients in a study some four years back [15] Table 4.

Table 2a: Mucocutaneous features found in the PLCC cases - n=80

Features	Number of patients	Percentage
Jaundice (mild to severe)	51	63.75
Pallor (conjunctival, tongue, nail bed)	35	43.75
Temperature (core)		
Less than 36,5° C	49	61.25
36.6-37.0 ° C	25	31.25
37.1-37.5° C	3	3.75
37.5° C	3	3.75
Pruritus/scratch marks	4	5.00
Leukonychia	8	10.00
Scanty hair- pubic /axillary	17	21.20
Macular hyper pigmentation	20	25.00
Palmar	38	47.50
Plantar		
Pityriasis versicolor moderate to severe	15	18.75
Proximal nail fold Hypo pigmentation	6	7.50
Dermatosis papulosa nigra	6	7.50
Hypo pigmentation Generalized	7	8.75
Localized/facial	5	6.25

Table 2b: Mucocutaneous features found in the PLCC cases-n==80

Features	Number of patients	Percentage	Comments
Hyper pigmentation Generalized	14	17.50	
Facial	7	8.75	
periumbilical	1	1.25	
Coated /furred tongue	9	11.25	
Scaliness /xerosis /ichthyosis	5	6.25	
Seborrhoeic dermatitis	3	3.75	
Acrocordion	1	1.25	
Idiopathic guttate hypo melanosis	6	7.50	
Gangrene	1	1.25	Left foot; all toes
Digital clubbing	6	7.50	
Palmar erythema	5	6.25	
Half-half nail (distal red /brown nail colour)	2	2.50	
Localized exogenous ochronosis	1	1.25	Patient had been using hydroquinone containing cream for more than 15 years
Erythematous papular /urticarial lesions	2	2.50	
Red /scrotal tongue	1	1.25	

Table 3: Other related clinical features found in PLCC –n=80

Clinical features	Number of patients	Percentage
Wasting /cachexia	12	15.00
Ankle /leg oedema	26	32.50
Ascites	11	13.75
Gynaecomastia	2	2.50

While these features are common to both LC and PLCC they are not specific to either disease or any malignant disease. A feature like pityriasis versicolor is common in blacks in the hot humid tropic; it however increases in situation where immune status deteriorates – it is thus not specific to the liver or to any specific malignancy. There are documented cases of pityriasis rotunda (PR) resembling pityriasis versicolor (PV) [16]. Pityriasis rotunda is uncommon in our skin clinic in UCH. Furthermore pityriasis versicolor is well recognized even by the non-health workers, as attested to by the name for it in the local languages [17]. PR and PV flare up whenever there is a cause for depressed immunity whether resulting from neoplasm or other causes such as malnutrition [18]. The presence of a rise in the incidence of either will thus depend on the prevalence of each entity in the environment. Liver diseases have been shown in blacks to be associated with a low core temperature [19]. Low core temperature in liver cirrhosis even in

the hot dry season had been hypothesized to be due to heat loss from dilatation of peripheral vessels and the presence of arterio-venous malformation [20]. Localized pigmentation of the palmo-plantar area was a striking abnormality in the previous study from this hospital in liver cirrhosis as well as in this study on PLCC. The pigmentation tends to be monomorphic in size and shape and demonstrated a smooth and well-circumscribed border. It is found even in normal individuals and it is believed to be related to trauma from walking bare footed or from occupation requiring much use of the hand. The more than five fold prevalence in liver cirrhotic was considered to be related to additional factors such as impaired metabolism possibly from increased estrogen [21] or melanocyte stimulating hormone. It is however not specific to liver cirrhosis or liver cell cancer.

Table 4: Some clinical features as seen in primary liver cell cancer patients in this study compared with liver cirrhosis in a previous study [6] from the same hospitals

Clinical features	Percentage		Comment
	Liver cell carcinoma	Liver cirrhosis	
Plantar macular hyper pigmentation	47.50	51.66	Found in normal individuals with increasing age
Palmar macular hyper pigmentation	25.00	31.66	
Corneal jaundice	63.75	33.33	Non malignant causes of hepatic function deterioration can cause this
‘Female’ pubic hair pattern	21.25	34.09 %	Varies in different normal population
Scanty hair- pubic /axillary	21.20	20.00	
Generalized wasting	15.00	70.00	

Mean core temperature in liver cirrhosis was 35.57 °C, the mean in the PLCC cases was 35.2 °C

While none of the features documented in this study are specific to PLCC, it may be helpful to realize that Jaundice and marked palmoplantar macular pigmentation, the complaint of pain /mass, and the presence of a tender nodular mass in the right hypochondrium should make one to consider the localization of the disease to the liver. Pain /tenderness in the right hypochondrium suggest rapid growth of the liver from increased mitosis in the

hepatocytes and a stretching of the liver capsule. Metastases to the liver accounts for a very small percentage in Nigerians. A nodular liver is thus likely to be from a primary liver pathology [22].

Conclusion

Our study has shown that most of the cutaneous findings in HCC are those of the underlying liver cirrhosis and are mainly relatively low core

temperature, jaundice, palmoplantar hyperpigmentation, generalized hyperpigmentation and pityriasis versicolor among others. Although, these findings on their own are not diagnostic of HCC, their presence in a clinical setting of tender nodular hepatomegaly make a strong case for the diagnosis of hepatocellular carcinoma.

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