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Paraneoplastic Manifestations of Hepatocellular Carcinoma- Are We Different?

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ABSTRACT

Objective: To determine the frequency of paraneoplastic manifestations in patients with hepatocellular carcinoma (HCC) presenting at tertiary care center. **Design:** Descriptive study. **Place of study:** Department of Gastroenterology - Hepatology, Shaikh Zayed Federal Post Graduate Medical Institute, Lahore. **Patients and Methods:** Patients of hepatocellular carcinoma were interviewed for symptoms suggestive of paraneoplastic manifestations of HCC. The patients were subsequently examined and investigated. The frequency of paraneoplastic features was determined using SPSS 13.0. **Results:** Of the total 100 patients included, musculoskeletal involvement with joint pain (11%) and muscle tenderness (4%) was noted. Skin lesions were noted in 2% of patients. On investigation 1% patient had erythrocytosis, 3% had thrombocytosis and eosinophilia was noted in 10% of patients. Calcium and cholesterol level were raised in 7% of patients each. **Conclusions:** Paraneoplastic features are seen in significant number of patients with hepato cellular carcinoma.

Key Words: Paraneoplastic, hepatocellular carcinoma, cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is among the leading causes of cancer deaths worldwide[1]. The incidence is highest in Africa and Asia[2]. HCC is known to be associated with a wide variety of paraneoplastic manifestations. The underlying pathophysiology is diverse. Erythropoeitin and thrombopoeitin[3] production by the tumour cells causes erythrocytosis and thrombocytosis. Commonly reported manifestations include hypercholertrolemia, hypoglycemia, erythrocytosis, and hypercalcemia[4]. The less commonly seen manifestations include diarrrhea, joint pain, skin manifestations and thrombocytosis[3]. There are a few case reports of polymyositis[5], eosinophilia and neurological manifestations. The incidence of paraneoplastic manifestation varies considerably in different regions of the world. In Taiwan the incidence was reported to be 19.4% and patients with paraneoplastic manifestation had significantly higher alpha fetoprotein levels. While in the Korean population the incidence was reported to be 43.6%[6]. The most commonly reported paraneoplastic manifestations in the Korean study included hypercholestrolemia followed by hypoglycemia and hypercalcemia[6] while in a Nigerian study the hypoglycemia was the most commonly reported feature[7]. The presence of paraneoplastic manifestation was considered to be a poor prognostic indicator. Presence and frequency of para-neoplastic manifestations in our population is largely unknown. Knowledge of type of para-neoplastic features existing in our patients will enable early diagnosis of this lethal complication of cirrhosis. The aim of our study is to determine the frequency and distribution of paraneoplastic manifestations in our patients of HCC.

PATIENTS AND METHODS

Patients were diagnosed to have HCC on the basis of ultrasonography, alpha fetoprotein bi-phasic CT scan or fine needle aspiration cytology .Patients with confirmed evidence of HCC on at least two of

above mentioned investigations were included in the study. Alpha fetroprotein >400 IU/ml was considered diagnostic for HCC.

Complete clinical history and physical examination with special stress on possible para-neoplastic features was performed in each patient. Complete blood examination with peripheral smear, liver function tests, renal function tests, serum electrolytes including calcium and phosphate, fasting lipid profile, fasting blood glucose were checked in each patient. The cut off level for thrombocytosis was set at > 4,50000 x 10^9/L while eosinophil count >4% was considered as paraneoplastic manifestation in patients with HCC. The calcium level 10.5 mg/dl, blood glucose level <60 mg/dl and cholesterol level >200 mg/dl were taken as cutoff level for hypercalcemia, hypo-glycemia and hypercholesterolemia respectively.

RESULTS

Total of 100 patients were included. Male to female ratio was 4:1 (80/20). The age group ranged from 14-82 years. Majority of our patients (82) had hepatitis C related liver disease while hepatitis B surface antigen was positive in 12 patients. The remaining 6 were negative for both viral markers. Mean Child Turcotte Pugh (CTP) score was 9. Predominant number of patients had advanced liver disease with 42 patients in Child class C 39 in Child B and 19 in Child class A. Paraneoplastic features were seen in 62 patients while 38 had no such evidence. Comparison of patients with and those without para-neoplastic features is shown in Table 1. The musculoskeletal system was most commonly involved with muscle weakness in 17% patients, muscle wasting in 24%, while muscle tenderness was noted in 4% of patients. Joint pain was present in 11% patients while evidence of arthritis was present in 4% of patients. Numbness and tingling was present in 17% patients while on examination neuropathy was present in 12% of the patients. Skin lesions were noted in 2% patients but none of the patients had porphyria, psoriasis or pemphigus. Thrombocytosis was seen in 3% of patients and eosinophilia in 10%. The calcium and cholesterol level was above the cut off level in 7% of patients.

Table 1: Comparison of patients with and without para-neoplastic syndrome in Hepatocellular carcinoma.

Variable	Patients with PNS	Patients without PNS features	P-value
Haemoglobin (g/dl)	10.34±0.28	10.23±0.34	0.82
Platelets (x10^9/L)	143.4±11.49	169.5±20.03	0.22
TLC (/cmm)	8.21±0.49	12.21±2.73	0.08
Total Bilir. (mg/dl)	3.39±0.50	3.84±0.92	0.64
ALT (IU/L)	138.25±16.74	175.13±30.94	0.25
Calcium (mg/dl)	8.64±0.17	8.44±0.17	0.45
Cholesterol (mg/dl)	152.34±67.22	135.8±10.98	0.20
Child score	8.78±0.32	9.88±0.68	0.11

PNS- Para-neoplastic syndrome.

DISCUSSION

Firm epidemiological evidence was found attesting that dermatomyositis and polymyostis may present as paraneoplastic syndromes[5]. The association of polymyositis with HCC has been reported in several case reports and the frequency was found to be 4% in our study while muscle weakness and wasting was probably the part of underlying liver disease as most of our patients were suffering from malnutrition due to cirrhosis of liver. Several other musculoskeletal disorders may be related to paraneoplastic syndrome, based on clinicians impressions, but with scarce epidemiological evidence supporting a causal determinism

Joint pain (11%) and arthritis (4%) was noted in our study. The association of malignancy with certain rheumatic syndromes was convincingly established, such as asymmetric polyarthritis presenting in the elderly with an explosive onset, rheumatoid arthritis with monoclonal gammopathy[8]. However the frequency of arthritis in association with HCC has not been previously reported.

Thrombocytosis was noted in 3% of our patients while in a study from China the frequency was found to be 2.7%[9]. There are multiple reports of increased level of thrombopoeitin released by malignant hepatocytes as a cause of thrombocytosis[3]

The frequency of erythrocytosis was noted to be 1% in our study and it was reported to be 2.5 % in a study from Nigeria[7] and those with high

hemoglobin levels had significantly higher erythropoeitin levels. The hypercholesterolemia and hypercalcemia was seen in 7% of patients in our study. Tetsuro Sohda and colleagues found that the expression of the LDL receptor was significantly decreased in all HCC cells derived from the 11 patients with hypercholesterolemia. In contrast, the expression was retained in the HCC cells of all patients without hypercholesterolemia. The reported frequency in the Chinese study was 12%[10]. The hypercalcemia in HCC is mainly due to the production of parathyroid harmone related peptide released by the hepatocytes and the incidence varied from 1.8-4.1%[11].

LIMITATIONS

The large number of patients with muscle tenderness was taken as polymyositis, as the deranged clotting profile and logistics were not supportive for muscle biopsy. The patient with neurological symptoms were not confirmed with neve conduction study

CONCLUSION

A significant number of patients with HCC develop paraneoplastic manifestations and looking for these symptoms may help in early diagnosis.

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