

## Case Report-II

# Hepatocellular Carcinoma Presenting with Troublesome Hypoglycemia

INDUMATI AMBULKAR, P. JAGANNATH, SURESH ADVANI

### ABSTRACT

Hypoglycemia is well known paraneoplastic manifestation of hepatocellular carcinoma (HCC). However, hypoglycemia as the first presentation is extremely uncommon. As many as 13% of patients with HCC however develop hypoglycemia early in the course of their illness. The later group of patients show a distinct pattern in their clinical course and pathology. Here we report a 34 years old male presented with episodes of hypoglycemia who was diagnosed as HCC. He received chemotherapy with gemcitabine and cisplatin, responded well symptomatically as well as radiologically.

### INTRODUCTION

Hepato cellular carcinoma is a common malignancy worldwide, but treatment outcome for HCC have remained generally poor. The majority of patients with HCC have inoperable disease with very poor prognosis. Survival in patients with curative resection carried out at dedicated centres is between 35-50% at 5 years and much lower elsewhere. Long term survival is uncommon because of frequent presence of recurrence, metastases or development of new primaries. There is also currently no accepted adjuvant or palliative treatment modalities that have conclusively shown to prolong survival in HCC.

Hypercholesterolemia, hypoglycemia, hypercalcemia and erythrocytosis are well

known paraneoplastic manifestations in patients with HCC. We report a case with severe hypoglycemia and hepatic mass suspected to have an insulin like growth factor I (IGF I) producing HCC. He responded well to chemotherapy with gemcitabine and carboplatin.

**Case** A 34 years old male presented in March 2005 with episodes of hunger, perspiration, ataxia and dysarthria of one month duration. Past and family history was not contributory. On examination, there was no evidence of peripheral lymphadenopathy or icterus. Per abdomen: enlarged liver 4.5 cms below right costal margin, it was hard, smooth and nontender. There was no splenomegaly or free fluid in abdomen. Respiratory examination revealed right sided pleural effusion. Central nervous system and cardiovascular system examination did not reveal any abnormality.

On investigation his complete blood picture, liver functions serum electrolytes and kidney function tests were within normal range. The CAT scan abdomen revealed enlarged liver with a diffuse ill defined heterogenous density (predominantly hypodense) mass lesion involving segment IV, V, VII, VIII of liver, post contrast study showed intense heterogenous enhancement with nonenhancing necrotic mass, mass measured about 17x12 cms in size, evidence of destruction of intrinsic vascular and biliary system, two small hypodense areas involving left lobe of liver there was evidence of right sided pleural effusion (Figure-I). Serum alfa fetoprotein (AFP) 7,35,350 ng/ml. Other tumour markers including CA-19.9 and CEA

Department of Medical Oncology (Indumati Ambulkar & Suresh Advani) Gastroenterologic Oncology (P. Jagannath) Asian Institute of Oncology S. L. Raheja Hospital Raheja Hospital Road, Mahim West, Mumbai -400 016 India

Correspondence: AMBULKAR INDUMATI  
E-Mail: ambulkarindu@gmail.com

Figure1-Mass lesion in the liver, before chemotherapy

were in the normal range. His serum cholesterol level, thyroid function tests, serum calcium level and serum fibrinogen levels were normal. He was hepatitis-B (HbsAg) positive. The plasma glucose level was 24mg%, serum insulin level (fasting) was 2.1  $\mu$ U/ml (N-5-25 $\mu$ U/ml), serum IGF level was 38.5ng/ml (normal range 100-494 ng/ml). Biopsy from the liver lesion was suggestive of hepatocellular carcinoma. Pleural fluid cytology was negative for malignancy.

This patient was treated with chemotherapy using gemcitabine and carboplatin regimen. The dose was gemcitabine 1000mg/m<sup>2</sup> day1 and 8,carboplatin (AUC 6) on day 1.His symptoms related to hypoglycemia responded to the first cycle of chemotherapy only. Blood investigations after 6 cycles of chemotherapy revealed normal serum insulin level of 20.5 $\mu$ U/ml, blood glucose level of 86mg% and serum IGF I level of 146 ng/ml. The CT scan also showed reduction in the size of the mass lesion of 6.3x 6x 5.6 cms with few small lesions seen in both lobes of liver. In view of good response to chemotherapy, the regimen was continued for 2 more cycles. After completion of 8 cycles, the size of liver lesion was further reduced to 4x2 cms (Figure-2).

Figure2- Mass lesion in the liver, 8 cycles after chemotherapy.

Because the patient was young, we had planned to resect the tumour. He underwent exploratory laparotomy in April 2006, the tumour was found to be unresectable. Presently the patient is alive with disease.

## DISCUSSION

Primary tumours of the liver represents one of the most common malignancies worldwide. The annual international incidence of the disease is 1 million cases with a male to female ratio of approximately 4:1.

Both case control studies and cohort studies have shown a strong association between chronic HBV carriage rates and increased incidence of HCC.<sup>1</sup> Our patient was HbsAg positive.

Common symptoms in patients affected with HCC include abdominal pain, weight loss, weakness, fullness in abdomen, anorexia, abdominal swelling, jaundice and vomiting. Common physical signs include hepatomegaly, hepatic bruit, ascites, splenomegaly, jaundice, wasting and fever.

A variety of paraneoplastic syndromes have been described. Most of these are biochemical abnormalities without associated clinical consequences. The most important ones include hypoglycemia (also caused end stage liver failure).The other abnormalities are hypercholesterolemia, erythrocytosis, dysfibrinogenemia, hypercalcemia,carcinoid syndrome, increased thyroxin-binding globulin levels, sexual changes (gynecomastia, testicular atrophy and precocious puberty) and porphyria cutanea tarda.<sup>2</sup> Jayaprasad et al reported a case of HCC from India who presented with hypoglycemia.<sup>3</sup> Our patient was presented with features of hypoglycemia in the form of ataxia and dysarthria. He did not have any ascites or any other feature of liver failure.

In 1929,Nadler and Wolfer first recorded the development of hypoglycemia in a patient with HCC.<sup>4</sup> In a study of 142 consecutive HCC patients by McFadzean and Yeung ,the majority of patients(87%) were designated Type A, having either no hypoglycemia or developing hypoglycemia only within two weeks of their

death. In these patients, the tumour was growing rapid and poorly differentiated and there was rapid wasting and muscle weakness. It was concluded that in Type A patients, hypoglycemia occurs solely as a consequence of a progressive encroachment on the residual liver tissue by the tumour and also to undernutrition. The remaining 13%, however, developed hypoglycemia early in the course of their illness and were designated Type B.<sup>5</sup>

Hypoglycemia occurs in two settings. Relatively mild hypoglycemia occurs in rapidly growing HCC among the Chinese as part of a terminal illness. In the other setting, the HCC is most slowly growing but the hypoglycemia may be profound. Its pathogenesis is unclear. In a review of the literature, Kahn et al found that mesenchymal tumours are responsible for 45% of hypoglycemia due to non islet cell tumours (non islet cell tumour hypoglycemia [NICTH] and HCC accounts for 23% of these tumours which are massive and slow growing.<sup>6</sup>

The clinical manifestations of NICTH are indistinguishable from those produced by an insulinoma. These patients are usually older; however, their hypoglycemia is severe and tumours are readily found on physical examination or by imaging. In addition to persistent hypoglycemia, the characteristic biochemical findings include hypoketonemia, suppressed insulin and lack of response to growth hormone and glucagons to hypoglycemia. The glucose response to glucagons, however is often normal in NICTH other than HCC.

Megyesi et al, in 1974, reported elevated plasma non-suppressible insulin like activity (NSILA) in three of seven patients with NICTH, raising the possibility of insulin like growth factors (IGF) being the responsible agent. However, his results could not be confirmed by other techniques to extract and assay IGF II from the serum.<sup>7</sup>

Recent studies have discovered changes in the insulin like growth factors (IGF) axis that affect the molecular pathogenesis of HCC, including autocrine production of IGFs, IGF binding proteins (IGFBPs), IGFBPs, proteases and IGF receptor expression. Characteristic

alteration detected in HCC and hepatoma cell lines comprise the over expression of IGFII and IGF I receptor emerging as critical events in malignant transformation and growth of the tumours. Simultaneous reduction of IGFBP expression and the increase in the proteolytic cleavage of IGFBPs results in an excess of bioactive IGFs. Finally defective functions of the IGFII mannose 6 phosphate receptor involved in degradation of IGFII, the activation of growth inhibitor TGF-beta 1 and the lysosomal targeting and cathepsin proteases capable to degrade extracellular matrix proteins may contribute to the development of HCC. The IGF axis has important autocrine, paracrine and endocrine roles in the promotion of the growth. Alteration of the IGF system have recently been implicated in the pathogenesis. In our patient, the serum glucose level, serum insulin level and serum IGF I level were low.<sup>8</sup>

HCC patients with paraneoplastic syndrome is a significant prognostic factor in survival and of clinical interest. Luo JC et al evaluated 903 HCC patients; 179 (20%) developed paraneoplastic syndromes either upon diagnosis or during follow up, age, sex and tumour volume-matched HCC patients without paraneoplastic syndromes were selected as controls. Multivariate cox regression analysis revealed child pugh's grade 'C', ineligibility for active treatment, serum AFP > 10,000 ng/ml and main portal vein thrombosis were all independent unfavorable prognostic factors for survival. The median survival from the occurrence of paraneoplastic syndromes to death was only 36 days.<sup>9</sup> Our patient is partially responded to chemotherapy and presently asymptomatic.

Mazzioti et al did a prospective study investigating the longitudinal correlation between modification in serum IGF I levels and the development of HCC in a cohort of patients with hepatitis C (HCV) related cirrhosis. They demonstrated that in patients with HCV related cirrhosis. The development of HCC is accompanied by a significant reduction of

serum IGFI levels independent of the grade of impaired liver function, modification of the IGFI level precedes the morphologic appearance of HCC, permitting a precocious diagnosis of the tumour.<sup>10</sup>

In a study by Stuver et al, 53 male patients were analysed. It was observed that the reduction in IGFI I level among HCC patients was found to be more than could be attributed to liver damage alone.<sup>11</sup> One study by Parikh et al reported a series of 30 patients who received the combination of gemcitabine and cisplatin. This regimen was well tolerated and did show activity in Indian patients with advanced unresectable HCC.<sup>12</sup> We have used gemcitabine and carboplatin for our patient.

The Prognosis is poor for stage IV tumours and no surgical treatment is recommended. Care must be taken to differentiate multifocal disease from intrahepatic metastasis because the later has a much worse prognosis. We could give chemotherapy to our patient because he did not have any evidence of cirrhosis and his liver function tests were normal.

Paraneoplastic syndrome as a presentation is not common in HCC. Our patient had only hypoglycemia at the time of diagnosis. His blood glucose became normal after first cycle of chemotherapy. Even the serum insulin and serum IGFI levels responded well to chemotherapy. HCC is a tumour in need of much new therapeutic developments to make a significant clinical impact.

#### REFERENCES:

1. Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet* 1981;2:1129
2. Chu CW, Hwang SJ, Luo JC, et al. Manifestations of hypercholesterolaemia, hypoglycaemia, erythrocytosis and hypercalcaemia in patients with hepatocellular carcinoma: report of two cases. *J Gastroenterol Hepatol*. 1999;14(8):807-10.
3. Jayaprasad N, T. Anees, T. Bijin, et al. Severe hypoglycemia due to poorly differentiated hepatocellular carcinoma. *JAPI*. Vol.54;413-415.
4. Nadler WH, Wolfer JA. Hepatogenic hypoglycemia associated with primary liver cell carcinoma. *Arch Intern Med* 1929;44:700-5.
5. McFadzean A J, Yeung R T et al. Further observation on hypoglycemia in HCC. *Am J Med* 1969;47:220-235.
6. Kahn CR. The riddle of tumour hypoglycaemia revisited. *J Clin Endocrinol Metab* 1980;9:335-60.
7. Megyesi K, Kahn C R, Roth J et al. Hypoglycemia in association with extrapancreatic tumours: demonstration of elevated plasma NSILAs by a new radioreceptor assay. *J Clin Endocrinol Metab*. 1974;38:931-934.
8. Scharf JG, Braulke T. The role of the IGF axis in hepatocarcinogenesis. *Horm Metab Res*. 2003;35:(11-12):685-93.
9. Luo JC, Hwang SJ, Wu JC, et al. Clinical characteristics and prognosis of hepatocellular carcinoma patients with paraneoplastic syndromes. *Hepatogastroenterology*. 2002;49(47):1315-9.
10. Mazziotti G, Sorvillo F, Morisco F, et al. Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a prospective study. *Cancer*. 2002;15;95(12):2539-45.
11. Stuver SO, Kuper H, Tzonou A, et al. Insulin-like growth factor 1 in hepatocellular carcinoma and metastatic liver cancer in men. *Int J Cancer*. 2000;1;87(1):118-21.
12. Parikh PM, Fuloria J, Babu G, et al. A phase II study of gemcitabine and carboplatin in patients with advanced hepatocellular carcinoma. *Trop Gastroenterol*. 2005;26(3):115-8.

