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Hypercalcemia as a Paraneoplastic Syndrome in association with Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma [HCC] is the third-leading cause of cancer related mortality worldwide. It typically presents as a solitary mass in a normal or cirrhotic liver with a raised serum alpha-fetoprotein. Paraneoplastic syndromes [PNS] such as hypercholesterolemia, hypoglycemia, erythrocytosis and hypercalcemia may be encountered, either at presentation or later during the clinical course, in some patients with HCC. Hypercalcemia, without bony metastasis, is uncommon and is associated with more advanced HCC and poor outcome. We report a case of an 80 year-old male with a past medical history of untreated hepatitis B who presented with marked hypercalcemia and was found to have advanced HCC. Parathyroid hormone-related peptide was elevated and there was no evidence of bone metastasis. He was not a candidate for surgical resection or chemotherapy and received palliative care beside treatment for hypercalcemia. Our case report aims to highlight such atypical presentations due to PNS in patients with HCC and the potential impact on patient outcome.

Keywords

hypercalcemia; hepatocellular carcinoma; paraneoplastic syndrome

Introduction

Hepatocellular carcinoma [HCC] is the third-leading cause of cancer related mortality worldwide [1]. According to one report the incidence rates of HCC tripled in the United States from 1975 through 2005 [2]. HCC typically presents as a solitary mass in a normal or cirrhotic liver with a raised serum alpha-fetoprotein. However, at presentation or during its clinical course, some patients with HCC may manifest a variety of paraneoplastic syndromes [PNS] including hypercholesterolemia, hypoglycemia, hypercalcemia and erythrocytosis [3-5].

Hypercalcemia without bony metastasis as part of a paraneoplastic syndrome [PNS] is recognized but uncommon and is rather due to the tumor secreting hormones such as intact parathyroid hormone [PTH] or its related peptide [PTHrP]. PNS such as parathyroid hormone related peptide [PTHrP] hypercalcemia is rare and is successfully treated with either tumor resection or embolization. Moreover, these patients have significantly higher alpha fetoprotein levels, more advanced TNM stage and shorter survival [6].

Case Presentation

A 80-year-old man with a past medical history of hypertension and untreated hepatitis B, presented to his primary care physician with a 6-week history of weight loss, poor appetite and fatigue. Vital signs were stable and apart from cachexia and a flat affect, the physical exam was otherwise normal with no stigmata of chronic liver disease or bone pain. Routine blood biochemistry showed a corrected calcium level of 3.47 mmol/L [normal range: 2.12-2.62 mmol/L] and he was referred to the hospital for further management. On admission, he was started on IV fluids and Pamidronate to reduce bone resorption.

Further blood tests showed: phosphorus 0.65 mmol/L [0.74-1.52 mmol/L], intact PTH 6 pg/ml [15-65 pg/ml], parathyroid hormone-related peptide [PTHrP] 27 pmol/L [0-2.3 pmol/L], 25-hydroxy Vitamin D 18.8 ng/mL [30-100 ng/mL], aspartate aminotransferase [AST] 104 IU/L [13-39 IU/L], alanine aminotransferase [ALT] 39 IU/L [7-42 IU/L], alkaline phosphatase [ALP] 150 IU/L [34-104 IU/L], total bilirubin 18.8 mol/L [5-21 μmol/L] and an alpha fetoptotein [AFP] level of >110,000 ng/mL [0-9 ng/mL]. Multiple myeloma screen, including serum and urine electrophoresis, was negative. CT of the abdomen revealed an extensive tumor throughout most of the right lobe of the liver, with invasion into the portal veins [figure 1]. This was further visualized by an MRI of the abdomen. He continued to receive treatment for hypercalcemia with normalization of serum calcium levels. A radiologic skeletal survey, including x-rays of the skull, vertebral column, pelvis, and extremities, did not reveal any evidence of bone metastasis.

He was diagnosed with advanced HCC and given the lack of bone metastasis and high PTHrP levels, the hypercalcemia, in our opinion, was a manifestation of a PNS secondary to HCC. He was not a candidate for radical tumor resection due to the extent of the disease and Sorafenib, the only chemotherapeutic agent used to treat HCC, was deemed unsuitable due to its side effects and following an overall risk to benefit assessment. The patient and his family opted for palliative care and did not want to pursue any further investigations including liver biopsy or ultrasound of the parathyroid gland. He was discharged home with home health care.

Discussion

Paraneoplastic syndromes are not uncommon in patients with advanced HCC and the survival of these patients is relatively shorter [7].The incidence of HCC and hypercalcemia reported in the literature ranges anywhere from 1% to 50%. The wide range in incidence may be attributed to the inclusion of patients with bony metastases [8].

The association of hypercalcemia and secondary tumors has long been recognized and although it has been proposed that HCC-associated hypercalcemia is caused by humoral factors derived from the tumor, the real mechanism remains elusive [9]. The two mechanisms implicated in hypercalcemia associated with malignancy are: a] hypercalcemia due to bone metastasis attributed to an increase in osteoclastic activity and bone resorption and b] secretion of intact PTH or its related peptide [PTHrP] in patients without bone metastases [3,5].

In patients with HCC, factors affecting prognosis include tumor morphology, AFP level, and tumor metastasis with many studies indicating paraneoplastic diseases as the worst prognostic indicators [3] Luo et al. reported that in a cohort study, 19.4 per cent of patients with HCC developed paraneoplastic

syndromes. These patients were less likely to be eligible for active treatment thus reducing survival [10]. A study conducted in China to assess the role of prognostic influence of paraneoplastic syndromes in patients with HCC showed that the 5-year survival rate of patients with HCC without paraneoplastic syndrome was 43.8 % as compared to 6.2 % in patients with paraneoplastic syndrome [4].

Patients presenting with hypercalcemia secondary to PTHrP secretion are managed with intravenous fluids for rehydration followed by bisphosphonates to decrease bone resorption, however, response to such therapy is usually poor [3]. These patients benefit from tumor resection or transplant, resulting in a significant drop in serum calcium levels and improved survival [3,4,9].

In addition to hypercalcemia, patients with HCC may present or develop during its clinical course varying number of manifestations of paraneoplastic syndromes, such as hypercholesterolemia, hypoglycemia, and erythrocytosis [3-5]. According to a study on the epidemiology of PNS in HCC from Southeast Asia that assessed 127 patients, hypercalcemia and hypercholesterolemia were associated with more advanced disease and reduced survival but not erythrocytosis [6]. The same study further showed that paraneoplastic hypercalcemia in particular is associated with more advanced HCC and poor outcome. Clinicians need to be aware of such atypical presentations due to HCC associated PNS and their potential impact on patient outcomes.

Learning Points

Hepatocellular carcinoma [HCC] is the third-leading cause of cancer related mortality worldwide, and according to one report, the incidence rates of HCC in the United States tripled between 1975 and 2005 [2].

HCC may be associated, either at presentation or later during its clinical course, with certain paraneoplastic syndromes, such as hypercholesterolemia, hypoglycemia, erythrocytosis and hypercalcemia.

Paraneoplastic syndromes in general and paraneoplastic hypercalcemia in particular may be associated with more advanced HCC and worse outcome.

Figures

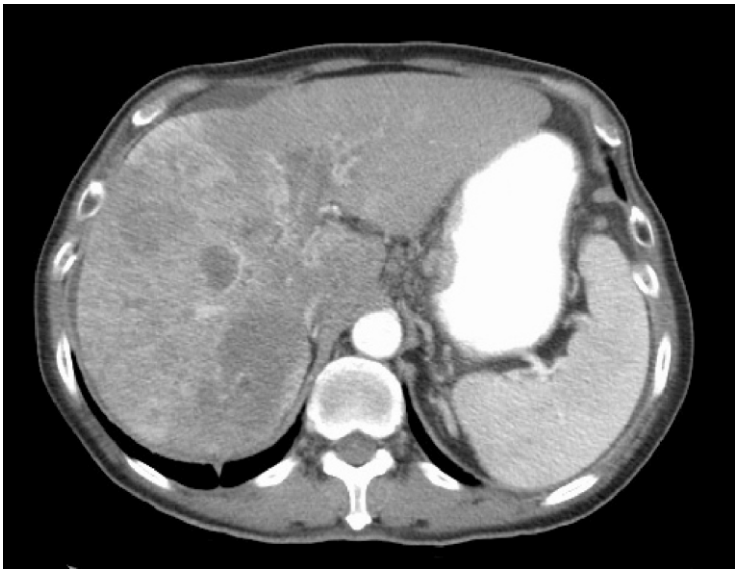

Figure 1: CT abdomen showing a markedly inhomogeneous right lobe of the liver with multiple areas of low attenuation suggestive of extensive tumor, such as hepatocellular carcinoma

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