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Case Report

Severe Hypercalcemia as Paraneoplastic Syndrome of Hepatocellular Carcinoma

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Abstract:
Hypercalcemia is very unusual initial symptom of hepatocellular carcinoma (HCC). It commonly occurs as paraneoplastic syndrome after confirmed diagnosis of HCC. In our case report, we describe a 64–year–old gentleman who presented with symptoms of acute severe hypercalcemia and tested positive for hepatitis C. Initial investigation excluded upper and lower gastrointestinal malignancies. Further laboratory workup confirmed hypercalcemia (serum calcium 4.11 mmol/L) with normal intact parathyroid hormone (2.0 pmol/L). His alpha fetoprotein markedly raised to 16511 ug/L. Imaging investigations revealed hypervascular mass in the segment VIII of the liver. HCC can manifest as paraneoplastic syndrome like hypercalcemia due to the release of the PTHrP (parathyroid hormone related peptide), as seen in our patient. Thus, HCC should be considered part of the differential diagnosis in a hypercalcemic patient.

Keywords: *hypercalcemia, hepatocellular carcinoma, paraneoplastic syndrome*
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Introduction

Hepatocellular carcinoma (HCC) is ranked as the fourth most common malignancy worldwide (1). In Malaysia, it ranked within the top ten of most frequently diagnosed cancers (2). Malaysia, being a country composed of multiple ethnicities, had its population estimated to be 34.3 million, with the majority being Malay (50.1%), followed by Chinese (22.6%), Indigenous (11.8%), and Indians (6.7%) (3). The majority of HCC cases are attributed to cirrhosis associated with chronic hepatitis B or C, alcoholism, or non –alcoholic steatohepatitis (NASH) (4). There was a report from a large multicenter study that revealed <2% of HCC are non-cirrhotic in origin (5). HCC development from cirrhotic liver is known to be from stepwise mutation, however, its progression from non –cirrhotic liver is not well understood, which is speculated to be from *de novo* carcinogenesis (6). It is rare to encounter HCC patients presented with hypercalcemia without bone metastasis, as one of its paraneoplastic syndromes, reported in 4–7% of patients (7).

There were some reported paraneoplastic syndromes associated with HCC, namely hypoglycemia (8), demyelination, pemphigus vulgaris (9), thrombocytosis (10), hypercalcemia, hypercholesterolemia, and erythrocytosis (11).

We would like to share our local experience, where our patient initially presented with symptoms of hypercalcemia and subsequent workup revealed HCC with hypercalcemia as paraneoplastic syndrome.

Case Presentation

A 64–year–old man with no prior medical problems presented with epigastric discomfort, constipations, loss of appetite, and weight loss of 10 kg in 1 month, with no known family history of malignancy. Physical examinations revealed palpable liver 2 cm below the costal margin. Laboratory results revealed elevated calcium 4.11 mmol/L (normal range 2.02-2.60), raised AFP (alpha fetoprotein) 16511 ug/L (normal range < 7.0), low albumin 34 g/L (35–50), positive for Hepatitis C screening. Other tumor markers and Hepatitis B screening were normal. He denied excessive intake of antacids or vitamins A and D. He was subsequently admitted to the general surgical ward.

Oesophagogastroduodenoscopy (OGDS) and colonoscopy did not reveal any abnormalities other than antral gastritis. Ultrasonography of abdomen revealed an ill-defined heterogenous mass at segment VIII of the liver (measuring approximately 6.8 x 7.3 x 7.0 cm). Computerized tomography (CT) scan showed solitary, well –defined liver mass in segment VIII (5.0 x 8.9 x 9.5

cm) in a non-cirrhotic background, with hepatic arterial enhancement and washout in the venous and delayed phase consistent with HCC, without evidence of bony metastasis (Figure 1).

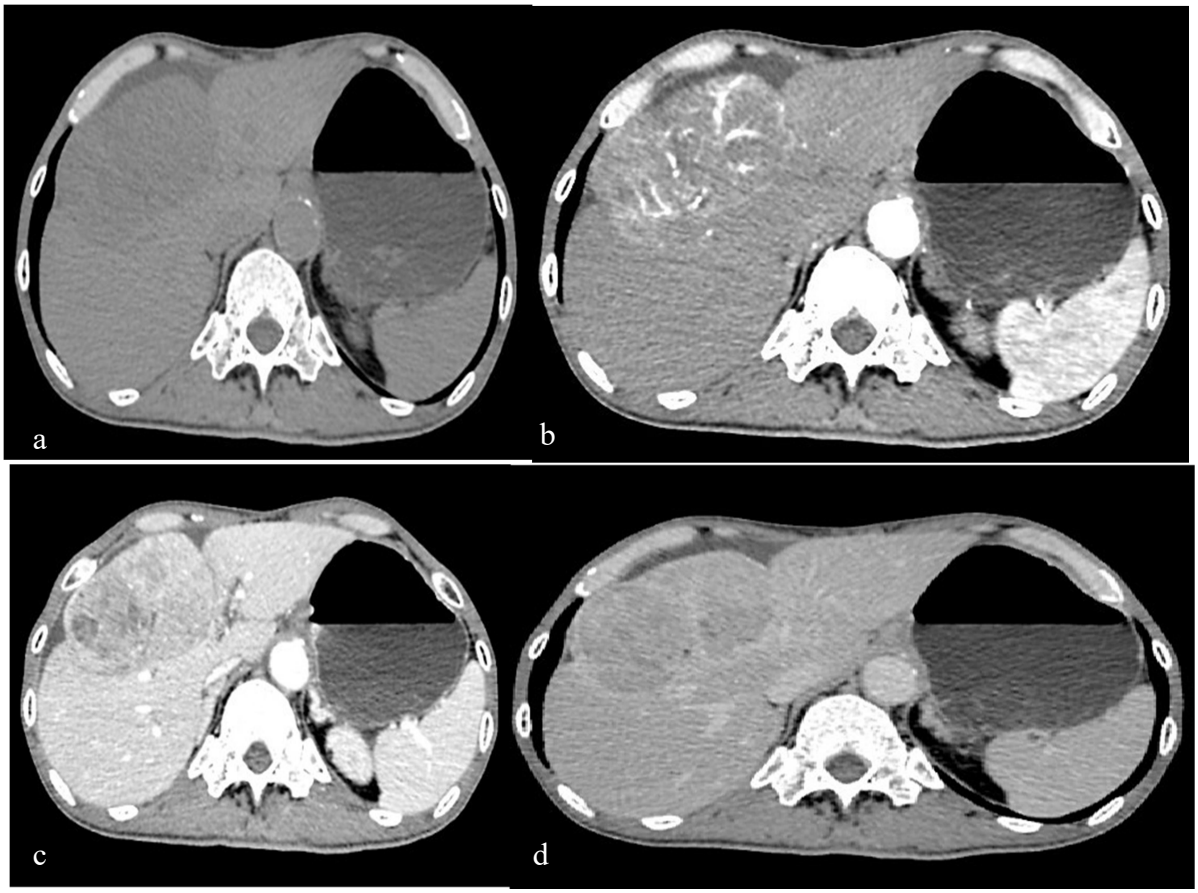

Figure 1. Axial CT images in (a) plain, (b) arterial, (c) porto-venous and (d) delayed phase. Hypervascular mass in segment VIII of liver which demonstrate arterial enhancement with washout in the porto venous and delayed phase.

His corrected calcium level was noted to be persistently high despite intravenous bisphosphonates and aggressive intravenous hydration with forced diuresis. Further workup for hypercalcemia revealed normal intact parathyroid hormone (PTH) 2.0 pmol/L (normal range 1.6-6.9), and a normal ultrasound neck (no sonographic evidence of parathyroid mass). A diagnosis of hypercalcemia as paraneoplastic syndrome associated with HCC (Barcelona Clinic Liver Cancer BCLC Stage B) was made. Diagnosis was revealed to the patient and his family members, where trans – arterial chemoembolization was offered; however, they were not keen. His clinical condition continued to deteriorate, and subsequently he expired after 2 months from the time of diagnosis.

Discussion

Identification of non–cirrhotic HCC generally was delayed due to its indolent nature of disease by virtue of being symptomatic at a later stage, as the case in our patient. Thus, they tend to have larger tumor burdens at initial presentation, with an average of 12 cm, in contrast to their cirrhotic counterparts with a smaller size range (12). Current literature suggests resection at the first step of treatment in those with good liver function (Child–Pugh score A), and a solitary mass (13).

There were four known mechanisms that lead to hypercalcemia in malignancy. About 80% of cases, commonly occur in squamous cell cancers, related to PTHrP (parathyroid hormone related peptide) secretion by cancer cells, also known as humoral hypercalcemia of malignancy. While 20% of cases are associated with osteolytic activity at sites of bone metastasis, most commonly seen in breast cancer, lymphomas, and multiple myelomas. There were unusual occasions where

some lymphomas were linked with vitamin D secretions from tumor cells or via ectopic tumor secretion of PTH (14).

Our patient was found to have hypercalcemia, normal intact parathyroid hormone, and a confirmed diagnosis of non–cirrhotic HCC, indicating humoral hypercalcemia of malignancy, while we do not have adequate resources to measure the PTHrP.
Our patient's unusual presentation of hypercalcemia leading to the diagnosis of non–cirrhotic HCC is challenging and tends to have a poor prognosis, as evidenced by a markedly high tumor marker (AFP > 10,000 ug/L) with the presence of paraneoplastic syndrome (hypercalcemia) (15).

Conclusion
Our patient had been diagnosed with non – cirrhotic HCC with accompanying hypercalcemia as paraneoplastic syndrome. Unfortunately, its detection carries a poor prognosis. HCC should be considered part of the differential diagnosis of hypercalcemia, though non –cirrhotic HCC tends to present late with isolated hypercalcemia.

Competing interests
There was no funding for the study and no conflicts of interest to disclose.

Consent
Patient's family members gave verbal consent for this case study.

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