Hepatocellular Carcinoma Without Cirrhosis Presenting With Hypercalcemia: Case Report and Literature Review

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Background: **Hepatocellular carcinoma (HCC) in non-cirrhotic livers is an uncommon finding and can present insidiously in patients. Another uncommon finding in HCC, and one of poor prognosis, is the presence of paraneoplastic diseases such as hypercalcemia. We report a case of a 66-year-old previous healthy Filipina woman who after routine laboratory evaluation was discovered to have hypercalcemia as the first sign of an advanced HCC without underlying cirrhosis. Because of the patient's relative lack of symptoms, healthy liver function, lack of classical HCC risk factors, and unexpected hypercalcemia, the diagnosis of a paraneoplastic syndrome caused by a noncirrhotic HCC was unanticipated.** ***Methods:*** **Case Analysis with Pubmed literature review.** ***Results:*** **It is unknown how often hypercalcemia is found in association with HCC in a non-cirrhotic liver. However, paraneoplastic manifestations of HCC, particularly hypercalcemia, can be correlated with poor prognosis. For this patient, initial management included attempts to lower calcium levels via zoledronate, which wasn't completely effective. Tumor resection was then attempted however the patient expired due to complications from advanced tumor size.** ***Conclusions:*** **Hypercalcemia of malignancy can be found in association with non-cirrhotic HCC and should be considered on the differential diagnosis during clinical work-up. (J Clin Exp Hepatol 2015;5:163–166)**

Hepatocellular carcinoma (HCC) is estimated to be the fourth most common cancer globally. In the United States alone, an approximated 33,000 new cases will be diagnosed in 2014 with men outnumbering women by a ratio of two to one.[1,2] Nearly 80–90% of cases of HCC are due to underlying cirrhosis caused by well-known risk factors such as chronic hepatitis B or C, alcoholism, alpha-1 antitrypsin (A1AT) deficiency, and non-alcoholic steatohepatitis (NASH).[2,3] One large prospective case series found cryptogenic cirrhosis to be the second most common background liver disease in a cohort of 105 HCC patients, accounting for 29% of cases studied. Half of these patients had either histologically diagnosed Non-Alcoholic Steatohepatits by prior biopsy or clinical features of Non-Alcoholic Fatty Liver Disease (BMI >30, diabetes mellitus, or hypertriglyceridemia).[4] While significantly less common, non-cirrhotic HCC still accounts for an unknown number of total cases. In fact, one large multicenter study in Italy demonstrated out of 3000 cases of HCC merely 52 patients, or <2% of cases, were due to non-cirrhotic HCC.[5] Other sources estimate non-cirrhotic HCC to account for 20% of all cases worldwide.[6] While the pathogenesis of HCC in patients with cirrhotic disease results from stepwise mutations, the disease progression of non-cirrhotic disease is still somewhat obscure and is possibly due to de novo carcinogenesis.[6] Spontaneous neoplastic transformation may also result from exposure to genotoxins (e.g. aspergillus) or other underlying metabolic diseases such as glycogen storage disease.[3,6]

HCC is occasionally associated with paraneoplastic syndromes, albeit at a low frequency. HCC has reported associations with hypoglycemia,[7] demyelination,[8] pemphigus vulgaris,[9] thrombocytosis,[10–14] hypercalcemia,[11–14] hypercholesterolemia,[11–15] and erythrocytosis.[11–14,16] The association between paraneoplastic syndromes and non-cirrhotic HCC is uncertain. We present a case describing humoral hypercalcemia of malignancy (HHM) as the first

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Abbreviations: AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CEA: carcinoembryonic antigen; HCC: hepatocellular carcinoma; HHM: hypercalcemia of malignancy; PTH: parathyroid hormone; PTHrP: parathyroid hormone related peptide
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sign of an underlying HCC in an asymptomatic woman with a non-cirrhotic liver.

METHODS

We conducted an internet-based literature search via Pubmed with key words, "hypercalcemia, paraneoplastic syndrome, hepatocellular carcinoma" on 11/21/14. Clinical, pathological, radiologic data and follow up information is reported.

CASE PRESENTATION

A 66-year-old Filipina woman with no prior medical problems presented to her primary care physician for routine annual physical exam at which time she reported an unintentional ten-pound weight loss. The patient had no history of smoking or alcohol use, and no known family history of cancer. Physical exam was remarkable only for the stigmata of recent weight loss. However, laboratory results revealed elevated calcium 13.2 mg/dL (normal range 8.5–10.2), calcitriol 89 μg/mL (18–72), alkaline phosphatase 194 U/L (33–130), and aspartate aminotransferase (AST) of 57 U/L (10–35). Albumin and bilirubin were within normal limits. The patient denied any excess intake of antacids or vitamins A and D, and was not taking any other prescribed medications.

Follow-up renal sonogram to detect a renal origin of the hypercalcemia incidentally revealed a sizeable hepatic mass of 14.4 × 14.9 × 13.9 cm, prompting an abdominal MRI which demonstrated a 14.0 cm × 10.2 cm × 13.5 cm solid mass occupying the right lobe of the liver compressing the inferior vena cava and displacing the right hepatic vein. Follow-up computerized tomography (CT) scan (Figure 1) found similar measurements for the primary liver lesion and demonstrated hepatic arterial enhancement with washout in the venous phase consistent with HCC. The follow-up CT scan also identified a small, irregular, spiculated lesion in the upper lobe of her right lung suspicious for a primary lung cancer.

Additional laboratory testing showed normal level of parathyroid hormone (PTH) 11 pg/dL (10–55) with an elevated level of parathyroid related peptide (PTHrp) 4.6 pg/dL (<2) and calcium of 12 mg/dl. Furthermore, tumor markers including Alpha-fetoprotein (AFP) were 18.0 ng/dL (<10), Carcinoembryonic antigen (CEA) 3.0 ng/mL (<2.5) and Carbohydrate antigen 19-9 (CA 19-9) 131.1 U/mL (<37) were measured. Viral hepatitis serologies including hepatitis B serologies (surface antigen, surface antibody, and core antibody) and hepatitis C antibody were confirmed to be negative.

The initial diagnostic suspicion was that this patient had experienced humoral hypercalcemia of malignancy due to a primary lung neoplasm with an additional primary neoplasm of the liver. Subsequent biopsy of the spiculated lung nodule demonstrated a 1.7 cm granuloma, ruling out a lung neoplasm. A CT-guided liver biopsy diagnosed HCC by performing an immunohistochemistry assay which was positive for Hep-par1(liver specific), glypican-3(HCC sensitive and specific) and CK-7(positive in 9–18% HCC). The stains were negative for other markers notably CK20, S100p, TTF-1 and Napsin-A. Analysis of the biopsy performed at 100× magnification and demonstrates poorly differentiated and disorganized morphology with numerous elongated spindled cells (Figure 2). A glypican-3 stain, specific for HCC, is shown at 40× to be positive on the biopsy (Figure 3). These biopsy results suggested that the HHM was a manifestation of HCC. Her physicians began treatment with 4 mg/dL of IV zoledronic acid, a bisphosphonate that is effective in lessening hypercalcemia, in addition to hydration with 1 L of normal saline. One week later, her calcium was at a nadir of 11.3 mg/dL but merely two days after was at 11.9 mg/dL. She was then given 20 mg of furosemide along with another liter of normal saline. Her calcium over a span of

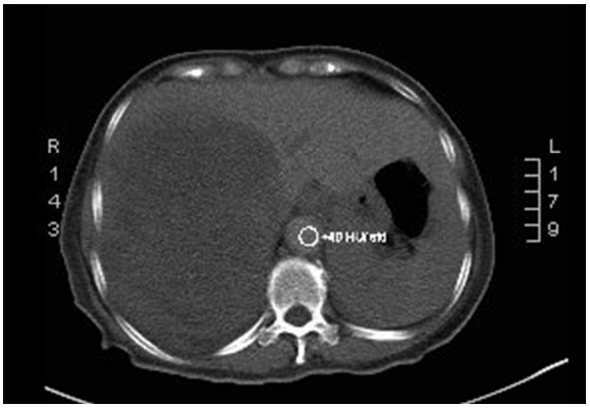

Figure 1 Baseline CT of patient showing large tumor in the right lobe of her liver.

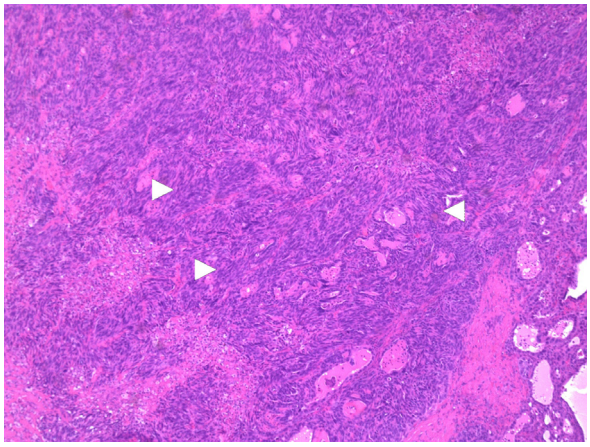

Figure 2 Hemotoxylin and Eosin stain from tumor biopsy demonstrating spindled cells (white arrowheads) and a poorly differentiated disorganized tumor at 100× magnification.