

Parathyroid Hormone related Peptide causing hypercalcaemia in a patient with hepatocellular carcinoma

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Abstract

The incidence of hepatocellular carcinoma (HCC) is increasing. In addition, its presentation without bony metastasis as a part of paraneoplastic syndrome is recognised but uncommon. This unusual presentation of HCC is highlighted in the case of a 63 years old lady, who presented with lethargy and tiredness and hypercalcaemia due to secretion of parathyroid hormone related peptide (PTHrP). Further imaging showed 11 cm hepatic mass, with normal alpha fetoprotein. She underwent partial hepatectomy and is doing well since then. Malignant hypercalcaemia is thought to arise from the secretion of PTHrP which is synthesised by tumour cells and has a similar action to parathyroid hormone. Early recognition of this uncommon condition can lead to complete cure as seen in our patient.

Keywords: Hepatocellular carcinoma, Hypercalcaemia, Parathyroid hormone related peptide.

Introduction

Primary liver cancers including hepatocellular carcinoma (HCC) is an uncommon condition and only accounts for 2-3% of all gastrointestinal cancers in the Western world.¹ However, in USA its incidence appears to be increasing because of growing prevalence of hepatitis C.² Typical presentation of HCC includes solitary mass in normal or cirrhotic liver with elevated alpha fetoprotein. However, at presentation or during its clinical course, some patients of HCC may manifest a variety of paraneoplastic syndromes including hypercholesterolemia, hypoglycaemia, erythrocytosis and hypercalcaemia.³

HCC associated with hypercalcaemia is due to either bony metastasis or secretion of hormones such as intact parathyroid hormone (PTH)⁴ or its related peptide (PTHrP) by the tumour which is successfully treated with either tumour resection or embolization.⁵ Moreover, these patients with paraneoplastic syndromes, including hypercalcaemia, usually present at an advanced stage, with high alpha fetoprotein, large tumour volume and have a poor prognosis.⁶

We report a case of primary HCC, who presented with

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hypercalcaemia due to the paraneoplastic secretion of PTHrP from her tumour. Despite the advanced stage, large tumour size at presentation she still remains well 3 years after partial liver resection, In addition, her calcium level also remains normal since her operation.

Case Report

A 63-year-old woman presented with generalized fatigue, weight loss and vague abdominal discomfort. On admission her examination revealed hepatomegaly but no stigmata of chronic liver disease. Routine blood biochemistry, showed high corrected serum calcium levels at 13.1mg/dl or 3.28 mmol/L. (normal value 2.2 to 2.6 mmol/L). She was subsequently referred to the hospital for urgent investigation and treatment of her hypercalcaemia. She was treated with intravenous fluids and pamidronate urgently. Her myeloma screen was negative. Serum parathyroid hormone (PTH) levels were found to be low at < 0.4 pmol/l. In addition, her serum cholesterol and glucose levels were normal.

An MRI scan of parathyroid gland did not reveal any abnormality. Interestingly her PTHrP levels were found to be markedly elevated at 7.8 pmol/l (normal <0.7 pmol/l.) An ultrasound and later a CT scan of the abdomen confirmed the presence of a large 11 cm mass in the right lobe of her liver with no involvement of any other organ. (Figure) Biopsy of the liver mass and subsequent biopsy from the surgical specimen confirmed the diagnosis of

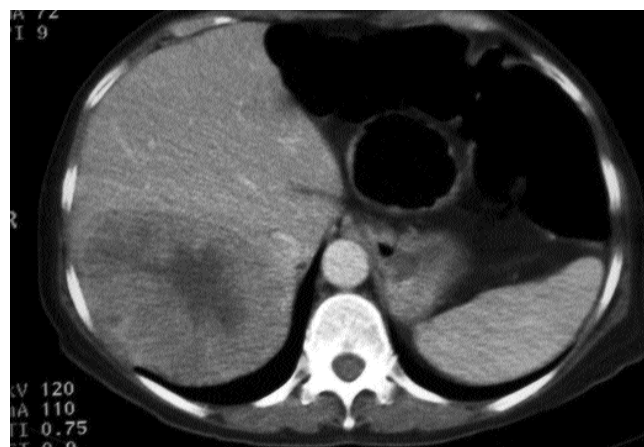


Figure: CT of the liver showing 11 cm mass in the right lobe of the liver.

HCC. Her alpha fetoprotein level was normal.

She underwent right lobe surgical resection of her liver. She made significant recovery after her operation with improvement both in her weight, symptoms and hypercalcaemia. Two months after her surgery her serum calcium level, PTH level and PTHrP levels were back to normal. This lady remains well since her surgery in June 2007. She had three annual surveillance CT scans of her liver and they have not shown any recurrence of her liver cancer. In addition, her serum calcium level, PTH levels, and PTHrP levels remain normal.

Discussion

Hypercalcaemia associated with HCC is either due to bony involvement which increases the osteoclastic activity resulting in bone resorption⁵ or secretion of intact PTH⁴ or its related peptide (PTHrP) from cancerous tissue, both have similar actions.^{6,7} PTHrP is recently characterized as 139-173 amino acid protein and because of similarity in the amino acid sequence to PTH, it cross-reacts with PTH receptors in bone and kidney resulting in hypercalcaemia.^{7,8}

The incidence of liver malignancy and hypercalcaemia varies in different case reports from 1.5% to 40%. This wide variation in the incidence is dependent on inclusion or exclusion of patients with bony metastasis in these reviews.⁹ However, hypercalcaemia due to secretion of PTHrP is most commonly associated with sclerosing hepatic carcinoma, a rare variant of hepatic neoplasm.¹⁰ In addition, the relationship of PTHrP with hypercalcaemia in hepatic malignancy is further supported by fall in the level of calcium and PTHrP after tumour resection,¹¹ This was seen in our patient when her calcium and PTHrP level returned to normal after hepatic resection.

The initial management of hypercalcaemia due to paraneoplastic secretion of PTHrP is the same as for primary hypercalcaemia, mainly rehydration with intra venous normal saline and then bisphosphonates to decrease bone resorption. A bisphosphonate such as Pamidronate can be used and that can take up to four days to take effect. Unfortunately, response to medical management is usually poor and associated with bad prognosis. The curative treatment is only surgery in the form of either partial hepatic resection or liver transplant. Our patient underwent partial resection with excellent outcome.

The poor prognostic indicators in patients with HCC include presence of paraneoplastic syndrome including humoral secretion of PTHrP, large tumour volume and raised alpha fetoprotein (AFP).⁶ The patients with HCC may present or

develop during its clinical course varying number of manifestations of paraneoplastic syndrome, such as hypercholesterolemia, hypoglycaemia, erythrocytosis and hypercalcaemia.³ A high serum AFP level can indicate greater activity of malignant cells which in turn can secrete other hormones such as insulin like growth factor I, PTHrP and erythropoietin,³ resulting in manifestations of paraneoplastic syndromes. Perhaps because our patient had normal level of AFP, full range of paraneoplastic syndromes was not exhibited. Surgical removal of the tumour or liver transplant remains the curative options. In our patient partial hepatectomy was carried out that normalized her calcium and she is leading a healthy life for the last 3 years.

Conclusion

Malignant hypercalcaemia, a rare paraneoplastic syndrome responsible for hypercalcaemia of malignancies is caused by secretion of PTHrP from the tumour. Paraneoplastic manifestation of malignancy usually indicate the advanced stage of the disease, however it is still important to identify the source of PTHrP secretion as it can be cured by tumour resection or liver transplant.

References

1. Roskams T, Willems M, Campos RV. Parathyroid related peptide expression in primary and metastatic liver tumours. *Histopath* 1993; 23: 519-25.
2. El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. *Arch Intern Med* 2000; 160: 3227-30.
3. Chen-Wei C, Shinn-Jang H, Jing-Chyuan L, Shyh-Haw T, Chung-Pin L, Full-Young C, et al. Manifestations of hypercholesterolemia, hypoglycaemia, erythrocytosis and hypercalcaemia in patients with hepatocellular carcinoma: Report of two Cases. *J Gastroenterol Hepatol* 1999; 14: 807-10.
4. Abe Y, Makiyama H, Fujita Y, Tachibana Y, Kamada G, Vebayashi M. Severe hypercalcaemia associated with hepatocellular carcinoma secreting intact parathyroid hormone: A case report. *Int Med* 2011; 50: 329-33.
5. Attali P, Houssin D, Roche A. Hepatic arterial embolization for malignant hypercalcaemia in HCC. *Dig Dis Sci* 1984; 29: 466-9.
6. Martin TJ, Suva LJ. Parathyroid hormone Related Peptide in hypercalcaemia of malignancy. *Clin Endocrinol (Oxf)* 1989; 31: 631-47.
7. Luo JC, Hwang SJ, Wu JC. Paraneoplastic Syndrome in Patients with HCC in Taiwan. *Cancer* 1999; 86: 799-804.
8. Broadus AE, Stewart AF. Parathyroid hormone Related Protein, structure, processing and physiological action. In: Bilezikian JP, Marcus R (eds). *The Parathyroids*. New York: Ravens, 1994; pp 259-94.
9. Szilagyi A, Alpert L. Clinical and histo-pathological variation in hepatocellular carcinoma with hypercalcaemia. *Am J Gastroenterol* 1995; 90: 15-23.
10. Albar JP, Miguel FD, Esbrit P, Miranda R, Fernando-Flores A, Sarasa JL. Immuno-histochemical detection of parathyroid hormone-related protein in a rare variant of hepatic neoplasm (sclerosing hepatic carcinoma). *Human Pathology* 1996; 27: 728-31.
11. Tamura K, Kubota K, Take H, Kurabayashi H, Shirakura T. Parathyroid Hormone Related Peptide as a possible cause of hypercalcaemia in a hepatocellular carcinoma patient. *Am J Gastroenterol* 1994; 89: 644-5.