

CASE REPORT

## 부갑상선 호르몬 관련 펩티드를 분비하는 간세포암종의 완전 절제

김은경, 김진수, 신기철, 이길태, 한철주, 김상범<sup>1</sup>, 구윤희

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### Complete Tumor Resection for a Hepatocellular Carcinoma Secreting Parathyroid Hormone-related Peptide

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Hepatocellular carcinoma (HCC) is the fifth most common cancer in Korea. Diverse paraneoplastic syndromes can occur in patients with HCC, but parathyroid hormone-related peptide (PTH-rP)-induced hypercalcemia is uncommon. Hypercalcemia due to PTH or particularly PTH-rP-secreting HCC is associated with poor outcomes. We report a 71-year-old man who presented with symptoms of vague abdominal discomfort, somnolence, lethargy, nausea, vomiting, and weight loss. Imaging studies revealed a large HCC without metastasis. The laboratory findings showed elevated serum calcium level, low intact parathyroid hormone (iPTH) level and elevated PTH-rP level. These results led to a diagnosis of a PTH-rP-secreting HCC and paraneoplastic hypercalcemia. After emergency management of the hypercalcemia, the patient underwent an extended right hemihepatectomy with cholecystectomy. One year after the surgery, he is alive with normal calcium, PTH-rP, and iPTH levels. This case demonstrates that the rare phenomenon of life-threatening hypercalcemia caused by HCC should not be overlooked. These symptoms offer a good opportunity to diagnose HCC early. Radical tumor resection makes it possible to cure patients with PTH-rP-secreting HCC. (*Korean J Gastroenterol* 2015;66:122-126)

**Key Words:** Hepatocellular carcinoma; Parathyroid hormone-related protein; Paraneoplastic syndromes

#### INTRODUCTION

Hypercalcemia is a feature of paraneoplastic syndromes often associated with malignancies of the lungs, breasts, ovaries, lymphatic system, or other organs. Although there are various causes of hypercalcemia in malignancies, parathyroid hormone-related peptide (PTH-rP)-associated hypercalcemia is the most common cause.<sup>1,2</sup>

According to the National Cancer Information Center ([www.cancer.go.kr](http://www.cancer.go.kr)) in Korea, hepatocellular carcinoma (HCC)

was the sixth most common cancer diagnosed in 2012, after thyroid cancer, stomach cancer, colon cancer, lung cancer and breast cancer. Patients with HCC may display a variety of paraneoplastic syndromes including hypercholesterolemia, hypoglycemia, erythrocytosis, and hypercalcemia.<sup>3,4</sup>

A few cases of hypercalcemia associated with PTH-rP-secreting HCC have been reported. However, no case that was cured has been described in Korea. Herein, we describe a 71-year-old man who was cured of a PTH-rP-secreting HCC by undergoing complete tumor resection.

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## CASE REPORT

A 71-year-old man presented with a four-month history of vague abdominal discomfort, somnolence, lethargy, nausea, vomiting, weight loss of approximately 7 to 8 kg, and poor oral intake. Because of these symptoms, abdominal ultrasonography was performed at a local clinic, revealing a large lesion in the liver. The patient was referred to our hospital. His height and weight were 167.3 cm and 56 kg. His medical and family history did not appear to contribute to the present illness. He had not undergone any regular screening for HCC. The patient had a history of stable angina treated with aspirin and 25 mg of captopril per day. He had been smoking 10 cigarettes a day for 35 years and had a history of heavy drinking (a bottle of soju 360 mL every day) for 30 years.

Physical examination revealed stable vital signs including a blood pressure of 120/80 mmHg and a regular heart rate of 68 beats per minute. Respiratory and cardiovascular examinations were within normal limits. A neurological examination showed intact cranial nerves and normal motor, sensory, and cerebellar functions with no focal neurological deficits. Abdominal palpation revealed a non-tender hepatomegaly without shifting dullness.

CT analysis of his abdomen and MRI of his liver showed an enlarged liver with a 13.5-cm solid mass with a central, ill-defined, low attenuated necrotic portion in segment 4 of the right hepatic lobe without portal vein thrombosis or ascites. The CT findings indicated early tumor staining and washout during the delayed phases (Fig. 1). MRI revealed a mass with high signal intensity on T2-weighted images and low signal intensity on T1-weighted images. These findings indicated HCC. There was no involvement of any other organ on PET-CT. The patient's bone scan was normal without evidence of skeletal metastases. Bone mineral density was within the normal range by dual energy X-ray absorptiometry. Esophagoduodenoscopy and colonoscopy were performed because of the patient's drastic weight loss and dyspepsia. However, they revealed only a benign polyp and chronic gastritis. Those findings were suggestive of T2N0M0 HCC (modified Union for International Cancer Control [UICC] stage II).

The results of the routine blood tests were as follows: white blood cell count, 8,400/mm<sup>3</sup>; hemoglobin, 13.3 g/L; hematocrit, 40.4%; mean corpuscular volume, 99 fL; platelet count, 305,000/mm<sup>3</sup>; phosphorous, 3.5 mg/dL; sodium,

137 mEq/L; potassium, 3.5 mEq/L; chloride, 104 mEq/L; BUN, 17.9 mg/dL; creatinine, 1.2 mg/dL; and glucose, 66 mg/dL. The patient was found to have a calcium level of 12.7 mg/dL (ionized calcium level, 6.39 mg/dL) with an albumin level of 4.6 g/dL. His intact parathyroid hormone (iPTH) level was suppressed (< 2.5 mg/dL; normal value, 14-72 mg/dL) and his PTH-rP level was elevated (3.30 pmol/L; normal value, < 0.7 pmol/L). Analysis of liver enzymes showed the following results: total bilirubin, 0.6 mg/dL; AST, 49 U/L; ALT, 38 U/L; and mildly elevated ALP, 192 U/L. The tumor marker levels were as follows: AFP, 7.38 ng/mL and proteins induced by vitamin K-II, 22 mAU/mL. The CA 19-9 level was found to be double that of the normal level (62.71 U/mL). The results of serology tests for HBV, HCV, human immunodeficiency virus, and syphilis were all negative.

All the above-mentioned results were compatible with the diagnosis of hypercalcemia associated with PTH-rP-secreting HCC. Although the tumor was resectable, the patient suffered hypercalcemia-associated symptoms. We decided to perform surgery after stabilizing his condition. The patient was treated with intravenous bisphosphonates (pamidronate, 60 mg) along with the daily administration of 3 L of normal saline hydration with furosemide. The calcium level decreased gradually to normal. After one week, the calcium level dropped to 8.9 mg/dL (ionized calcium level, 4.92 mg/dL) and the iPTH level increased to the normal range (15 mg/dL). The patient's symptoms completely disappeared in two weeks. The



**Fig. 1.** Hepatocellular carcinoma at the time of diagnosis. A 13-cm tumor is visualized in the right hepatic lobe.

patient then underwent a successful extended right hemihepatectomy with cholecystectomy. There was no sign of metastasis in any of the lymph nodes analyzed and no evidence of cirrhosis in the liver tissue. Hematoxylin and eosin-stained tissue revealed the presence of a typical HCC. Immunohistochemical staining of the tissue showed positive staining for glypican-3, negative staining for CA 19-9, and negative staining for PTH (Fig. 2). All of the histopathological findings were compatible with our pre-operative diagnosis.

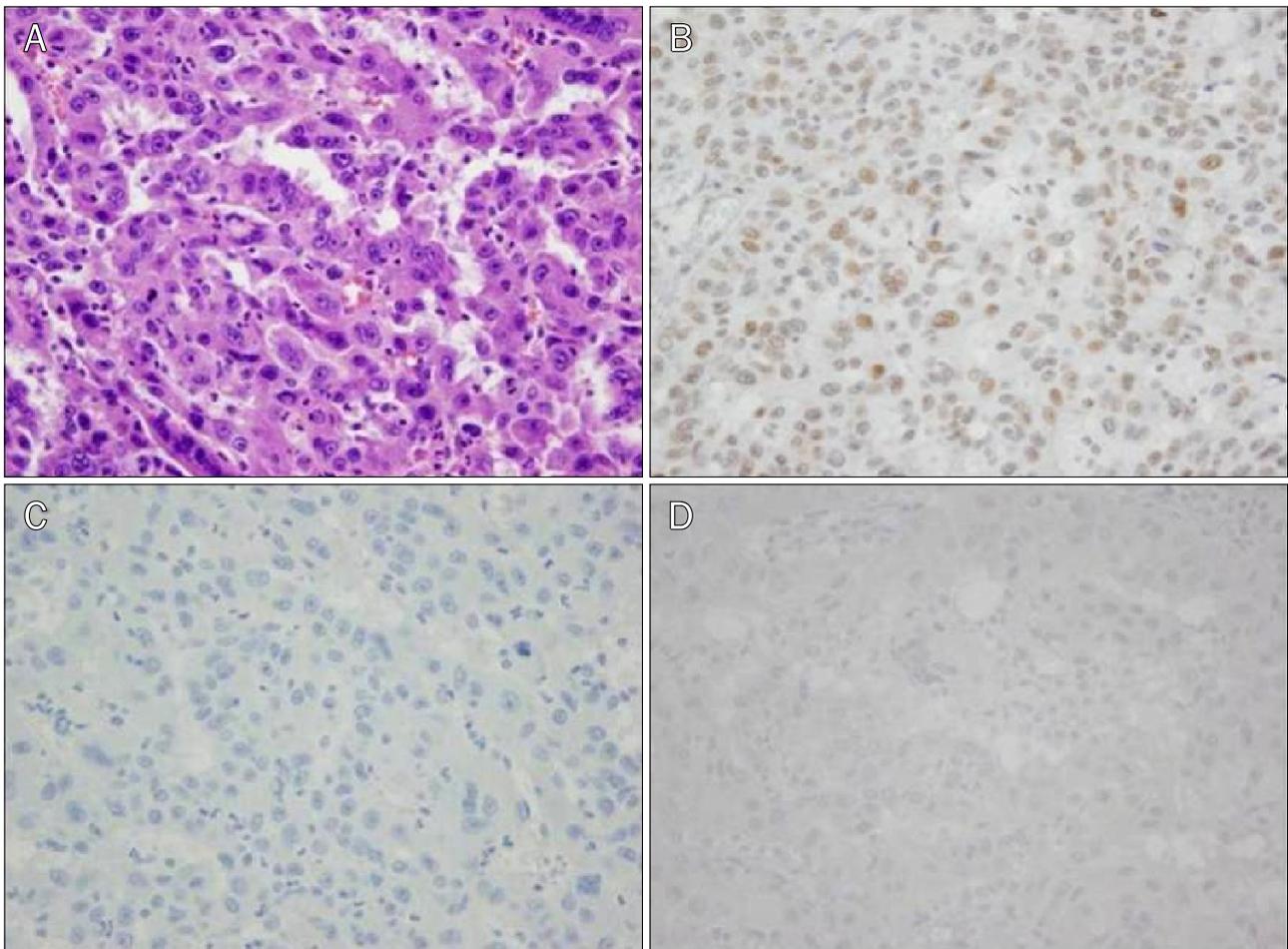
Two weeks after the surgery, the patient was found to have a calcium level of 8.9 mg/dL (ionized calcium level, 4.33 mg/dL) with an albumin level of 3.3 g/dL. His iPTH was 20 mg/mL (normal value, 14-72 mg/dL) and his PTH-rP was not detectable (normal value, <0.7 pmol/L). After 15 months, an abdominal CT showed no evidence of HCC recurrence and results of subsequent serial blood tests were all within the normal range. The patient is still alive with no evidence of

recurrence.

## DISCUSSION

The risk of hypercalcemia induced by PTH-rP associated with HCC was first assessed in 1982 in a retrospective study. Of the 152 patients analyzed, 5.2% had hypercalcemia due to HCC without bone involvement.<sup>5</sup> A study in the Korean Journal of Hepatology reported that the prevalence of paraneoplastic syndromes associated with HCC in Korea is 35% in Korea is 43.6%.<sup>2</sup> The most common paraneoplastic syndrome was hypercholesterolemia (14.5%), followed by hypoglycemia (12.7%), and hypercalcemia (7.8%).<sup>2</sup>

Paraneoplastic hypercalcemia in patients with HCC is associated with more advanced disease, as evidenced by significantly higher AFP levels, bilobar disease, multiple lesions and more advanced TNM stage at diagnosis, which reflect a



**Fig. 2.** Immunohistochemistry of the tumor specimen. (A) Microscopically tumor cells show trabecular growth patterns separated by sinusoids (H&E, ×400). (B) Positive staining for glypican-3 (×400). (C) Negative staining for CK19 (×400). (D) Negative staining for parathyroid hormone (×400).

greater tumor burden in patients with paraneoplastic hypercalcemia.<sup>6</sup> Hypercalcemia occurs abruptly and generally indicates a poor prognosis.<sup>2,7</sup> In one study, nearly 50% of patients with PTH-rP associated hypercalcemia died within 30 days of commencing treatment, and within three months, up to 75% of these patients died.<sup>8</sup> In addition, some studies reported that paraneoplastic hypercalcemia associated with HCC is often a life-threatening medical emergency<sup>9,10</sup> that requires prompt treatment. In Korea, a few cases of hypercalcemia associated with PTH-rP secreting HCC have been reported.<sup>11-14</sup> The patients were diagnosed with HCC at the advanced stage, though it was uncertain whether they had undergone any regular screening for HCC. Literature reports find that hypercalcemia was revealed with HCC simultaneously. Despite supportive care for hypercalcemia, curative treatment for HCC was not effective and all eventually expired in a few months.

There are several causes of malignancy-associated hypercalcemia. Overall, approximately 80% of patients with malignancy-induced hypercalcemia display PTH-rP secretion, which most commonly occurs with squamous cell tumors.<sup>7</sup> The biochemical structure of PTH-rP resembles that of PTH, and both share the same PTH receptor.<sup>15,16</sup> Similar to PTH, PTH-rP interacts with the PTH/PTH-rP receptor that activates renal calcium reabsorption and promotes absorption of calcium from the bones. The second most common cause for hypercalcemia is the osteolytic action of skeletal metastatic lesions. Rarely, hypercalcemia may arise from vitamin-secreting tumors, particularly in patients with lymphoma, or from ectopic tumors secreting PTH.<sup>17</sup>

The clinical features of hypercalcemia include gastrointestinal symptoms such as constipation, anorexia, nausea, varying degrees of vomiting, renal failure, as well as cardiovascular and neurological changes. With increasing severity of hypercalcemia, symptoms may gradually progress to depression, confusion, and even coma. Muscle weakness is commonly observed. The presence or absence of symptoms correlates both with the degree of the serum calcium elevation (calcium level > 14 mg/dL is considered severe) and with the rapidity of the increase. Especially, older patients with preexisting neurologic or cognitive dysfunction may have severe exacerbations in the presence of mild hypercalcemia, and the concomitant administration of sedatives may worsen the neurologic complications of hypercalcemia.<sup>17</sup>

For correcting hypercalcemia, available medical treatments include calcitonin and intravenous administration of bisphosphonates along with large amounts of saline hydration and furosemide, which further inhibit renal calcium reabsorption. Intravenous administration of bisphosphonates, such as pamidronate and zoledronic acid, inhibits osteoclast bone resorption, and they are the preferred agents because of their favorable efficacy and lower toxicity. Usually, serum calcium level decline within two to four days, reach a maximum between four and seven days after injection, and persist for three weeks.<sup>15,17</sup> The calcium-lowering effect of calcitonin is caused by both a decrease in bone resorption and an inhibition of the renal tubular reabsorption of calcium. Calcitonin has a rapid effect, but it is usually short-lived. Its effect can disappear after only a few days despite continued use. Therefore, calcitonin is generally administered as an adjunct medication along with other therapies. Occasionally, corticosteroids may be used for the management of hypercalcemia via direct antitumor effects in lymphoma and myeloma cells.<sup>7</sup>

Symptoms of paraneoplastic syndrome at an early stage of cancer may lead to favorable clinical outcomes and the improved quality of life. In this case, surgical cure may have been possible because the PTH-rP-induced hypercalcemia symptoms led the patient to visit a hospital early and to be diagnosed with a resectable stage of HCC.

In summary, we presented a case of HCC that secreted PTH-rP, which induced symptomatic hypercalcemia. This case emphasizes that symptoms of paraneoplastic syndrome such as hypercalcemia may be helpful to diagnose HCC at the resectable stage and to receive surgical cure.

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