Combined Hepatocellular Carcinoma and Neuroendocrine Carcinoma with Ectopic Secretion of Parathyroid Hormone: A Case Report and Review of the Literature

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Primary combined hepatocellular carcinoma (HCC) and neuroendocrine carcinoma is a rare entity, and so is hypercalcemia due to ectopic parathyroid hormone (PTH) secretion by tumor. A 44-year-old man with hepatitis B virus associated chronic liver disease presented with a hepatic mass. Hemihemipatectomy discovered the mass as combined HCC and poorly differentiated cholangiocarcinoma. During adjuvant chemoradiation therapy, he presented with nausea, and multiple systemic metastases were found. Laboratory tests revealed hypercalcemia with markedly elevated PTH and neuron specific enolase. Parathyroid scan showed normal uptake in parathyroid glands, suggestive of ectopic PTH secretion. Subsequently, immunohistochemistry of neuroendocrine marker was performed on the primary lesion, and confirmed the neuroendocrine differentiation in non-HCC component. The patient died 71 days after surgery. This report may suggest the possibility of ectopic PTH secretion by neuroendocrine carcinoma of hepatic origin causing hypercalcemia. Caution for neuroendocrine differentiation should be exercised when diagnosing poorly differentiated HCC.

CASE REPORT

A 44-year-old man presented with a hepatic mass discovered during a regular abdominal ultrasound for hepatitis B virus associated chronic liver disease. The chronic liver disease was diagnosed 9 years ago and the patient was on Tenofovir. Laboratory findings showed elevated white blood cells (17,000/μL), mildly elevated aspartate aminotransferase (4 IU/L), alanine transaminase (22 IU/L), and normal calcium and phosphate levels. Computed tomographic scan identified one huge mass in segment...
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(8) 8 and the other small mass in S6, with thrombi in right portal and hepatic veins. No other systemic lesion was found. The patient underwent right hemihepatectomy with partial diaphragm resection and lymph node dissection.

On pathological examination, the cut section of S8 revealed a yellow-whitish mass measuring 10.5 × 8.0 with irregular margins and necrosis. The mass in S6 was a yellowish multinodular mass that measured 1.3 × 1.0. Tumor thrombosis was noted in the right portal vein, and cirrhosis was observed in the non-neoplastic liver. Histologically, the main mass in S8 consisted of two components; a dominant poorly differentiated carcinoma component (60%) composed of small tumor cells with enlarged vesicular irregular nuclei, high nuclear to cytoplasmic ratio, large nucleoli, and frequent mitoses, and multiple foci of typical HCC component (40%) showing trabecular architecture and grade 2 nuclei (Fig. 1). The tumor penetrated the Glisson’s capsule directly invading the diaphragm and showed extensive necrosis and microvessel invasion. The poorly differentiated carcinoma component was focally positive for cytokeratin (CK) 7 and negative for α-fetoprotein, hepatocyte, glypican-3, and CK19 immunohistochemistry, and was interpreted as poorly differentiated cholangiocarcinoma component. The pathologic diagnosis of S8 mass was combined HCC and cholangiocarcinoma. The other mass in S6 showed typical histologic features of HCC. There was no metastasis in 22 lymph nodes.

The patient subsequently received adjuvant concurrent chemoradiation therapy (CCRT) of one cycle of 5-flourouracil chemotherapy and two cycles of 5 fluor radiation. On postoperative day 59, he visited the emergency room for nausea and vomiting. Laboratory results showed elevated levels of total calcium (13.2 mg/dL; normal range, 8.8 to 10.5), ionized calcium (2.3 mmol/L; normal range, 1.05 to 1.35), blood urea nitrogen (33 mg/dL; normal range, 10 to 26), and creatinine (2.16 mg/dL; normal range, 0.7 to 1.4) with normal to low levels of phosphate. Further evaluation of hypercalcemia revealed markedly increased PTH (3,859 by enzyme-linked immunosorbent assay; normal range, 15 to 65), and neuron-specific enolase (101.04 ng/mL; normal range, 0 to 16.3). Parathyroid scan was performed to exclude primary hyperparathyroidism, which showed no abnormality. Whole body positron emission tomography revealed multiple hypermetabolic lesions in the liver and whole skeleton, and biopsy of an osteolytic lesion involving a left rib discovered metastatic poorly differentiated carcinoma. Only the poorly differentiated carcinoma component, not the HCC component, was identified in the metastatic lesion. Regarding hypercalcemia, elevated PTH could not be explained with bone metastasis or PTHrP, and hypercalcemia persisted despite management. Finally, ectopic PTH production by the tumor was suggested as the cause of hypercalcemia.

Meanwhile, the clinician in charge enquired to the pathologist of the presence of NEC component in the tumor based on the possibility that ectopic hormone could be secreted by NEC, the rapid progression of the tumor and the elevated neuron-specific enolase level. Subsequent immunohistochemistry of neuroendocrine markers and PTH were performed on both primary (S8 mass) and metastatic tumor specimens. CD56 stained positive while chromogranin and synaptophysin were focally positive in the poorly differentiated area on both specimens, implying neuroendocrine differentiation (Fig. 2). The component with typical HCC morphology was negative for all three markers (Fig. 2). There was no immunoreactivity for PTH on either specimen. Symptomatic treatment including continuous renal replacement therapy was applied for the acute renal failure induced by hypercalcemia. However, the patient expired of disease progression 2 months after diagnosis.

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1801-442-702), and patient consent was waived.

DISCUSSION

Primary combined HCC and NEC is very rare. The initial pathologic diagnosis of this case was combined HCC and cholangiocarcinoma because its poorly differentiated component bore little resemblance to typical NEC morphology. However, with clinical suspicion, immunohistochemistry revealed multifocal areas within the poorly differentiated component that stained positive for neuroendocrine markers. Therefore, we classified it as combined HCC and NEC.

The clinical characteristics of the 18 reported cases of primary mixed HCC and NEC are summarized in Table 1. Most cases
were associated with chronic hepatitis B or C. The reported carcinomas have been classified to two types according to its spatial histologic arrangement. Combined types have a transition zone in which HCC and NEC intermingle with each other whereas collision types show clear separation of the histologically different components, usually by fibrous septa. In our case, the HCC was tightly intermingled with the NEC component, their borders almost indiscernible due to transition zones. Therefore, we classified it as combined HCC and NEC.

Primary mixed HCC and NEC generally tend to have a poorer prognosis than conventional HCC. Of the 18 cases summarized, eight patients experienced recurrence, six patients died within the year of operation from the disease, and only two patients were confirmed to be alive 2 years after surgery (Table 1). Remarkably, in the cases with biopsy-confirmed metastasis, the NEC component was solely found in all occasions, similar to the presenting case. This indicates that the NEC component acts more aggressively, which has a much poorer prognosis than primary HCC. Therefore, it is important to identify the neuroendocrine component and assure proper treatment be given to the patient.

None of the reported combined HCC-NEC described paraneoplastic syndrome or ectopic hormone production. To our knowledge, our case may be the first to report primary mixed HCC and NEC associated with malignancy-related hypercalcemia caused by ectopic PTH production. The patient had multiple bone metastases, and one of which was histologically confirmed. In hypercalcemia caused by osteolytic lesions or PTHrP produced by tumors, however, PTH levels are usually suppressed. It led us to favor ectopic PTH production to be the cause for hypercalcemia than bone metastasis or PTHrP, even though serum PTHrP level was not available.

The prevalence of hypercalcemia accounts for 7.8% of the paraneoplastic syndromes observed in HCC, and is associated with short survival. Ectopic PTH production has been reported in only three HCC cases (Table 2) and not in any primary hepatic NEC case. All three cases performed PTH immunohistochemistry on their biopsy specimens which were negative. Our case also showed negative results. These findings, rather than acting as counter-evidence of hormone production, may suggest that the tumor cells do not store PTH but secrete it into circulation soon after synthesis. We were not able to perform genetic analysis or RNA sequencing for PTH mRNA. As hypercalcemia developed during adjuvant CCRT, comparison of intact PTH levels of before and after the operation or CCRT was impossible. However, in our case, the patient developed hypercalcemia with elevated intact PTH as the metastatic lesions formed. Considering that the metastatic component was NEC, it may be possible to suggest that the intact PTH was synthesized by the NEC cells.

Primary hepatic NEC has poor prognosis, and the NEC component of primary mixed HCC and NEC behaves aggressively.

Fig. 2. (A) The main hepatic tumor consists of neuroendocrine carcinoma (right side) and hepatocellular carcinoma (left side) components. On immunohistochemistry, the neuroendocrine carcinoma component is focally positive for CD56 (B), chromogranin (C), and synaptophysin (D).
| Barisky et al.2 | 43/M | B | Large | Negative | Combined | None | - | Chemotherapy (doxorubicin, 5-fluorouracil) | Dead (26 mo) |
|----------------|------|---|-------|----------|----------|------|---|----------------------------------|---------------|
| Artopoulos and Destouni3 | 69/M | B | 10 | Negative | Combined | None | - | Surgery | Not given |
| Ishida et al.4 | 72/M | C | 3 | Positive (NEC) | Collision | None | - | Surgery | Not given |
| Yamaguchi et al.5 | 71/M | C | 4.1 | Negative | Combined | None | Recurred (5 mo, bone) | Surgery | Alive (F/U 5 mo) |
| Garcia et al.6 | 50/M | C | 5.3 | Negative | Collision | None | Recurred (4 mo, liver) | Surgery \( \rightarrow \) recur: chemotherapy | Alive (F/U 16 mo) |
| Yang et al.7 | 65/M | B | 7.5 | Positive (NEC) | Combined | None | Recurred (3 mo, liver) | Surgery | Dead (12 mo) |
| Tazi et al.8 | 68/M | B | 4.0 | Positive (NEC) | Collision | None | - | Surgery \( \rightarrow \) chemotherapy | Alive (F/U 28 mo) |
| Nakanishi et al.9 | 76/M | C | 3.0 | Negative | Combined | None | Recurred (6 mo, bone) | TACE \( \rightarrow \) surgery | Dead (7 mo) |
| Aboelenen et al.10 | 51/M | C | 7.5 | Negative | Combined | None | - | Surgery | Alive (F/U 6 mo) |
| Nishino et al.11 | 72/M | C | 2.5 | Negative | Combined | None | Recurred (1 wk, lymph nodes) | Surgery \( \rightarrow \) recur: chemotherapy | Dead (2 mo) |

| Nomura et al.12 | 71/M | C | 4.1 | Not given | Combined | None | Recurred (liver) | Surgery | Dead (8 mo) |
|----------------|------|---|-------|----------|----------|------|---|----------------------------------|---------------|
| Nomura et al.13 | 71/M | C | 3.0 | Not given | Collision | None | Recurred (liver) | RFA \( \rightarrow \) surgery | Dead (2 mo) |
| Nomura et al.14 | 58/M | B | 4.3 | Not given | Combined | None | - | Surgery | Alive (F/U 20 mo) |
| Nomura et al.15 | 50/M | B | 1.8 | Not given | Combined | None | - | Surgery | Alive (F/U 19 mo) |
| Nomura et al.16 | 63/M | C | 3.0 | Not given | Combined | None | - | IFN \( \rightarrow \) surgery | Alive (24 mo) |
| Baker et al.17 | 76/M | None | 5.5 | Negative | Collision | None | - | Surgery \( \rightarrow \) chemotherapy (platinum-based) | Alive (F/U not given) |
| Choe et al.18 | 72/M | C | 2.5 | Negative | Collision | None | Recurred (6 mo, liver) | Surgery \( \rightarrow \) recur: chemotherapy | Alive (F/U 10 mo) |
| Liu et al.19 | 65/M | C | 4.3 | Positive (NEC) | Collision | None | - | Surgery | Dead (1.3 mo) |

M, male; NEC, neuroendocrine carcinoma; F/U, follow-up; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; IFN, interferon therapy.
Clinicians and pathologists are advised to take caution for neuroendocrine differentiation when diagnosing poorly differentiated HCC.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Table 2. Summary of previously reported hepatocellular carcinoma cases with ectopic PTH production

| Age/Sex | Chronic hepatitis type | Hepatocellular carcinoma | Calcium (mg/dL) | Intact PTH (pg/mL) | PTH+P (pmol/L) | AFP (ng/mL) | Parathyroid lesion | Treatment | Method of ectopic PTH confirmation | Survival |
|---------|------------------------|--------------------------|-----------------|-------------------|----------------|--------------|------------------|-----------|-------------------------------|----------|
| Koyama et al. 20 | 83/M | C | Single 8 cm mass | 13.0 (8.9–10.1) | 360 (15–50) | 18.7 (13.8–55.3) | 29.348 (0–10) | None | TAE | Venous sampling | Decreased serum calcium and intact PTH after TAE | Alive (F/U 24 mo) |
| Mahoney et al. 19 | 72/M | None | Multiple large lesions, extends into portal vein | 14.5 (8.5–10.5) | 92 (12–65) | <0.7 (<1.3) | Not given | Parathyroid adenoma | Parathyroid resection and TACE | Sestamibi SPECT scan Immunoradiometric assay and rapid assay | Dead (not given) |
| Abe et al. 18 | 73/F | B | Large mass with multiple metastasis | 12.9 (8.5–10.5) | 99 (<60) | <1 (not given) | 189.3 (not given) | None | TACE | Decreased serum calcium and intact PTH after TACE | Dead (2 mo) |

PTH, parathyroid hormone; PTH+P, PTH-related peptide; AFP, α-fetoprotein; M, male; TAE, transcatheter arterial embolization; F/U, follow-up; TACE, transarterial chemoembolization; SPECT, single-photon emission computed tomographic.
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