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Combined Hepatocellular Carcinoma and Neuroendocrine Carcinoma Presenting with Hypercalcemia

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Background

- Malignancy-associated hypercalcemia (MAHC) occurs in 20-30% of cancer patients (1, 2), and is a common cause of hypercalcemia among hospitalized patients (3).
- Its pathophysiology is generally based on bone metastases or the production of parathyroid hormone-related peptide (PTHrP) by tumor cells (4).
- The secreted PTHrP causes hypercalcemia via increased calcium absorption at the kidney and increased bone resorption.
- Hypercalcemia as the first presentation of malignancy in a combined hepatocellular carcinoma (HCC) and neuroendocrine carcinoma (NEC) is extremely rare (5).

Aim

- To report on a rare case of combined HCC and NEC presenting with hypercalcemia.

Case History

- A 67-year-old Caucasian male with a past medical history of alcohol abuse and previously treated Hepatitis C in 2012 with ledipasvir/sobosbuvir, was referred to our hospital for evaluation of hypercalcemia.
- Patient was in his usual state of health until 3 weeks ago when he started having fatigue, nausea, and anorexia. This was also associated with impaired memory and confusion.
- He was seen at an outside hospital and was found to have a calcium of 16.1 mg/dL (normal range 8.5-10.2 mg/dL), so he was given IV fluids, zoledronic acid and calcitonin with improvement in calcium to 10.8 mg/dL.
- Computerized tomography (CT) scan of chest/abdomen/pelvis showed a cirrhotic liver and a 6.5 cm hypodense mass within the left hepatic lobe. CT scan of thoracolumbar spine was negative for lytic or blastic lesions with no acute fracture or dislocation.
- Patient was stabilized and transferred to our hospital for escalation of care.
- Physical examination was remarkable for RUQ tenderness, hepatomegaly and ascites.
- His calcium level was still elevated at 13 mg/dL.
- His parathyroid hormone (PTH) was low at 8 pg/ml (15-65 pg/ml) and PTHrP was high at 105 pg/ml (14-27 pg/ml).

Case History (cont'd)

- Repeat imaging with liver MRI showed a 17 x 8 cm area of signal abnormality with 2 more focal anomalies within, suspicious for malignancy which may be infiltrative. MRI of the thoracolumbar spine was negative for any metastasis, fractures or lytic lesions. Skeletal series was also negative for lytic lesions.
- Microscopic evaluation of the CT-guided liver biopsy showed two distinct patterns. A typical moderately differentiated HCC and a second malignant focus composed of hyperchromatic small to intermediate sized cells with apoptosis, atypical mitoses, vaguely palisading tumor cells around foci of necrosis. This second focus stained positively with CD56 and CAM 5.2 was suggestive of neuroendocrine differentiation and epithelial lineage (**Refer to Figures 1-3**). Background hepatic parenchyma showed early cirrhosis likely secondary to long standing hepatitis C or due to alcohol abuse.
- Tumor markers including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9) were all negative. His workup was negative for another primary malignancy.
- His disease course was complicated by altered mental status and *Klebsiella pneumoniae* bacteremia. His PTHrP increased to 335 pg/ml. He received supportive care and expired 3 weeks from initial presentation.

Conclusions

- Primary HCC and NEC generally tend to have a poorer prognosis than conventional HCC.
- To our knowledge, this case is the second report of primary mixed HCC and NEC associated with MAHC caused by the production of PTHrP.

References

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Figures

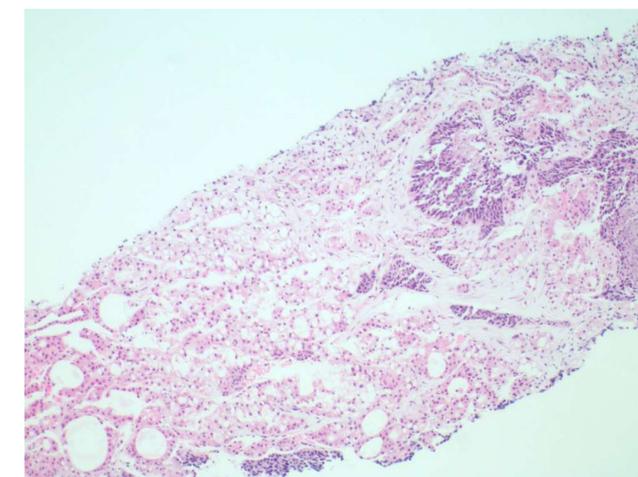


Figure 1. Moderately differentiated hepatocellular carcinoma with admixed high-grade neuroendocrine component (10 X magnification)

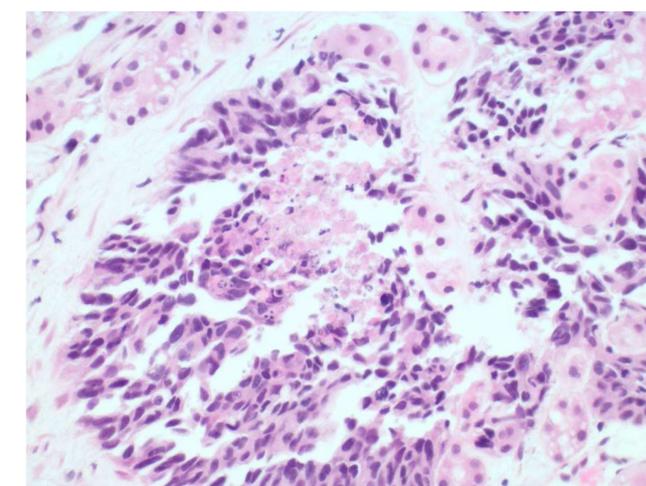


Figure 2. High grade component with hyperchromatic nuclei, abundant apoptotic activity, mitoses and necrosis (40 x magnification)

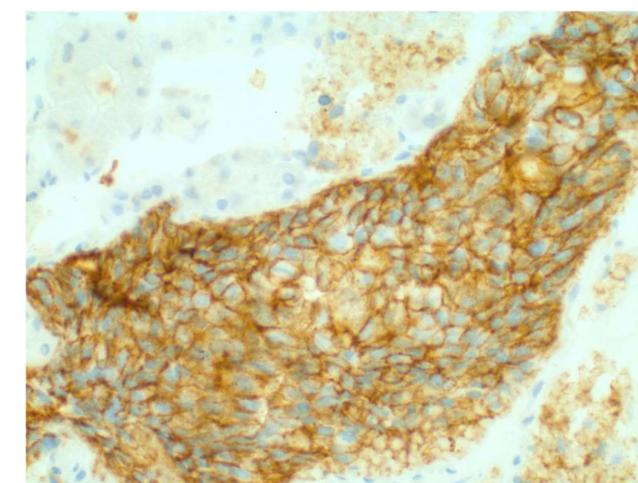


Figure 3. CD56 immunoperoxidase staining in high grade neuroendocrine component (40 x magnification)