Sclerosing Hepatocellular Carcinoma with Hypercalcemia

—A Case Report—

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Summary: A case of sclerosing hepatocellular carcinoma (SHCC) with hypercalcemia was reported. Clinical studies revealed a tumor at the liver hilum with invasion into the bile duct. Light microscopy of the tumor disclosed a moderately differentiated hepatocellular carcinoma (HCC) of the trabecular type with diffuse fibrous stroma. Abundant dense granules were observed in the cytoplasm of the tumor cells with electron microscopy. The elevated serum calcium (13.9 mg/dl) returned to the normal range after resection of the tumor.

Key words: sclerosing hepatocellular carcinoma—hypercalcemia—electron dense granules—paraneoplastic syndrome—intrabile duct tumor growth

Introduction

Most HCC are histologically composed of trabecular parenchyma and sinusoid-like blood spaces for a stroma; however, there is an unique type of HCC characterized by a dense fibrous stroma (Peters, 1976; Edmondson, 1985).

Furthermore, Omata et al. (1981) described a sclerosing hepatic carcinoma; which is an unique primary liver cancer with dense fibrous stroma frequently accompanied by hypercalcemia, a pseudo-hyperparathyroidism.

A case of SHCC with hypercalcemia and dense granules in the tumor cells on electron microscopy, alluding to an endocrine character of the tumor, is presented.

Case Report

A 62 year-old Japanese male was admitted to Kurume University Hospital with a several weeks history of jaundice. The ocular conjunctiva and entire skin were icteric. Physical examination disclosed a palpable non-tender smooth liver edge, 4 cm below the xyphoid process. No tumors were palpable at the neck.

Laboratory examinations showed elevations of serum bilirubin (total bilirubin, 19.1 mg/dl; conjugated bilirubin, 11.6 mg/dl) and alkaline phosphatase (82.7 KAU). A high value for serum alpha-fetoprotein (2057 ng/ml) was also noted. The serum calcium was elevated to 13.9 mg/dl.

Computed tomography and ultrasono-
graphy revealed a space occupying lesion at the liver hilum with marked dilatation of the intrahepatic bile ducts. Cholangiography disclosed a filling defect at the bifurcation. Celiac angiography revealed a tumor stain at the medial segment of the liver. There was no evidence of bone metastases from X-ray studies and bone scintigraphy. The patient was transferred to surgery for resection of the tumor.

The resected tumor was a whitish hard tumor, $5 \times 4 \times 3$ cm in size, at the medial segment of the liver with invasion into the bile duct. The non-cancerous portion of the liver was not associated with cirrhosis. The intra-abdominal organs, except for the liver, were grossly intact. There was no apparent evidence of lymph-node metastases or ascites. A left hepatectomy with hepaticojejunostomy was performed. The gross features of the resected tumor are shown in Fig. 1. A schematic presentation of the tumor and biliary system are included in Fig. 2. Light microscopic examination of the resected tumor disclosed a moderately differentiated HCC of the trabecular type with an eosinophilic granular cytoplasm, large oval nuclei and prominent nucleoli. A diffuse fibrous stroma was also observed (Figs 3 and 4). Electron microscopy of a tumor cell revealed a large nucleus with a prominent nucleolus and dense stromal collagen. Most of the tumor cells had abundant dense granules with lucent peripheries, being compatible with the morphological appearance of secretory granules (Figs 5 and 6). The serum calcium returned to the normal range after resection of the tumor.

![Fig. 1. Cut surface of the tumor in a non-cirrhotic liver. The left hepatic duct (*) adjacent to the bifurcation is occupied by the tumor.](image1)

![Fig. 2. Schematic presentation of the tumor and biliary system.](image2)

![Fig. 3. Light microscopic sections showing a moderately differentiated HCC (a: H.E. stain b: Azan stain ×50).](image3)
Discussion

Pseudohyperparathyroidism is a term proposed by Fry (1962) to describe hypercalcemia and hypophosphatemia in a patient with a non-parathyroid malignant tumor without bone metastases. Furthermore, Lafferty (1966) reported 50 cases that met the criteria for pseudohyperparathyroidism, in which nearly two-thirds of the tumors were renal or bronchogenic carcinomas.

Primary liver carcinomas associated with hypercalcemia have also been described in a more limited number of studies (Samuelsson and Werner, 1963; Keller et al. 1965; Naide et al. 1968; Knill-Jones et al. 1970; Dunn and Nystrom. 1973; Kiely et al. 1973). Omata et al. (1981) described SHC which is a clinicopathologically unique carcinoma of the liver. SHC is a primary liver cancer characterized by a dense fibrous stroma with pseudohyperparathyroidism. In the literature, tumor-derived parathyroid hormone-like activity and osteolytic hormonal factors are suggested to be the mechanism of pseudohyperparathyroidism.

In the present case, the possibilities of bone metastases and parathyroid disorders could not be completely excluded; however, the normalized serum calcium levels after the tumor resection indicates that the tumor cells had parathyroid hormone-like activity. The presence of abundant dense granules, similar to the secretory granules often observed in endocrine tumors, supports an endocrine character such as pseudohyperparathyroidism.

This case report is the first ultrastructural description of a SHCC with hypercalcemia, but the precise biochemical characteristics of the dense granules were not studied.

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YAMASHITA, ET AL.

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