Undifferentiated Carcinoma in the Cardioresophageal Junction which Produces Parathyroid Hormone Related Protein

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A 68-year-old man with undifferentiated carcinoma occurring in the cardioesophageal junction accompanied by hypercalcemia is reported. The serum level of parathyroid hormone-related protein (PTHrP) was remarkably elevated. Serum calcium and PTHrP levels decreased following chemotherapy, but this amelioration was temporary. He died of hypercalcemia. On autopsy, a significant amount of immunoreactive PTHrP was detected in the tumor tissue extract, and the tumor cells were stained strongly positive for PTHrP by immunohistochemistry. This is the first case of undifferentiated carcinoma in the gastrointestinal tract which demonstrated hypercalcemia due to PTHrP produced by the malignant tumor.

Key words: paraneoplastic syndrome, esophageal cancer, gastric cancer, humoral hypercalcemia of malignancy

Introduction

Humoral hypercalcemia of malignancy (HHM) is a well-known metabolic complication of malignant tumors. It has been shown that parathyroid hormone-related protein (PTHrP) is a major pathogenetic factor for HHM (1). We report here a patient with undifferentiated carcinoma in the cardioesophageal junction, who presented with hypercalcemia due to PTHrP produced by the tumor.

Case Report

A 68-year-old Japanese man experienced several episodes of hematemesis on November 22, 1992. He was immediately transferred to our hospital by ambulance, and admitted for further examination and treatment. On admission, his height was 160 cm, and he weighed 65 kg. Blood pressure was 140/92 mmHg, and heart rate was 90 beats/min. He had anemia but no jaundice. No superficial lymph nodes were palpable. The laboratory data on admission were as follows: hemoglobin: 9.8 g/dl, white blood cell count: 6,900/mm³, C-reactive protein: 3.1 mg/dl, glutamic-oxaloacetic transaminase: 51 IU/l, glutamic pyruvic transaminase: 49 IU/l, lactate dehydrogenase: 432 U, alkaline phosphatase: 675 mU/ml (increased liver isoenzyme), sodium: 148 mEq/l, potassium: 4.3 mEq/l, calcium (Ca): 12.5 mg/dl and phosphorus: 1.1 mg/dl. Tumor markers examined, including alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9, pancreatic oncofetal antigen and squamous cell carcinoma-related antigen, were all within normal limits, except for neuron-specific enolase which was elevated to 12.6 ng/ml. Endocrinological studies such as adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), growth hormone and cortisol were normal, whereas the intact-parathyroid hormone (PTH) was decreased (<5 pg/ml). An endoscopic examination revealed a protruding lesion with an easily-bleeding ulcer in the cardioesophageal junction. The lesion was pathologically diagnosed as undifferentiated carcinoma by biopsy specimens. The lungs were normal on plain X-ray, computed tomography (CT) and bronchofiberscopy. Abdominal CT revealed multiple low density areas on the whole liver lobe, a finding compatible with hepatic metastases. A bone scintigram with technetium 99m demonstrated no increased uptake of radioactivity at any site. After admission, hypercalcemia was not improved in spite of various medical treatments (intravenous administration of diuretics, calcitonin and prednisolone with sufficient amounts of fluid). The patient was given a course of chemotherapy with cisplatin (130 mg, intravenously, on day 1), epirubicin (50 mg, intravenously, on day 1) and etoposide (100 mg, intravenously, from day 1 to day 5). This chemotherapy successfully decreased his serum Ca con-
concentration to the normal range, and the primary and metastatic lesions were reduced in size. But this improvement was temporary, and hypercalcemia developed again. Although the same regimen of chemotherapy was given 2 more times, the effectiveness of the therapy was gradually decreased. Because hypercalcemia became unresponsive to the chemotherapy regimen, the patient was treated with a different protocol of chemotherapy with cyclophosphamide (1,000 mg, intravenously), epirubicin (40 mg, intravenously) and vincristine (1.4 mg, intravenously), which was ineffective. Hypercalcemia deteriorated progressively, and the patient died on April 3, 1993.

Pathologic study
At autopsy, the lesion (5x2 cm) which extended from the abdominal portion of the esophagus to the lesser curvature of the cardia, and was located mainly around the cardioesophageal junction, had a gross appearance of poorly-defined protrusion covered by normal-appearing mucosa with central ulceration (Fig. 1). The tumor existed mainly in the submucosa layer expanding to the muscularis. The tumor was composed of oval or round cells which were arranged in a solid, nest or trabecular pattern (Fig. 2). Most tumor cells had basophilic, moderately scanty cytoplasm with small, round or oval hyperchromatic nuclei. In some areas, the tumor cells had moderately abundant cytoplasm with larger nuclei. Alcian-blue-PAS staining was negative for the neoplastic cells. The tumor did not show any findings of squamous cell carcinoma or adenocarcinoma differentiation as characterized by keratinization or glandular formation.

The liver, weighing 2,200 g, had white-gray multiple nodules with shallow central depression, which were consistent with metastatic tumors. Metastatic lesions also were found in the lungs, left adrenal gland, perigastric lymph nodes and peripancreatic lymph nodes. Histologically, metastatic lesions were composed of neoplastic cells that were similar to those of the primary tumor.

Electron microscopy
The specimens from the primary lesion were fixed in 1% osmium tetroxide for electron microscopic observations. Tumor cells with oval nuclei which appeared partly indented were closely apposed. The nuclei were clear and had abundant euchromatin with well-developed nucleoli showing elongated and twisted strands (Fig. 3). The relatively scanty cytoplasm contained well-developed ribosomes and polysomes. Electron-dense bodies also were found in the cytoplasm. The cell membrane was slightly interdigitating, and the desmosome was observed occasionally. However, extensive search failed to reveal any components of squamous cell differentiation such as...
Cisplatin 130 mg dayl
Epirubicin 50 mg dayl
Etoposide 100 mg dayl-5
Vincristine 1.4 mg dayl

Figure 4. Time-course changes in serum C-PTHrP and calcium levels. Chemotherapy led to a decrease in serum C-PTHrP and calcium levels. During the clinical course, changes in serum C-PTHrP level in response to chemotherapy were parallel to those of the serum calcium level.

Figure 5. Immunohistochemical findings of the primary lesion (×200). Tumor cells were stained strongly positive for immunoreactive PTHrP.
complex (ABC) method with a Vectastain ABC kit (Vector Laboratories, Burlingame, CA). The N-PTHrP antiserum used for RIA was applied. Tumor cells in both primary and metastatic lesions were stained strongly positive for PTHrP (Fig. 5).

Discussion

Hypercalcemia is a well-known metabolic complication of malignant tumors, and it is often life-threatening unless adequately treated. About 75% of cases with malignancy-associated hypercalcemia were reported to be HHM (6). In the present case, the serum C-PTHrP level was highly increased on admission, and decreased in response to chemotherapy, which was concomitantly accompanied by the normalization of serum Ca level and the reduction of tumor size. Serum and tissue N-PTHrP contents were also elevated, and the tumor cell was immunohistochemically positive for N-PTHrP. These findings strongly suggest that the tumor produced PTHrP, which in turn caused hypercalcemia.

HHM is a common complication of malignant cancers, particularly of squamous cell carcinomas (6) and hematopoietic malignant diseases such as adult T cell leukemia. The incidence of HHM in esophageal cancers is reported to range from 13-28% (7-9), and Tachimori et al demonstrated that esophageal squamous cell carcinomas could produce PTHrP (10). On the other hand, HHM is rare in gastric carcinomas because the most common histologic type of this malignant tumor is adenocarcinoma. Although Yamaura-Idei et al recently reported that it is not completely rare for gastric carcinomas to stain immunohistochemically positive for PTHrP (11); there is no reported case of gastric carcinoma showing that circulating PTHrP released from tumor cells induces hypercalcemia.

Undifferentiated carcinomas generally undergo an aggressive clinical course. Since undifferentiated carcinoma cells are frequently already disseminated at the time of diagnosis, it is difficult to determine the primary lesion of carcinomas. In the present case, we endoscopically found at the cardioesophageal junction a protruded tumor with central ulceration, which was covered by the normal mucosa. Since these gross appearances are common for esophageal undifferentiated carcinomas in the early stage (12), the cardioesophageal lesion in the present case was thought to be the primary tumor. Although the primary tumor was relatively small, the patient had already suffered massive hepatic metastases on admission. There was a report of massive hepatic metastases occurring in early gastric undifferentiated carcinoma within a short period of time after a curative operation (13). Because of this biological behavior, there are few cases in which surgical treatment is performed as the primary therapy for esophageal or gastric undifferentiated carcinomas.

For the treatment of undifferentiated carcinomas in the esophagus or stomach, intensive chemotherapy may be effective at any stage of this tumor. In fact, various protocols of chemotherapy have been attempted as primary or post-operative therapy in combination with radiation, but no controlled studies as to the efficacy of chemotherapy have been reported presumably because of rarity of this disease. Several recent reports have shown that undifferentiated carcinomas in the esophagus are responsive to chemotherapy using anti-cancer agents that are effective for lung undifferentiated carcinomas (14-16), including cisplatin, etoposide, cyclophosphamide, Adriamycin or vincristine. We employed a standard protocol used for small cell lung cancer, which consisted of cisplatin, etoposide and epirubicin, and also tried another protocol of cyclophosphamide, epirubicin and vincristine. The former chemotherapy appeared to bring about a temporary remission.

The prognosis of undifferentiated carcinomas is extremely poor. According to McFadden et al (16) who made a review of 129 patients with small cell carcinomas of the esophagus in the world literature, the overall survival period is 20.7 weeks after diagnosis. Kuhara et al (17) reported that only one of the surveyed 7 Japanese patients with small cell carcinoma in the stomach survived for more than 5 years, but the others died within 1 year.

In summary, we described a patient with PTHrP-producing undifferentiated carcinoma occurring in the cardioesophageal junction, which was definitely proven by RIA and immunohistochemistry. To our knowledge, this is the first case of PTHrP-producing undifferentiated carcinoma in the gastrointestinal tract.

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