CASE REPORT

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Paraneoplastic hypercalcemia with adenosquamous carcinoma of the colon

Received: April 22, 2004 / Accepted: August 10, 2004

Abstract Hypercalcemia is a well-known manifestation of paraneoplastic syndromes associated with a variety of malignancies. However, colon cancer has only rarely been associated with hypercalcemia. Here we present the first case of adenosquamous carcinoma of the sigmoid colon in a patient who was found to have hypercalcemia associated with parathyroid hormone-related protein (PTHrP), with no radiological evidence of metastasis to other organs. A 78-year-old woman was admitted to our hospital complaining of lower abdominal pain. Physical examination and computed tomography revealed a tumor, 13cm in diameter, in the sigmoid colon. Laboratory data showed an elevated serum calcium level (11.2mg/dl). Primary colostomy was performed. After the primary operation, the patient was found to have hypercalcemia and an elevated PTHrP level. We performed sigmoidectomy, total hysterectomy, and partial urinary bladder resection 1 month after the primary operation, and both PTHrP and calcium levels immediately returned to normal. The histopathologic diagnosis was poorly differentiated adenosquamous carcinoma. The patient died due to tumor recurrence 4 months after the second surgery.

Key words Paraneoplastic hypercalcemia · Adenosquamous carcinoma · Sigmoid colon

Introduction

Many primary malignant tumors of the colon, except for those of the lower rectum, are adenocarcinomas, while adenosquamous carcinoma of the colon is rare, comprising just 0.05%–0.1% of all colon cancers.1–7 Colon cancer has only rarely been associated with paraneoplastic hypercalcemia, the incidence of which is just 0.05% of all carcinomas of the colon and rectum. In the literature, there are eight reported cases of adenosquamous carcinoma with hypercalcemia associated with parathyroid hormone-related protein (PTHrP), and all of these patients had radiological evidence of liver metastasis at the time the hypercalcemia was detected. Here, we report a patient with primary adenosquamous carcinoma (originating from the sigmoid colon) who had hypercalcemia arising from the production of PTHrP. The patient had no radiological evidence of metastasis to other organs.

Case report

A 78-year-old woman was admitted to the hospital on October 22, 2001, complaining of sudden abdominal pain with nausea. Before admission, she had suffered abdominal discomfort and constipation for a month. She was 150cm in height and 35kg in weight on admission. Physical examination and computed tomography revealed a tumor, 13cm in diameter, located in the sigmoid colon. Laboratory data showed that the white blood cell count was elevated, to 15000/mm³ (normal range, 3500–9000/mm³) and serum calcium was elevated, to 11.2mg/dl (normal range, 8.5–10.5mg/dl). A plain abdominal X-ray showed the sigmoid colon to be distended. Abdominal computed tomography (CT) revealed a mass, 13cm in diameter, located in the sigmoid colon (Fig. 1). Emergency surgery was performed, with the diagnosis of severe bowel obstruction due to a sigmoid colon tumor, and revealed that the tumor originated from the sigmoid colon and had invaded the left ureter, urinary bladder, and uterus. Because severe tachycardia and arrhythmia occurred intraoperatively, we abandoned the curative resection and made a colostomy at the transverse colon. After this primary operation, serum calcium (13.2mg/dl; normal range, 8.5–10.5mg/dl) and serum PTHrP (3.7pmol/l; normal level, <1.3pmol/l) were elevated. On the other hand, her intact parathyroid hor-
mone (intact-PTH) level was low, at 0.1 pg/ml (normal level, >2.0 pg/ml). Further tests, including bone scintigraphy and chest and neck CT, revealed no evidence of any other lesion. Extensive medication for the hypercalcemia was effective for a short time, but her serum calcium returned to a high level soon after the discontinuation of the medication. After the patient’s general condition was well controlled, sigmoid colon resection, total hysterectomy, and partial urinary bladder resection were performed, on November 20, 2001. Gross pathology examination revealed a 13.0 × 8.0 cm solid tumor, irregularly shaped, with necrosis and hemorrhage (Fig. 2). Microscopically, the tumor was composed of pleomorphic epithelial cells in a cobblestone-like arrangement. Immunohistochemically, many of the cells were positive for carcinoembryonic antigen (CEA) and involucrin (Fig. 3). The histopathologic diagnosis was poorly differentiated adenosquamous carcinoma (si, ly3, v3, ow(−), aw(−), n2, stage III b), originating from the sigmoid colon. After the second surgery, serum calcium, PTH, and PTHrP levels returned to the normal ranges (calcium, 9.6 mg/dl; PTH, 7.7 pg/ml; PTHrP, 1.2 pmol/l), with no treatment for hypercalcemia (Fig. 4). These levels remained stable for almost 4 months. The patient died 4 months after the second surgery, due to tumor recurrence and severe hypercalcemia. No systemic chemotherapy or radiotherapy had been given because of the patient’s poor performance status.

**Discussion**

Colorectal adenosquamous carcinoma is rare, with an estimated incidence of between 0.05% and 0.1%. It occurs most frequently in the cecum, ascending colon, and rectum. Takemura et al. reported that the mean age of the patients was 53 years, most tumors were 5 cm or more in diameter, and lymph node metastasis was found in 55% of cases. The origin of colorectal adenosquamous carcinoma is unknown, but several mechanisms have been proposed. One such proposal involves the proliferation of uncommitted mucosal basal cells into squamous cells, which subsequently undergo malignant change. Another suggestion involves the stimulation of abnormal mucosa, by conditions such as ulcerative colitis, schistosomiasis, or human papilloma virus, or by irradiation, leading to squamous metaplasia and subsequent tumor development. Yet another suggestion is that these tumors develop from areas of squamous metaplasia within colorectal adenomas. In the present patient, systemic examination revealed no other lesion, and serum calcium, PTH, and PTHrP levels returned to normal after resection of the tumor, without medical treatment for hypercalcemia. So we concluded that the PTHrP had originated from the sigmoid colon tumor. Paraneoplastic syndrome with hypercalcemia is associated with various malignancies; for example, these of lung and kidney, but only rarely with colon cancer. Kubota et al. reported the incidence of this syndrome to be 0.02% of all carcinomas of the colon and rectum. Including the present case, only nine cases of adenosquamous carcinoma of the colon with...