Postoperative Aggravation of Hypercalcemia-Leukocytosis Syndrome in a Case of Squamous Cell Type Cholangiocarcinoma

It has been reported, mainly in Japan, that hypercalcemia and leukocytosis often coexist in malignancies, especially squamous cell carcinomas (1-4). Sato and his colleagues reported that squamous cell carcinoma with hypercalcemia and leukocytosis was successfully transplanted into nude mice, which caused granulocytosis and hypercalcemia and showed both bone-resorbing and colony-stimulating activities *in vitro* (2, 3). They proposed that hypercalcemia and leukocytosis constitute a new paraneoplastic syndrome (2, 3). We formerly demonstrated with immunohistochemistry that each component of this syndrome, *ie* hypercalcemia and leukocytosis, was attributable to parathyroid hormone-related protein (PTHrP) and granulocyte-colony stimulating factor (G-CSF), respectively, in a case of thyroid anaplastic carcinoma (5) and in four cases of lung cancer (6). Here we report a case of squamous cell type cholangiocarcinoma with hypercalcemia-leukocytosis syndrome, which was aggravated after the surgery.

The case is a 69-year-old man presenting with fever and body weight loss. The imaging studies revealed a single large tumor with multiple small lesions of the liver, and the patient was admitted to the department of surgery on June 20, 1996. The laboratory examination showed leukocytosis (white blood cell count: 13,700/ μ l) and normocalcemia (10.1 mg/dl). Serum intact PTHrP and G-CSF levels were examined, both of which were high (intact PTHrP 4.4 pg/ml; G-CSF 82.5 pg/ml). The resection of the main tumor with radical hepatectomy was performed under the tentative diagnosis of hepatocellular carcinoma on July 22, 1996, whereas multiple intrahepatic metastatic lesions were left intact. The pathological diagnosis of the resected tumor was squamous cell type cholangiocarcinoma. Postoperatively after the transient decrease in both serum calcium and leukocyte number, the patient developed marked hypercalcemia (14.7 mg/dl) with concomitant worsening of leukocytosis up to 43,800/ μ l in two weeks after the operation. Serum PTHrP was increased to 12.0 pg/ml. The immunohistochemical study of the resected tumor indicated positive staining of both PTHrP and G-CSF. Although hypercalcemia was successfully treated with pamidronate, leukocytosis continued to increase. The patient died on August 28. An autopsy was not permitted.

The present case showed hypercalcemia-leukocytosis syndrome, which was markedly aggravated after the operation despite the evident mass reduction of the tumor. The immunohistochemistry demonstrated that hypercalcemia and leukocytosis were, at least partly, due to PTHrP and G-CSF secretion by the tumor, respectively, as previously reported (5, 6). It is to be noted that granulocytes and osteoclasts share a common hematopoietic precursor. The clinical course of this case suggested that surgical intervention resulted in aggravation of hypercalcemia-leukocytosis syndrome, suggesting a possibility that surgical stress may cause an increase in synthesis and/or release of PTHrP and G-CSF of the residual hepatic tumors. In general, major surgery has been earlier reported to result in transient hypocalcemia, rather than hypercalcemia (7), and leukocytosis (8). It cannot be disregarded, however, that aggravation of both hypercalcemia and leukocytosis in the present case might have been

caused by a metastatic locus other than the intrahepatic ones; thorough examinations for searching metastasis in other regions could not be done due to the severe condition of the patient, although the routine examinations, such as abdominal computed tomography, did not detect any metastatic lesion.

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