Tumor-Induced Hypercalcemia and Parathyroid Hormone-Related Protein in Lung Carcinoma

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BACKGROUND. Although lung carcinoma is the most common cause of tumor-induced hypercalcemia (TIH), the precise incidence of TIH remains obscure. Furthermore, the role of parathyroid hormone-related protein (PTHrP) has not been clearly elucidated.

METHODS. This study included 690 consecutive patients who were newly diagnosed as having lung carcinoma between 1989 and 1994 (379 adenocarcinomas, 207 squamous cell carcinomas, 75 small cell carcinomas, and 29 large cell carcinomas). All patients were treated for lung carcinoma and were also periodically monitored for their serum level of calcium (Ca). Hypercalcemia was defined as a serum Ca concentration higher than 11 mg/dL. The serum levels of PTHrP (109-141) were measured by a C-terminal-region-specific radioimmunoassay.

RESULTS. TIH was observed in 17 of 690 patients (2.5%). All 17 patients demonstrated an advanced stage of lung carcinoma (Stage III or IV), 10 squamous cell carcinomas, 5 adenocarcinomas, 1 small cell carcinoma, and 1 large cell carcinoma. In 15 patients, the serum level of C-PTHrP (109–141) was substantially high, ranging from 99 pmol/L to 890 pmol/L (normal range, 21–50.7 pmol/L). There was no significant difference in the serum PTHrP level between patients with or without bone metastasis. The reduction of tumor burden decreased both the serum level of PTHrP and that of Ca in parallel. The median survival time after diagnosis of TIH was only 27 days.

CONCLUSIONS. TIH in lung carcinoma was most likely attributable to PTHrP, and its occurrence appears to be an ominous prognostic sign. ***Cancer* 1996; 78: 1384–7.** © *1996 American Cancer Society.*

KEYWORDS: hypercalcemia, parathyroid hormone-related protein, lung carcinoma, C-terminal-regional-specific radioimmunoassay.

Hypercalcemia is one of the most common paraneoplastic syndromes. Depending on its cause, tumor-induced hypercalcemia (TIH) was previously classified into either local osteolytic hypercalcemia or humoral hypercalcemia of malignancy. However, recent advances in biochemical technology have revealed that TIH is caused more frequently by the latter mechanism than by the former.[1–3] Furthermore, of the several humoral factors exhibiting osteoclastic activity, parathyroid hormone-related protein (PTHrP) has been reported to be the most common.[4–7]

The serum level of PTHrP can now easily be assessed with a C-terminal-region-specific radioimmunoassay using serum samples, stored without addition of protease inhibitors. In the present study, we reviewed our recent experiences with TIH in lung carcinoma and investigated the role of PTHrP.

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MATERIALS AND METHODS

Patients

This study included 690 consecutive patients who were newly diagnosed as having lung carcinoma and admitted to the National Kyushu Cancer Center from 1989 to 1994. The group consisted of 501 men and 189 women, with a mean age of 64 years (range, 29 to 94). Tumors were histologically classified as adenocarcinoma in 379 patients (234 men, 145 women), squamous cell carcinoma in 207 (176 men, 31 women), small cell carcinoma in 75 (66 men, 9 women), and large cell carcinoma in 29 (25 men, 4 women). The staging of all conditions is reported either pathologically in resected patients (Stage I, II, and IIIA) or clinically in nonresected patients (Stage IIIA, IIIB, IV), according to the new International Staging System for Lung Cancer.[8]

Diagnosis of Hypercalcemia

All patients were treated for lung carcinoma by various methods including surgical resection, radiation therapy, or chemotherapy. All patients were periodically monitored for serum levels of electrolytes including calcium (Ca). The serum Ca level was determined by means of orthocresolphthalein complexone.[9]

Hypercalcemia was defined as a serum Ca concentration greater than 11 mg/dL. When the serum albumin level was lower than 4 g/dL, the value of the serum Ca level was readjusted according to the following formula: adjusted Ca conc. = actual Ca conc. + 4.0 − albumin conc. (g/dL).

C-Terminal-Region-Specific Radioimmunoassay of PTHrP (109–141)

At the time hypercalcemia was diagnosed, aliquots of blood samples were stored at −80 °C until use. The serum levels of C-PTHrP (109–141) were measured with a radioimmunoassay (RIA) using commercially available kits (Daiichi RI Lab. Ltd., Tokyo, Japan). The intraassay coefficient of variation of the RIA kits ranged from 1.9% to 5.9%, whereas the interassay coefficient of variation ranged from 5.5% to 7.4%. All sample were assayed in duplicate. The mean value of serum C-PTHrP (109–141) concentration from 76 healthy subjects was 31.4 ± 7.4 pmol/L (range, 21.0 to 50.7 pmol/L).[10]

Statistics

The significance of differences between the two groups was assessed by Student's unpaired *t* test, and the two-sided *P* values are reported.

RESULTS

Incidence of TIH

From 1989 (Table 1) to 1994, we observed 17 patients with TIH. The incidence of TIH among the 690 patients with lung carcinoma was 2.5%. Those 17 patients with TIH demonstrated advanced stages of lung carcinoma (Stages III and IV), and the incidence of TIH was 4.2%. TIH was observed in all histologic types, but squamous cell carcinoma was the most common cause. The incidence of TIH in advanced stage squamous cell carcinoma was 8.5%.

TABLE 1
Incidence of Hypercalcemia in Lung Carcinoma

	% of total no. of patients	% of patients with stage III, IV
Squamous	4.8	8.5
Adeno	1.3	2.5
Small	1.3	1.6
Large	3.4	4.8
All	2.5	4.2

Squamous: squamous cell carcinoma; Adeno: adenocarcinoma; Small: small cell carcinoma; Large: large cell carcinoma.

Patient Profiles with TIH

The 17 patients (Table 2) with TIH consisted of 12 men and 5 women with a mean age of 65 years (ranging, 47 to 78). These included 10 squamous cell carcinomas, 5 adenocarcinomas, 1 small cell carcinoma, and 1 large cell carcinoma. The serum Ca concentrations ranged from 12.6 to 17.6 mg/dL at the time of diagnosis. Bone metastasis was observed in 10 patients. In addition, one of five patients with Stage III disease also showed a direct skeletal involvement of the primary tumor (Patient 10). The remaining six patients did not show any evidence of bone lesions at the time of occurrence of TIH. The serum levels of PTHrP ranged from 40.0 to 890.0 pmol/L in those 17 patients. Except for two patients (Patients 4 and 15), the serum level of PTHrP was substantially above the normal upper limit. Although it was reported that the serum level of C-terminal fragments of PTHrP is high in the presence of renal failure,[6] the serum creatinine concentration was less than or equal to 2.5 mg/dL in all patients. There was no significant difference in the serum PTHrP level between the patients with bone metastasis and those without bone metastasis (mean ± standard deviation, 252.6 ± 212.2 pmol/L vs. 433.2 ± 332.6 pmol/L; $P = 0.189$).

Of 17 patients, 2 (Patients 10 and 16) were successfully treated for their tumors with either surgical resection or chemotherapy. In Patient 10, the primary tumor could be resected completely, and thereafter both the serum Ca level and the PTHrP level decreased to within normal range (Fig. 1a). In Patient 16 with small

TABLE 2
Patient Characteristics

Patient no	Age (yr)	Gender	Histologic type	Stage	T	N	M	Bone metastasis	Ca (mg/dl)	C-PTHrP (pmol/l)	Cr (mg/dl)	Prognosis[a]
1	57	M	Squamous	IIIB	4	0	0	–	16.6	790	1.9	15
2	61	M	Squamous	IV	2	1	1	+	17.6	390	2.2	15
3	65	M	Squamous	IV	4	0	1	+	16.2	99	0.9	39
4	52	M	Squamous	IV	2	2	1	+	14.0	58	1.0	16
5	60	F	Squamous	IIIA	3	0	0	–	14.2	890	1.1	18
6	74	M	Squamous	IV	4	1	1	+	12.8	420	2.5	27
7	73	M	Squamous	IV	4	2	1	+	13.8	243	1.8	35
8	59	F	Squamous	IV	2	3	1	–	13.1	180	1.5	43
9	73	M	Squamous	IIIA	3	0	0	–	13.1	130	0.9	23
10	75	M	Squamous	IIIA	3	0	0	–	13.7	158	0.9	182
11	47	F	Adeno	IIIA	3	0	0	–	16.7	423	0.7	29
12	68	M	Adeno	IV	4	3	1	+	14.1	203	1.0	27
13	63	M	Adeno	IV	4	2	1	+	17.1	780	2.4	18
14	78	F	Adeno	IV	2	2	1	+	12.6	200	0.9	39
15	72	F	Adeno	IV	2	2	1	+	15.6	40	2.1	20
16	70	M	Small	IV	2	3	1	+	15.4	188	1.8	74
17	67	M	Large	IV	3	2	1	–	12.7	186	0.6	35

Squamous: squamous cell carcinoma; Adeno: adenocarcinoma; Small: small cell carcinoma; Large: large cell carcinoma.
[a] Survival time (days) after diagnosis of hypercalcemia.

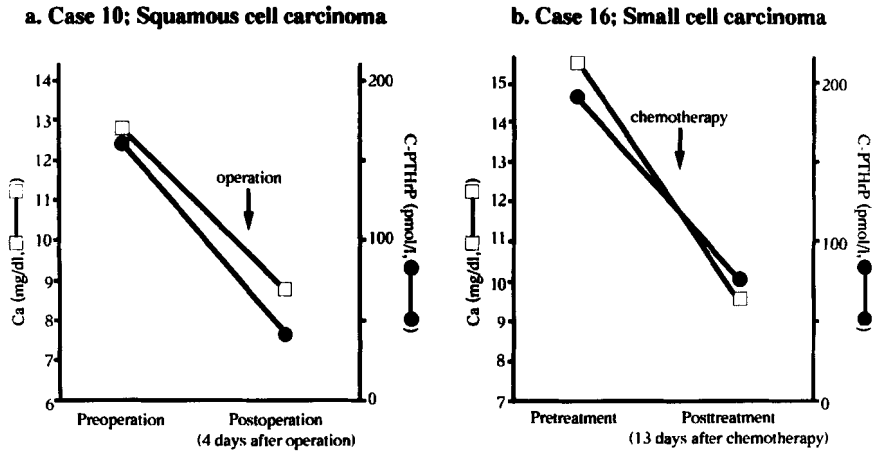

FIGURE 1. Influence of tumor regression on the serum levels of both Ca and PTHrP.

cell carcinoma, systemic chemotherapy (cisplatin plus etoposide) achieved an 87.8% tumor regression, thus resulting in a normalization of both the serum Ca level and the PTHrP (Fig. 1b).

In 14 of 17 patients, intensive antihypercalcemic therapy was performed. Therapy consisted of calcitonin alone in six patients and calcitonin plus bisphosphonates in eight. The use of calcitonin or bisphosphonates temporarily decreased the serum Ca levels, but all patients died. The duration from the diagnosis of TIH to death ranged from 15 days to 180 days (median, 27 days) (Table 2).

DISCUSSION

Although TIH can occur in any type of carcinoma, lung carcinoma is the most common cause along with breast carcinoma.[2] However, the precise incidence of TIH in lung carcinoma remains obscure. In the present study, TIH was found in all histologic types of lung carcinoma, but only in advanced stages of disease. The incidence of TIH was 4.2% in patients with advanced stage disease (Stages III and IV). Of the four histologic types, squamous cell carcinoma was the most common type with hypercalcemia.

In the following points, the present study sup-

ported the recent concept concerning hypercalcemia of malignancy, in which TIH is most likely attributed to humoral factors produced by tumor cells such as PTHrP. First, of the 17 patients with TIH, 7 did not have any evidence of bone metastasis until death. Second, in 15 of 17 patients with TIH, the serum levels of PTHrP were considerably high regardless of the existence of bone metastasis. Third, the reduction of tumor burdens by either a surgical resection or systemic chemotherapy also decreased both the serum level of PTHrP and that of Ca in parallel.

Kitazawa et al.[11] immunohistologically showed that PTHrP was commonly produced by squamous cell carcinoma, but far less by other histologic types of lung carcinoma. Their results were compatible with the histologic distribution of TIH in lung carcinoma. However, the incidence of TIH was only 8.5% even for advanced stage squamous cell carcinoma. In our preliminary immunohistologic studies, only a proportion of the tumor cells were positive for PTHrP in squamous cell carcinoma tissue specimens. Because PTHrP is normally present in the keratinocyte layer of squamous epithelia, only a population of squamous cancer cells with some degree of differentiation might produce PTHrP.

It is known that the occurrence of TIH is an ominous prognostic sign in various types of carcinoma. In the present study, the median survival time after the occurrence of TIH was only 27 days. Antihypercalcemic therapy using calcitonin and bisphosphonates can decrease serum Ca concentration, but its effect is only temporary. There is no doubt that the primary therapy for TIH should be against tumors themselves. However, patients whose conditions are complicated with TIH are usually already in advanced stages of cancer and can hardly be cured by such standard therapies as surgery, radiotherapy, or chemotherapy. Therefore, when no positive effect of antitumor therapy is expected, antihypercalcemic therapy may be prognostically meaningless.

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