Hypercalcemia of Malignancy: A Study of Clinical Features and Relationships among Circulating Levels of Calcium, Parathyroid Hormone and Parathyroid Hormone-Related Peptide

Sutin Sriussadaporn MD*, Meta Phoojaroenchanachai MD*,
Sirirat Ploybutr MSc*, Nattachet Plengvidhya MD*,
Thavatchai Peerapatdit MD*, Wannee Nitiyanant MD*,
Sathit Vannasaeng MD*, Apichati Vichayanrat MD*

** Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University*

Objective: *Examine the clinical and biochemical features including serum intact PTH (iPTH) and plasma PTH-related peptide (PTHrP) levels in patients with malignancy-associated hypercalcemia (MAHC).*
Material and Method: *Forty-eight patients with histopathological or cytological proven malignancies and MAHC who were admitted to Siriraj Hospital were studied.*
Results: *The malignancies that caused MAHC were squamous cell carcinoma (45.8%), non-squamous cell solid tumors (31.3%), and hematological malignancies (22.9%). Most patients (93.8%) had advanced stage malignancies. Corrected serum total calcium (cTCa) levels were 10.8-19.1 mg/dL (13.6 $\pm$ 2.4) and severe hypercalcemia was observed in 17 cases (40.5%). Serum iPTH levels were 0.95-17.1 pg/mL (3.9 $\pm$ 3.6). Most patients had suppressed serum iPTH levels of < 10 pg/mL. Plasma PTHrP levels were 0.2-44.0 pmol/L (3.8 $\pm$ 6.8). There were 27 cases (56.3%) that had humoral hypercalcemia of malignancy (HHM) with plasma PTHrP levels of > 1.5 pmol/L, and 22 cases had squamous cell carcinoma. There was no difference in serum cTCa, phosphorus, alkaline phosphatase, and iPTH levels between patients with HHM and non-HHM. In 48 MAHC patients, serum cTCa correlated to plasma PTHrP (r = 0.35, p = 0.029) and to serum iPTH (r = 0.49, p = 0.003). In 25 patients with HHM, a stronger correlation between serum cTCa and serum iPTH (r = 0.55, p = 0.005) but not between serum cTCa and plasma PTHrP levels (r = 0.41, p = 0.05) was observed. Stepwise multiple regression analyses showed that serum iPTH but not plasma PTHrP levels independently correlated to serum cTCa levels (r = 0.39, p = 0.04).*
Conclusion: *The clinical manifestations of MAHC observed in the present study were similar to those previously reported. Serum calcium correlated to serum iPTH more strongly than to plasma PTHrP levels. The low but detectable serum iPTH level might play a role in the development of severe MAHC particularly in HHM.*

Keywords: *Hypercalcemia, Malignancy, Intact PTH, PTH-related peptide*

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Hypercalcemia is a frequent complication of malignancies[1]. Based on the mechanism by which malignancies induced hypercalcemia, the malignancy-associated hypercalcemia (MAHC) can be simply classified into two main groups including humoral hypercalcemia of malignancy (HHM) that comprises up to ~80% of cases, and local osteolytic hypercalcemia (LOH) or non-HHM that comprises up to ~20% of cases[2-9]. HHM is most commonly mediated by parathyroid hormone-related peptide (PTHrP), a humoral factor synthesized and secreted by tumor cells[10,11].

Correspondence to : Sriussadaporn S, Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Prannok Rd, Bangkok Noi, Bangkok 10700, Thailand. Fax: 0-2419-7792, E-mail: sisdp@mahidol.ac.th

PTHrP exerts its biological actions *via* binding to PTH/PTHrP receptors of its target tissues, *i.e.* bone and kidney, which subsequently results in hypercalcemia and other biochemical changes similar to those observed in primary hyperparathyroidism[2,6,12]. A number of previous studies have demonstrated a correlation between circulating levels of calcium and PTHrP in MAHC[13,14]. However, the correlation reported in those studies was quite weak. Although an elevated serum calcium concentration physiologically inhibits parathyroid hormone (PTH) secretion resulting in a suppressed serum PTH level[15,16], there are some studies demonstrating positive correlation between serum PTH and calcium concentrations in MAHC[17,18]. In addition, the degree of correlation between circulating calcium and PTH levels observed in these studies[17,18] were higher than the degree of correlation between circulating calcium and PTHrP levels observed in other studies[13,14]. These findings have raised an issue of interest that PTH might play a role in the pathogenesis of MAHC. However, there is no study comparing between PTH and PTHrP in relation to the severity of hepercalcemia in MAHC in the same study. The present study was aimed to examine the clinical and biochemical characteristics of patients with MAHC and to examine the relationships among circulating PTH, PTHrP, severity of hypercalcemia and other biochemical parameters in MAHC.

Material and Method

Patients

Patients with histopathological or cytological proven malignancies and MAHC who were admitted to Siriraj Hospital were studied. Patients who had one or more of the following conditions were excluded: elevated serum parathyroid level, pre-existing renal diseases and medications known to interfere with calcium and bone metabolism including calcium supplement, vitamin D, bisphosphonates, and glucocorticoids. Blood samples were obtained and immediately processed for biochemical analyses before specific and supportive treatments for hypercalcemia were started. Plasma and serum samples were properly stored for subsequent measurements of plasma PTHrP levels and serum intact PTH (iPTH), respectively.

Biochemical analyses

Serum total calcium, phosphorus, alkaline phosphatase, albumin, globulin, blood urea nitrogen, and creatinine were measured by an auto-analyzer (Hitachi model 917, Japan). The measured serum total calcium levels were corrected for the change in serum albumin levels by using the following formula: corrected serum total calcium (cTCa, mg/dL) = measured serum total calcium (mg/dL) + 0.8 x [4 – measured serum albumin (g/dL)][19]. Serum intact PTH (iPTH) levels were measured by immunoradiometric assay using an assay kit obtained from CIS Bio International, France. Plasma PTHrP levels were measured by immunoradiometric assay using an assay kit containing two antibodies directed against PTHrP (1-40) and PTHrP (57-80) with recombinant human PTHrP (1-84) as a standard (Incstar Corporation, USA). The normal values of serum iPTH and plasma PTHrP levels in the laboratory obtained from healthy volunteers were 10-60 pg/mL and < 1.5 pmol/L, respectively.

Definitions

Hypercalcemia was defined by a serum cTCa level of $\geq$ 10.5 mg/dL. Severe hypercalcemia was defined by a serum cTCa level of $\geq$ 13 mg/dL. Hypophosphatemia was defined by a serum phosphorus level of $\leq$ 2.0 mg/dL. An increased serum alkaline phosphatase level was defined as the value of $\geq$ 200 U/dL. Impaired renal function was defined by a serum creatinine of > 2 mg/dL. A suppressed serum iPTH level was defined as the presence of a serum iPTH level of lower than the lower limit of normal range of 10 pg/mL. MAHC was diagnosed if cancer patients had hypercalcemia with suppressed or low normal serum iPTH levels in the absence of other causes of hypercalcemia. HHM was diagnosed if an MAHC patient had plasma PTHrP level higher than the upper normal limit of 1.5 pmol/L. Non-HHM was diagnosed if an MAHC patient had plasma PTHrP level equal or lower than the upper normal limit of 1.5 pmol/L.

Statistical analyses

Data were expressed as mean $\pm$ standard deviation (SD) or percent as appropriate. Statistical analyses were performed using Statistical Packages for the Social Sciences (SPSS) version 11. Pearson's correlation analyses were used to examine the correlation between two parameters. In order to identify factor(s) independently associated with the severity of hypercalcemia, stepwise multiple regression analyses were performed to adjust for the confounding effects of other factors. A *p*-value of < 0.05 was considered statistically significant.

Results

Forty-eight patients with MAHC (19 males

and 29 females), aged 26-87 years (57.7 ± 13), were included in the present study. The patients' clinical and biochemical characteristics are shown in Table 1. The types of malignancy included squamous cell carcinoma (22 cases, 45.8%), non-squamous cell solid tumors (15 cases, 31.3%), and hematological malignancies (11 cases, 22.9%) as shown in Table 2. Forty-five cases (93.8%) had advanced stage malignancies whereas only three cases (6.2%) had localized malignancies. Serum cTCa levels were 10.8-19.1 mg/dL (13.6 ± 2.4). Severe hypercalcemia as determined by serum cTCa levels of ≥ 13 mg/dL was observed in 17 cases (40.5%). Serum phosphorus levels were 0.62-6.8 mg/dL (3.39 ± 1.46). Hypophosphatemia was observed in five of 48 cases (11.63%) with MAHC including three cases with HHM and two cases with non-HHM. Serum alkaline phosphatase levels were 39.0-814.0 U/L (170.8 ± 149.4). Eleven patients had increased serum alkaline phosphatase levels of ≥ 200 U/dL including two cases with bone metastasis, two cases with liver metastasis, and seven cases with plasma PTHrP levels of > 1.5 pmol/L. Serum iPTH levels were 0.95-17.1 pg/mL (3.9 ± 3.6). All except three cases had suppressed serum iPTH levels of less than the lower normal limit of 10 pg/mL. Plasma

Table 1. Characteristics of 48 patients with malignancy-associated hypercalcemia

	Range	Mean ± SD	Normal values
Age (years)	26.0-87.0	57.7 ± 13.0	
Corrected serum total calcium (mg/dL)	10.8-19.1	13.6 ± 2.4	8.5-10.4
Serum phosphorus (mg/dL)	0.6-6.8	3.4 ± 1.5	2.2-5.0
Serum creatinine (mg/dL)	0.6-5.0	1.5 ± 0.9	0.5-2.0
Serum alkaline phosphatase (U/L)	39.0-814.0	170.8 ± 149.0	39.0-117.0
Serum intact PTH (pg/mL)	0.95-17.1	3.9 ± 3.6	10.0-60.0
Plasma PTHrP (pmol/L)	0.2-44.0	3.8 ± 6.7	<1.5

Table 2. Types of malignancy in patients with humoral and non-humoral hypercalcemia of malignancy

	MAHC (n = 48) Cases (%)	HHM (n = 27) Cases (%)	Non-HHM (n = 21) Cases (%)
Squamous cell carcinoma	22 (45.8)	22 (81.5)	-
Lung	13 (22.1)	13 (48.1)	-
Head and neck	4 (8.3)	4 (14.8)	-
Esophagus	1 (2.1)	1 (3.7)	-
Cervix	2 (4.2)	2 (7.4)	-
Penis	1 (2.1)	1 (3.7)	-
Skin	1 (2.1)	1 (3.7)	-
Non-squamous cell carcinoma	15 (31.3)	4 (14.8)	11 (52.3)
Breast	3 (6.2)	-	3 (14.3)
Carcinoid	1 (2.1)	-	1 (4.8)
Hepatoma	2 (4.2)	-	2 (9.5)
Pancreas	1 (2.1)	-	1 (4.8)
Ovary	2 (4.2)	1 (3.7)	1 (4.8)
Unknown primary tumor	6 (12.5)	3 (11.1)	3 (14.3)
Hematologic malignancies	11 (22.9)	1 (3.7)	10 (47.6)
Lymphoma	7 (14.6)	1 (3.7)	6 (28.6)
Multiple myeloma	3 (6.2)	-	3 (14.3)
Leukemia	1 (2.1)	-	1 (4.8)

MAHC, malignancy-associated hypercalcemia
HHM, humoral hypercalcemia of malignancy defined by plasma PTHrP > 1.5 pmol/L
Non-HHM, non-humoral hypercalcemia of malignancy defined by plasma PTHrP ≤ 1.5 pmol/L

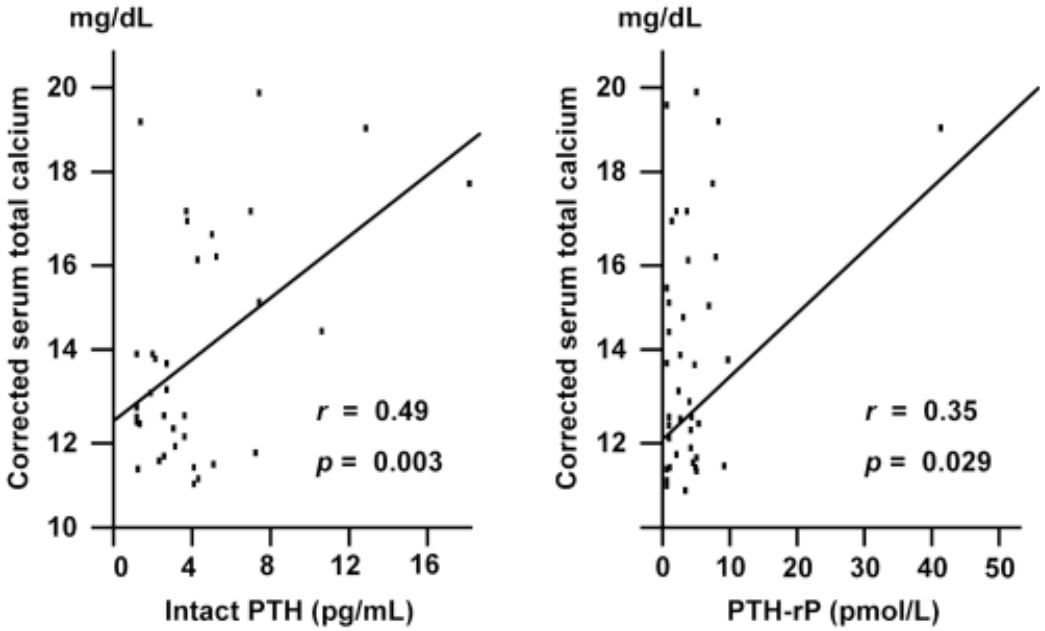

Fig. 1 Pearson's correlation study in 48 patients with malignancy-associated hypercalcemia shows statistically significant correlation between corrected serum total calcium and serum iPTH levels and between corrected serum total calcium and plasma PTHrP levels

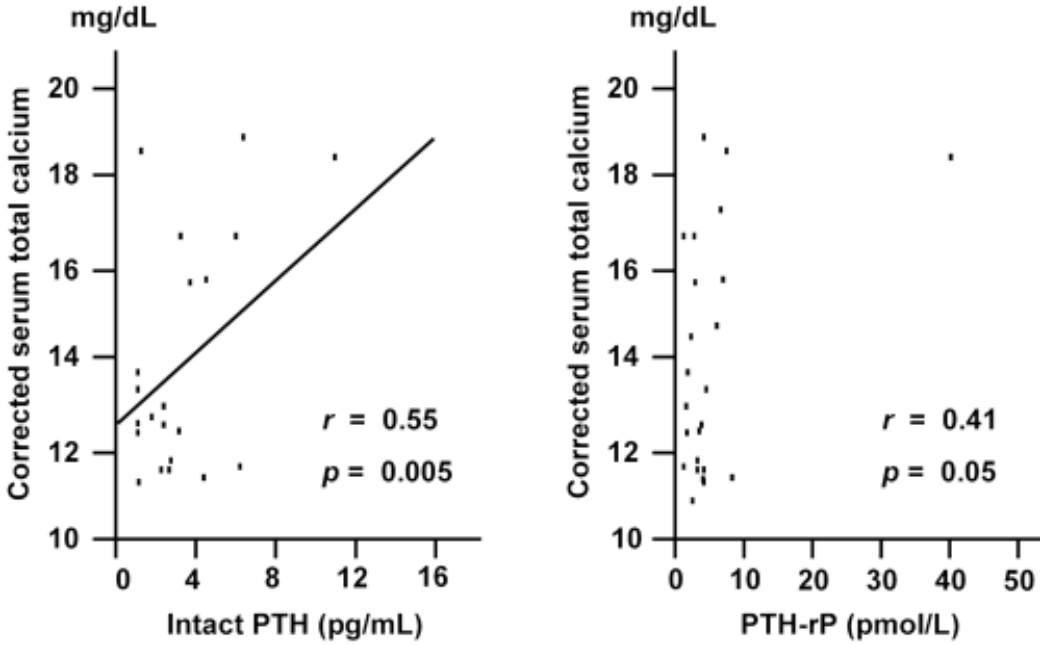

Fig. 2 Pearson's correlation study in 27 patients with humoral hypercalcemia of malignancy (plasma PTHrP levels > 1.5 pmol/L) shows statistically significant correlation between corrected serum total calcium and serum iPTH levels (left panel) but not between corrected serum total calcium and plasma PTHrP levels (right panel)
Regression line is not shown in the right panel because the result was not statistically significant ($p = 0.05$)

PTHrP levels were 0.2 - 44.0 pmol/L (3.8 ± 6.8). There was no difference in average serum cTCa (12.5 ± 2.2 *vs.* 13.5 ± 1.58 mg/dL), phosphorus (3.2 ±1.3 *vs.* 3.6 ± 1.6 mg/dL), and iPTH (3.82 ± 3.63 *vs.* 4.91 ± 4.38 pg/mL) levels between 34 cases with normal and 14 cases with impaired renal function. Of the 48 cases with MAHC, there were 27 cases (56.3%) that met the criteria for diagnosis of HHM with plasma PTHrP levels of higher than the upper normal limit of 1.5 pmol/L and 19 cases (39.6%) had plasma PTHrP levels of higher than the mean plasma PTHrP level in 48 MAHC patients of 3.8 pmol/L. Among the 27 cases with HHM, 22 cases (81.5%) had squamous cell carcinoma, four cases (14.8%) had other carcinomas, and one case (3.7%) had hematological malignancy. All of the 22 patients with squamous cell carcinoma had high plasma PTHrP levels (Table 2). Pearson's correlation analyses in all 48 cases with MAHC showed that serum cTCa correlated to plasma PTHrP ($r = 0.35$, $p = 0.029$) and to serum iPTH ($r = 0.49$, $p = 0.003$) but not to serum phosphorus levels (Fig. 1). When studied in 27 patients with HHM whose plasma PTHrP levels of > 1.5 pmol/L, a stronger correlation between serum cTCa and serum iPTH ($r = 0.55$, $p = 0.005$) but not between serum cTCa and plasma PTHrP levels ($r = 0.41$, $p = 0.05$) was observed (Fig. 2). Stepwise multiple regression analyses showed that serum iPTH but not plasma PTHrP levels independently correlated to serum cTCa levels ($r = 0.49$, $p = 0.04$) (Table 3). There was no difference in average serum cTCa (12.3 ± 2.6 *vs.* 13.1 ± 2.3 mg/dL), phosphorus (3.7 ± 1.5 *vs.* 3.1 ± 1.3 mg/dL), alkaline phosphatase (172.8 ± 167.4 *vs.* 168.9 ± 143.0 U/L), and iPTH (3.99 ± 2.19 *vs.* 4.35 ± 4.47 pg/mL) levels between patients with non-HHM (plasma PTHrP levels of ≤ 1.5 pmol/L) and HHM (plasma PTHrP levels of > 1.5 pmol/L).

Table 3. Stepwise multiple regression analyses between corrected serum total calcium levels and other biochemical parameters (n = 48)

	r-value	*p*-value
Serum intact PTH	0.49	0.04*
Plasma PTHrP	0.28	0.15
Serum phosphorus	-0.28	0.16
Serum alkaline phosphatase	0.31	0.11
Serum chloride	0.28	0.16
Serum bicarbonate	-0.03	0.88

* *p*-value considered significant at < 0.05

Discussion

The present study has shown that clinical and biochemical characteristics of patients with MAHC are mostly consistent with those generally described[20-22]. The most common malignancy that caused MAHC in the present study was squamous cell carcinoma of various sites which accounted for 45% of cases and the other less common malignancies were non-squamous cell solid tumors of various tissues and hematological malignancies. Regarding the relationship between tumor size and the presence or absence of hypercalcemia, most of MAHC patients in the present study (> 90%) had advanced malignancies at the time of developing hypercalcemia. This observation is consistent with other studies showing that MAHC was rarely observed in patients with small and occult tumors or in the other words MAHC usually occurs in patients with large or advanced tumors[6,7,23]. In addition, the presence of MAHC indicates the poor prognosis of malignancy as shown by the study of Ralston *et al* that patients with MAHC usually die within a few months with a 30-day survival rate of only 50% after hypercalcemia was discovered[24].

The present study has shown that severity of hypercalcemia varied from mild degree with a slightly elevation of serum cTCa level of 10.4 mg/dL to severe degree with markedly elevation of serum cTCa levels of > 13 mg/dL and ~40% of the patients had severe hypercalcemia with serum cTCa levels of ≥ 13 mg/dL. The authors' observations are consistent with those of previous studies demonstrating that > 50% of MAHC patients had hypercalcemia of moderate to severe degree[6,7]. It is generally known that an increase in serum calcium concentration physiologically inhibits PTH secretion and results in a suppressed serum PTH level[15,16]. Suppressed serum PTH levels were, therefore, usually observed in almost all patients with MAHC as shown in the present and other previous studies[3,4,6,17,25]. Serum iPTH levels observed in the present study (3.9 ± 3.6 pg/mL) were comparable to those observed in other studies of Body *et al* (4.6 ± 2.47 pg/mL)[17] and Nussbaum *et al* (3.2 ± 0.76 pg/mL)[25]. The presence of hypercalcemia with suppressed serum PTH levels in patients with malignancies is therefore considered one of the criteria for the diagnosis of MAHC[20,21]. The present and other studies[7,26] showed that some MAHC patients had significantly non-suppressible serum PTH levels, which were inappropriately high for the elevated serum calcium concentrations in MAHC patients. The mechanism underlying this phenomenon is not clearly known. Calcium independent PTH secretion[27], altered calcium set-point

that needs a higher serum calcium concentration to suppress PTH secretion[28,29] and decreased PTH clearance[30] have been demonstrated to be the mechanism of non-suppressible serum iPTH levels in hypercalcemia. However, whether these mechanisms could be applied in MAHC needs to be examined. In addition, concomitant primary hyperparathyroidism should be considered in MAHC patients with elevated serum PTH levels[4]. There might be an argument that the presence of non-fully suppressed serum PTH levels in MAHC might be the result of impaired renal function. In the present study, there was no difference in serum cTCa, phosphorus, and iPTH levels between the MAHC patients with impaired and normal renal function. In addition, there was only one case of 13 MAHC patients with impaired and normal renal function (serum creatinine 2.4 mg/dL) who had a non-fully suppressed serum iPTH level of 15.5 pg/mL. These observations suggest that impaired renal function was not the cause of non-fully suppressed serum PTH levels in MAHC.

The prevalence of HHM reported in previous studies varied from 47% to ~80% depending on the criteria used for the diagnosis of HHM and the immunoassay methods used for measurement of circulating PTHrP levels[2-9]. An early study of Stewart *et al* in 50 patients with MAHC showed that the prevalence of HHM diagnosed by the presence of elevated nephrogenous cyclic AMP without elevated serum PTH levels was 82%[6]. Subsequent studies in 65 cases by Budayr *et al* and 36 cases by Kao *et al* demonstrated that the prevalence of HHM diagnosed by the presence of elevated serum PTHrP levels measured by radioimmunoassay (RIA) using an antibody against PTHrP (1-34) was 55% and 47%, respectively[5,8]. A study in 38 patients with MAHC by Burtis *et al*[3] showed that the prevalence of HHM diagnosed mainly by the presence of elevated urinary excretion of cyclic AMP was ~80% (78.9%), whereas the prevalence of HHM diagnosed by the presence of elevated plasma PTHrP levels measured by IRMA using two antibodies against PTHrP (1-36) and PTHrP (37-74) and by radioimmunoassay (RIA) using an antibody against PTHrP (109-138) were 65.8% and 78.9%, respectively. In the present study, the prevalence of HHM diagnosed by the presence of elevated plasma PTHrP levels of > 1.5 pmol/L measured by IRMA was 56.3% which was comparable to that observed in previous studies.

As generally described[20-22], the present study showed that squamous cell carcinoma was not only the most common cause of MAHC but also of HHM. Most of the presented patients with HHM (81.5%) had squamous cell carcinoma and 18.5% had other carcinomas and hematological malignancies. The authors' findings agreed with those of unselected series of patients with HHM that ~50% of the cases had squamous cell carcinoma of various organs and the rest had non-squamous cell carcinoma of the kidney, ovary, breast, and hematological malignancies[22].

Though PTHrP possesses some biological actions that resemble those of PTH including inhibition of tubular phosphorus re-absorption[6], however, there was no significant difference in serum phosphorus levels and prevalence of hypophosphatemia between patients with HHM and non-HHM. The lack of difference in serum phosphorus levels as well as serum cTCa, alkaline phosphatase and iPTH levels between patients with HHM and non-HHM indicates that these biochemical parameters are not useful in the differential diagnosis of between HHM and non-HHM.

As PTHrP induces hypercalcemia *via* stimulation of osteoclastic bone resorption[12,31-33], the severity of hypercalcemia is theoretically expected to correlate positively to plasma PTHrP levels. However, studies on the correlation between serum calcium and plasma PTHrP demonstrated inconsistent results. The present study has demonstrated a weak but significant positive correlation between serum calcium and plasma PTHrP levels ($r = 0.35$, $p = 0.03$) which was consistent with those of Ratcliffe *et al* ($r = 0.34$, $p < 0.05$)[13] and Lee *et al* ($r = 0.48$, $p < 0.001$)[14]. Whereas, some studies such as that of Burtis *et al* found no correlation between serum calcium and plasma PTHrP levels[3]. The inconsistent results of the correlation between serum calcium and plasma PTHrP levels observed among these studies might be explained by the differences in the method used for PTHrP assay in each study and factors affecting serum calcium levels such as the hydration status of the patients.

Though serum PTH levels are usually suppressed by the increased serum calcium concentrations in patients with MAHC[3,4,6,17,25], some studies such as that of Body *et al*[17] and Fukumoto *et al*[18] demonstrated a significant correlation between serum calcium and the suppressed but detectable serum PTH levels with correlation coefficient (r) values of 0.89 and 0.79, respectively which were higher than the r-values of the correlation study between serum calcium and plasma PTHrP levels observed by different studies such as that of Lee *et al* ($r = 0.48$)[14] and Ratcliffe *et al* ($r = 0.34$)[13]. In the present study, the correlation between serum cTCa and iPTH levels was slightly higher but not significantly than the correla-

tion between serum cTCa and plasma PTHrP levels ($r = 0.49$ *vs.* $r = 0.35$, $p = 0.21$) when studied in all of the 48 MAHC patients. However, when 25 MAHC patients caused by HHM were studied, serum cTCa levels significantly correlated to serum iPTH levels at a higher *r*-value of 0.55 but not to plasma PTHrP levels. In addition, stepwise multiple regression analyses demonstrated that serum iPTH but not plasma PTHrP levels independently associated with serum cTCa levels. The observations that serum calcium levels or severity of hypercalcmia correlated to serum iPTH more strongly and more consistently than to plasma PTHrP levels as shown in the present and other studies suggest that the suppressed but detectable serum PTH levels might play a role in the development of severe MAHC. However, the mechanism by which PTH attenuates the severity of MAHC particularly in HHM is not clearly known. Difference in binding affinity to PTH receptors should not be the case[34] as PTH and PTHrP of which the receptor binding domains located within the region 14-34 have equal binding affinity to PTH receptor[35]. Higher biological potency of PTH as compared to that of PTHrP is the likely explanation for the role of suppressed but detectable serum PTH levels in MAHC since human PTH (1-34) has been demonstrated to have 3- to 10-fold more potent than human PTHrP (1-34) in the induction of biological effects such as increasing serum calcium and urinary cAMP in healthy subjects[36]. However, this postulation needs to be elucidated as there is another study in healthy subjects showing that human PTH(1-34) has a comparable potency to human PTHrP (1-36)[37].

In conclusion, the clinical manifestations of MAHC observed in the present study were similar to those previously reported. Serum calcium correlated to serum iPTH more strongly than to plasma PTHrP levels. The low but detectable serum iPTH levels might play a role in the development of severe MAHC particularly in HHM.

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ภาวะแคลเซียมสูงในเลือดจากมะเร็ง: การศึกษาลักษณะทางคลินิก และความสัมพันธ์ระหว่างระดับแคลเซียม, ฮอร์โมนพาราไทรอยด์ และเป็พไทด์คล้ายฮอร์โมนพาราไทรอยด์ในเลือด

สุทิน ศรีอัษฎาพร, เมธา ภู่เจริญชนะชัย, ศิริรัตน์ พลอยบุตร, ณัฐเชษฐ์ เปล่งวิทยา, ธวัชชัย พีระพัฒน์ดิษฐ์, วรรณี นิธิยานันท์, สาธิต วรรณแสง, อภิชาติ วิชญาณรัตน์

คณะผู้รายงานได้ทำการศึกษาผู้ป่วยภาวะแคลเซียมสูงในเลือดจากมะเร็งจำนวน 48 ราย พบว่า มะเร็งที่เป็นสาเหตุ ได้แก่ สะแควมัสเซลล์คาร์ซิโนมาของอวัยวะต่าง ๆ (22 ราย, ร้อยละ 45.8), มะเร็งทางโลหิตวิทยา (11 ราย, ร้อยละ 22.9) และมะเร็งของเนื้อเยื่ออื่น ๆ (15 ราย, ร้อยละ 31.9) ผู้ป่วยเกือบทุกราย (ร้อยละ 93.8) มีมะเร็งอยู่ในขั้นลุกลาม ระดับซีรัมแคลเซียมรวมที่ปรับแล้ว (cTCa) มีค่า 10.8-19.1 (13.6 $\pm$ 2.4) มก./ดล. โดยที่ร้อยละ 40.5 ของผู้ป่วยมีภาวะแคลเซียมสูงในเลือดขั้นรุนแรง ระดับซีรัมฮอร์โมนพาราไทรอยด์ (iPTH) มีค่า 0.9-17.1 (3.9 $\pm$ 3.6) พิโคกรัม/มล. ผู้ป่วยเกือบทุกราย (ร้อยละ 93.8) มีระดับซีรัม iPTH ต่ำกว่าเกณฑ์ปกติ มีเพียง 3 ราย ที่มีระดับซีรัม iPTH สูงกว่าเกณฑ์ต่ำของค่าปกติ ระดับพลาสมาเป็พไทด์คล้ายฮอร์โมนพาราไทรอยด์ (PTHrP) มีค่า 0.3-44 (3.8 $\pm$ 6.8) พิโคโมล/ลิตร ผู้ป่วย 27 ราย (ร้อยละ 56.3) มีระดับพลาสมา PTHrP สูงกว่าเกณฑ์ปกติและได้รับการวินิจฉัยเป็นภาวะแคลเซียมสูงในเลือดจากมะเร็งชนิดฮิวโมรอล (HHM) ในจำนวนนี้เป็นผู้ป่วยสะแควมัสเซลล์คาร์ซิโนมาทั้ง 22 ราย ไม่มีความแตกต่างกันในระดับซีรัม cTCa, ฟอสฟอรัส, แอลคาไลน์ฟอสฟาเทส และ iPTH ระหว่างผู้ป่วยที่มีระดับพลาสมา PTHrP สูงและไม่สูง ระดับซีรัม cTCa มีความสัมพันธ์กับระดับซีรัม iPTH ($r = 0.49$, $p = 0.003$) และพลาสมา PTHrP ($r = 0.35$, $p = 0.029$) อย่างมีนัยสำคัญทางสถิติ เมื่อศึกษาเฉพาะในกลุ่มผู้ป่วย HHM 25 ราย พบว่า ระดับซีรัม cTCa มีความสัมพันธ์กับ iPTH ชัดเจนขึ้น ($r = 0.55$, $p = 0.005$) แต่ไม่สัมพันธ์กับระดับพลาสมา PTHrP ($r = 0.41$, $p = 0.05$) โดยสรุป ลักษณะทางคลินิกของภาวะแคลเซียมสูงจากมะเร็งที่พบในการศึกษานี้คล้ายคลึงกับการศึกษาอื่นที่ผ่านมา ระดับซีรัม iPTH ที่แม้ว่าอยู่ในเกณฑ์ต่ำอาจมีบทบาทส่งเสริมให้ภาวะแคลเซียมสูงในเลือดจากมะเร็ง เป็นรุนแรงขึ้นโดยเฉพาะในกลุ่มที่เป็น HHM