The Causes of Hypercalcemia in Okinawan Patients: An International Comparison

Yasuharu Tokuda¹, Kyouko Maezato² and Gerald H. Stein³

Abstract

Objective Our objective was to determine the causes and relative prevalence of hypercalcemia in patients at a major community hospital in Okinawa, Japan. Additionally, we compared these causes of hypercalcemia with the previously published international data.

Materials and Methods We analyzed all patients with hypercalcemia in a community teaching hospital in Okinawa, Japan, from 1999 to 2002 and determined the cause of hypercalcemia in each patient. We also performed a literature review of the original articles describing causes of hypercalcemia in patients from Eastern as well as Western countries.

Results We identified 145 patients with hypercalcemia (median age, 69; range, 22 to 97). Major causes included malignant disorders (n=100; 69%), primary hyperparathyroidism (n=31; 21%), vitamin D-induced (n=4; 3%), and miscellaneous or unknown cause in 11 (8%). Among malignant disorders, adult T cell leukemia was the most frequent (n=35), being followed by lung cancer (n=25). Breast carcinoma was less prevalent (n=4).

Conclusion The major causes of hypercalcemia are malignancy and primary hyperparathyroidism in Okinawan Japanese patients. Adult T cell leukemia and lung carcinoma are among the top leading malignancies, while breast carcinoma is less frequent in this patient population. The etiologic prevalence of hypercalcemia in the Eastern population including Okinawans is significantly different from that in the Western population.

Key words: calcium, hypercalcemia of malignancy, hyperparathyroidism, vitamin D, differential diagnosis

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Introduction

Hypercalcemia is defined as an abnormal elevation in serum calcium concentration (1). Many different disorders can cause hypercalcemia (2). The most common categories among hospitalized patients are malignancy, primary hyperparathyroidism (PHP) and vitamin D-induced hypercalcemia (3, 4). The less frequent causes include other drug-induced conditions (thiazide diuretics, lithium, etc), tuberculosis, immobilization, and recovery phase of rhabdomyolysis. Identification of the underlying disease is important, since the subsequent management is different for the various causes of hypercalcemia.

Although detailed medical history, physical examination, and carefully directed laboratory measurements can differentiate the causes in most cases, hypercalcemia remains a challenging problem for general internists especially during the initial step of diagnostic evaluation. When facing a newly admitted patient with hypercalcemia of unknown etiology, it is important to consider the relative frequency of several main causes (5). Although a few previous studies have addressed geographic variations on international perspective, few reports are available about Asian populations. Thus, our objective was to determine the causes and relative prevalence of hypercalcemia in Japanese patients. Additionally, we compared the causes of hypercalcemia found in this study to those reported from other parts of Japan and from

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other countries. Conducting studies on the causes of hypercalcemia among Asian patients may be important because of the wide global immigration of Asians.

**Table 1. Causes and Relative Prevalence of Hypercalcemia (N=145)**

<table>
<thead>
<tr>
<th>Causes</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant disorders</td>
<td>100</td>
<td>69.0 (60.6-76.4)</td>
</tr>
<tr>
<td>Adult T cell leukemia / lymphoma</td>
<td>35</td>
<td>24.1 (17.4-31.9)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>25</td>
<td>17.2 (11.5-24.4)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>5</td>
<td>3.5 (1.1-7.9)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4</td>
<td>2.8 (0.8-4.9)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>4</td>
<td>2.8 (0.8-4.9)</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>4</td>
<td>2.8 (0.8-4.9)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>4</td>
<td>2.8 (0.8-4.9)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>3</td>
<td>2.1 (0.4-4.9)</td>
</tr>
<tr>
<td>Uterine cervix carcinoma</td>
<td>2</td>
<td>1.4 (0.2-4.9)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>14</td>
<td>9.7 (5.4-15.7)</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>30</td>
<td>20.7 (14.4-28.2)</td>
</tr>
<tr>
<td>Vitamin D-induced</td>
<td>4</td>
<td>2.8 (0.8-4.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>2.1 (0.4-4.9)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>8</td>
<td>5.5 (2.4-10.6)</td>
</tr>
</tbody>
</table>

C=confidence interval
One patient had myeloma and primary hyperparathyroidism and is included into malignancy.

**Patients and Methods**

**Study patients**

We reviewed adult patients (16 years old and older) at Okinawa Chubu Hospital, a 550-bed community teaching hospital providing care for native Asians in an urban area of Okinawa, Japan. Okinawa is a subtropical island, located north of Taiwan, west of China, and south of mainland Japan. We analyzed all measurements of serum calcium concentrations for the four-year period (from 1999 to 2002). We counted multiple admissions of a single patient as a single occurrence. Serum calcium concentrations were determined by an automated biochemical system with daily calibrations. All biochemical analyses were performed without knowledge of clinical information. The clinical laboratory participated in a regular external quality assessment for blood electrolytes concentrations. The authors conducted a review of all computerized biochemical records. Hypercalcemia was defined as a calcium level equal to or greater than 2.70 mmol/L after correction based on serum albumin concentration by using the following formula (6):

Corrected calcium (mmol/L) = serum calcium (mmol/L) - ([0.02×albumin (g/L)] + 0.8)

The abnormal calcium concentration of individual patients was measured at least twice for laboratory reliability. We reviewed the medical records for patients with hypercalcemia noting complete blood count, multi-channel chemistry panel, and selected imaging studies where appropriate (echo, CT, radioisotope scan of parathyroid, etc). In addition, we analyzed serum concentrations of albumin, blood urea nitrogen, chloride, creatinine, phosphate, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and alkaline phosphatase, and compared these laboratory data of patients with PHP to those having the hypercalcemia of malignancy. We also calculated the chloride phosphate ratio. Intact parathyroid hormone (iPTH) and parathyroid hormone related protein (PTHrP) concentrations were measured by immunoradio-metric assays (SRL Institute, Tokyo, Japan) when clinically indicated. Normal concentrations for iPTH and PTHrP were 10-65 pg/ml and <1.1 pmol/L, respectively (7, 8). The Hospital Ethics Committee approved the study.

**Causes for hypercalcemia**

Two investigators independently reviewed the medical records. They determined the most likely cause of hypercalcemia in individual patients by consensus. We diagnosed PHP based primarily on hypercalcemia and elevated iPTH. We also used positive parathyroid scans, ultrasound results, or confirmatory post-parathyroidectomy tissue reports. The diagnosis of malignant disease was based on appropriate pathologic confirmation. We classified the cause of hypercalcemia as unknown when a patient did not meet any criteria for an underlying disorder. We excluded patients with chronic renal failure who received vitamin D therapy.

Furthermore, we sought to identify published investigations designed to analyze causes for hypercalcemia. We searched Medline databases of peer-reviewed articles by using MeSH terms such as hypercalcemia, hyperparathyroidism, parathyroid hormone related protein, and differential diagnosis. We compared our results to the distribution of tumor types of the previous malignancy series of hypercalcemia from general hospitals involving 50 patients or more reported from Western and Eastern countries.

**Statistical analysis**

We calculated the overall incidence and relative prevalence of different causes of hypercalcemia with 95% confidence interval (CI). We compared clinical laboratory data between PHP and hypercalcemia of malignancy. We presented the laboratory values as the mean ± standard deviation (SD). Non-parametric tests (Wilcoxon tests) were used for comparison between laboratory values since most data were not normally distributed and chi-square test was used for comparison of binary data. All p values were two-tailed. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 12.0J, 2003, Chicago, Illinois).

**Results**

We confirmed a diagnosis of hypercalcemia in 0.75% (N=145) of 19,396 hospital admissions (95% CI, 0.63-0.88%) during the study period. The median age was 69 years old (range, 22 to 97 years old). All patients were Japanese (Asians). Sixty-eight (47%) patients were women. The prevalence of hypercalcemia was 0.65% (95% CI, 0.51-0.83%) in women (10,421 admissions) and 0.86% (95% CI, 0.68-1.07%) in men (8,975 admissions).

The causes of hypercalcemia in 145 patients are shown in Table 1. Malignant disorder was the most common cause for
hypercalcemia, accounting for nearly two-thirds (100 patients; 69%; 95% CI, 61-76%) of all patients with hypercalcemia. The second most frequent cause was PHP (30 patients; 21%; 95% CI, 14-28%). Patients with PHP were middle-aged (median age, 66 years old); fifteen patients (50%) were women. One patient had both PHP and malignancy (multiple myeloma) and this patient was categorized as having malignancy as the cause of hypercalcemia. No patient with PHP had multiple endocrine neoplasia or familial hypocalciuric hypercalcemia. Vitamin D-induced hypercalcemia was the third frequent cause (4 patients; 3%; 95% CI, 1-7%). There were no cases of granulomatous diseases with hypercalcemia such as sarcoidosis or tuberculosis among the patients of this study.

Adult T cell leukemia/lymphoma (ATL) was the most frequent malignancy (35 patients; 24% of total cases; 95% CI, 17-32%). It was followed by lung carcinoma (25 patients; 17%; 95% CI, 12-24%) and Non-Hodgkin’s lymphoma (5 patients). Other malignant diseases included renal cell carcinoma, 4 patients; multiple myeloma 4; ovarian carcinoma 4; breast cancer 4; hepatocellular carcinoma 3; uterine cervical carcinoma 2; and carcinomas of the tongue, pharynx, larynx, thyroid, esophagus, duodenum, pancreas, maxillary sinus, prostate, rectum, gallbladder, biliary tract, urinary bladder, vagina, and penis each in a single patient, respectively.

Table 2 shows the distribution of tumor types among different published series of hypercalcemia of malignancy. Our study is similar to other Asian series which documented a higher prevalence of hematologic tumors (9) and a lower prevalence of breast carcinoma compared to Western series (10).

Table 3 compares the laboratory values between hypercalcemia of malignancy and PHP. Serum calcium, phosphate, AST, and LDH were significantly higher in patients with malignancy than in those with PHP in a univariate analysis. Serum albumin, total protein, chloride phosphate ratio, and hemoglobin were significantly higher in those with PHP than in those with malignancy also in a univariate analysis. In a multivariable adjusted logistic regression analysis, only serum albumin and chloride phosphate ratio were identified
as statistically significant variables (p<0.05). By including only these two significant covariates in a logistic regression model, we obtained 80% overall classification accuracy. However, by using this logistic regression as a prediction model, only 50 percent of patients with PHP were accurately classified as more likely PHP than hypercalcemia of malignancy.

Serum concentrations of iPTH were measured in 38 patients. All PHP patients had high iPTH concentrations (median 130 pg/ml; range 89-270), while all patients with malignancy had low or undetectable concentrations (median 8 pg/ml; range 1-43), except for one patient who had both multiple myeloma and PHP. All PHP patients had low PTHrP concentrations (median 0.2 pmol/L; range 0.2-0.3), while patients with malignancy had variable concentrations of PTHrP (median 2.7 pmol/L; range 0.2-18.3).

Discussion

The major causes of hypercalcemia were found to be malignancy and PHP in Okinawan Japanese patients. Hypercalcemia was infrequent among hospitalized patients. Additionally, the present study showed the different etiologic prevalence of hypercalcemia of malignancy in Eastern patients compared to that in Western patients. The relative prevalence of malignancy-related hypercalcemia seemed to reflect the relative prevalence of malignancy in the local population. It is essential to detect the primary tumor in patients with hypercalcemia of malignancy to predict the prognosis (11-14) and to determine specific and effective anti-tumor therapy (6).

Hematologic diseases, especially adult T cell leukemia/lymphoma (ATL), were the most frequent type among malignancy-related hypercalcemia in our hospital in Okinawa, Japan. With an unusually high association of hypercalcemia, about 40% of patients with ATL are known to eventually develop hypercalcemia (15, 16). On the other hand, breast carcinoma was relatively uncommon in our series as well as in other Asian studies (9, 10), in contrast to Western series with this carcinoma typically accounting for more than 20% (3, 6, 17-19). The low prevalence of hypercalcemia due to breast carcinoma may reflect the low incidence of this tumor in Asia (9), while the high prevalence of hypercalcemia due to ATL may be due to the high incidence of this hematologic malignancy in Okinawa and southern areas of Japan (20-23). Furthermore, ATL is more prevalent in the southern area of Japan than in northern areas (24). Thus, the etiologic prevalence of hypercalcemia in other parts of Japan, especially the northern areas such as Hokkaido and Tohoku, can be quite different from that of the present study conducted in Okinawa (25).

Many previous studies of the hypercalcemia of malignancy have presented important sites of malignancy along with relative prevalence (3, 6, 12, 13, 17-19, 26). However, when applying these results to actual clinical practice, it is important to consider whether the geographical settings are similar. For example, the present study population had endemic ATL, which was found to be the leading cause of hypercalcemic malignancy in this study. Moreover, the prevalence of hematologic malignancy in this study was higher than in other Asian series. This probably results from the endemic status of ATL in Okinawa. On the contrary, we had a relatively low incidence of breast carcinoma similar to other Asian populations, which probably made this disease a less likely cause.

The relative frequency of major categorical causes in our hypercalcemic patients was similar to that observed in several general hospital surveys (3, 4, 17). Malignant neoplasm accounted for nearly half of the cases of hypercalcemia. Primary hyperparathyroidism was the next major group. The frequency of vitamin D-induced disorders was relatively low since we excluded chronic renal failure patients with active vitamin D therapy and those on hemodialysis (27). Because this study was performed using hospitalized patients, only about 15% had PHP. PHP is known to be the most common etiology for hypercalcemia in the outpatient setting (28, 29). For example, Mundy et al reported that primary hyperparathyroidism was diagnosed in 111 patients (54%) in 207 hypercalcemic patients in an urban area of 1 million people over a period of 5 months in the US (28). A study in Norway also noted a high prevalence of primary hyperparathyroidism in older women (29).

On the other hand, one study, reported from a hospitalized population in Hong Kong, showed that PHP was relatively uncommon (5.5%) (9). Two reports from Taiwan also noted this point (10, 30). PHP itself may be less prevalent in Asian populations. However, the cutoff point for serum calcium used in the present study appeared relatively high when considering that many PHP patients present with a mild degree of hypercalcemia. Thus, we might have underestimated the prevalence of PHP in the present study. Of note, men vs women had equal prevalence of PHP, which is rather unusual compared to other studies. This may reflect bias using only an inpatient population or it might indicate that there is less gender difference of PHP in the Japanese general population. Further investigations should be considered to clarify these issues.

We detected no cases of granulomatous diseases. Sarcoidosis was relatively rare but its incidence has recently increased in the northern part of Japan (31). The reason may be that our site, located in southern part of Japan, has a low prevalence of sarcoidosis in general. Tuberculosis was shown to be an important cause of hypercalcemia in two Hong Kong studies (9, 32), although the present study found no case of tuberculosis. Another reason for these variations may be the time of data collection, since the incidence of granulomatous diseases may fluctuate over time (33).

The immunoradiometric assay for iPTH provides adequate discrimination to diagnose PHP (34), while PTHrP is the most useful analysis method in the majority of patients with hypercalcemia of malignancy (35). In the era of technological improvements employing iPTH and PTHrP assays, we
propose the diagnostic strategy to routinely measure iPTH for newly identified patients with hypercalcemia (36). This strategy may also be advised when evaluating patients with hypercalcemia of malignancy, since some patients with malignancy may possibly develop PHP at a higher rate than the general population (37, 38). One patient in our study had such an etiologic combination.

Although several common laboratory values such as the chloride phosphate ratio and serum albumin may serve as a guide for the differential diagnosis between PHP and hypercalcemia of malignancy (39, 40), our data showed these values were less specific. Incorrect classification remained a significant problem, although 80 percent discrimination could be achieved by the chloride phosphate ratio and serum albumin using logistic regression analysis in our study. These laboratory tests are not as precise as to the iPTH and PTHrP assays (41, 42).

There is a possible limitation in this study, as it was conducted at a single hospital in Okinawa. The data may not represent the accurate prevalence of hypercalcemic patients throughout Okinawa. More extensive evaluations involving multiple hospitals may be needed to accurately describe the etiologic prevalence of causes of hypercalcemia in hospitalized patients of Japan.

In conclusion, malignancy and primary hyperparathyroidism were the two major causes of hypercalcemia among hospitalized patients at our institution in Okinawa, Japan. Hypercalcemia of malignancy was the most frequent cause; ATL and lung carcinoma were among the top leading malignancies, while breast carcinoma was less frequent in patients of our study. Further comparative investigations using different regional populations are needed to define the global etiologic characteristics of hypercalcemia among hospitalized patients.

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