Clinica Chimica Acta 453 (2016) 190–193

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Incidence of humoral hypercalcemia of malignancy among hypercalcemic patients with cancer

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ARTICLE INFO

Article history:
Received 12 September 2015
Received in revised form 11 December 2015
Accepted 14 December 2015
Available online 17 December 2015

Keywords:
Hypercalcemia
Malignancy
PTHrP
Prevalence

ABSTRACT

Background: Malignancy-associated hypercalcemia (MAHC) is the most common cause of hypercalcemia among hospitalized patients. MAHC can result from the production of parathyroid hormone related peptide (PTHrP) which is known as humoral hypercalcemia of malignancy (HHM). HHM is commonly thought to account for approximately 80% of MAHC.
Methods: We conducted a 12-year review of PTHrP testing at our institution to establish the prevalence of HHM among patients with MAHC.
Results: A total of 524 PTHrP immunoassays were performed during the study period of which 470 tests qualified for inclusion in the analysis. Evidence of malignancy was found for 242 of 470 patients (51%). No etiology could be determined for 98 cases of MAHC (40%) and increased PTHrP contributed to 92 cases (38%) of MAHC. Age, race and gender were not associated with HHM. Increased PTHrP was observed at initial malignancy diagnosis in 20% of cases. PTHrP was never increased outside of the context of malignancy.
Discussion: The prevalence of HHM among patients with MAHC is likely to be lower than previously described.

1. Introduction

Malignancy-associated hypercalcemia (MAHC) occurs in 20–30% of cancer patients [1,2] and is the most common cause of hypercalcemia among hospitalized patients [3]. MAHC usually results from osteolytic bone lesions or from the production of parathyroid hormone related peptide (PTHrP), the latter of which is known as humoral hypercalcemia of malignancy (HHM).

Nine of the 13 N-terminal amino acids of human PTHrP are homologous to those of parathyroid hormone, and PTHrP exerts its effects through binding to the parathyroid hormone 1 (PTH-1) receptor [4]. PTHrP is a peptide widely expressed throughout the body and circulates at low levels in the plasma of healthy individuals [5]. PTHrP is also ectopically secreted at much higher levels by some solid tumors and in some hematologic malignancies [6]. In these cancers, secreted PTHrP causes hypercalcemia via increased calcium absorption at the kidney and increased bone resorption [7].

Diagnostic workup of suspected HHM begins with the measurement of ionized calcium and PTH [1,8]. In patients with high ionized calcium and low PTH, measurement of PTHrP can confirm the diagnosis of HHM. HHM has been commonly thought to account for approximately 80% of MAHC [1,7]. This value is based on studies either predating the identification of PTHrP [9] or during validation of the original PTHrP immunoassay [10]. However, some early PTHrP immunoassay studies [11], and a recent, smaller study [8] reported lower prevalence of HHM. Our experience with PTHrP as a "resident-approval" test also challenged the accepted high prevalence of HHM in MAHC.

2. Methods

2.1. Study design

To determine the prevalence of HHM in hospitalized patients with MAHC, we conducted a single-institution, cross sectional study of all PTHrP tests ordered at Barnes-Jewish Hospital in St. Louis over a twelve-year period from January 1, 2002 through December 31, 2013. PTHrP values were excluded from the study if they were not the first measurement for a given hospital admission, if they were performed on patients with normal or low calcium, or if associated patient records were unavailable. For each included PTHrP measurement, a chart review was performed to establish patient demographics, history of malignancy, relevant admitting laboratory values, etiology of hypercalcemia, and hospital admission outcome. This study was approved by the Washington University Institutional Review Board.

2.2. PTHrP immunoassays

During the period of investigation, samples for PTHrP analysis were sent to one of four reference laboratories: Mayo Medical Laboratories

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http://dx.doi.org/10.1016/j.cca.2015.12.017
0009-8981/

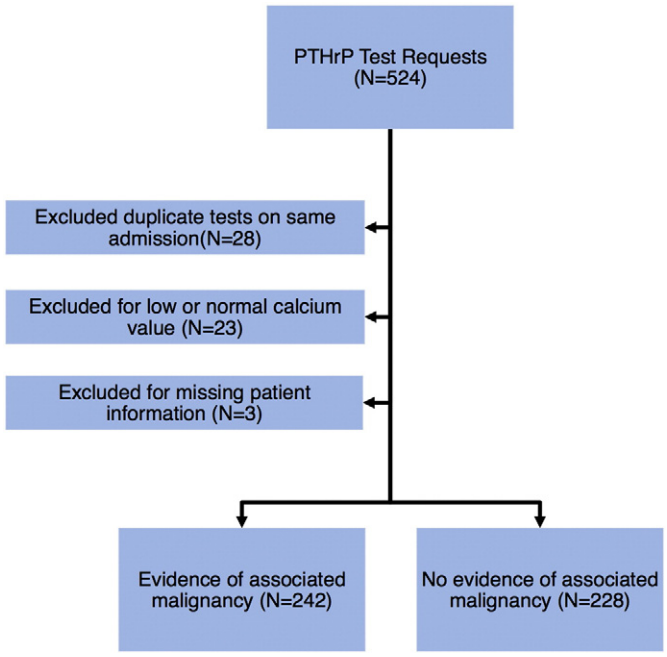

Fig. 1. Study design.

(311 assays), Quest Diagnostics (88 assays), Specialty Laboratories — Nichols Institute Diagnostics (30 assays), and ARUP Laboratories (41 assays). For all reference laboratories, PTHrP was determined using sandwich immunoassay. Results were evaluated against the reference interval provided by each laboratory and those exceeding the upper limit of the reference interval (1.9, 4.0, 4.7, or 1.3 pmol/l for the above mentioned reference laboratories, respectively) were considered increased. Positivity rates ranged from 7% to 20%. Specimens for PTHrP testing were collected according to the requirements given by each of the referral laboratories.

2.3. Clinical data collection

PTHrP results and patient age and sex were collected from the hospital laboratory information system (Cerner Millennium). Patient race and admitting laboratory values were collected from the hospital electronic medical record (Clinical Desktop 2). Laboratory values included total and ionized calcium, albumin, PTH, phosphate, and 25-OH vitamin D. Total calcium (by colorimetric methods), total ionized calcium (by direct ion-selective electrode), albumin (by bromocresol green), PTH (by chemiluminescence enzyme immunoassay), phosphate (by ammonium molybdate), and 25-OH vitamin D (by immunoassay) were determined in-house.

Length of stay and inpatient mortality were obtained from the hospital billing department. Type of malignancy and etiology of hypercalcemia were determined by a manual review of laboratory values and patient charts by residents and fellows in the Department of Pathology and Immunology at Washington University. PTHrP was considered to contribute to MAHC if a patient had increased plasma total (>10.3 mg/dl) or ionized (>5.1 mg/dl) calcium and an initial PTHrP value higher than the upper limit of the reference interval as provided by each of the reference laboratories. Osteolytic bone lesions were considered to contribute to MAHC if such lesions were documented on a radiographic imaging study or at autopsy. Other etiologies of hypercalcemia were identified through manual review of the electronic medical record. The etiology of a patient's hypercalcemia was considered unknown only if both PTH and PTHrP were normal and no cause was suggested or stated in pathology, radiology, or oncology notes or the discharge summary.

Table 1
Etiology of hypercalcemia among 242 patients with both elevated serum calcium and evidence of malignancy. Some patients had multiple causes of hypercalcemia. HHM: humoral hypercalcemia of malignancy.

Etiology	Number of patients	Percent of patients
Undetermined	98	40.5
HHM	92	38.0
Osteolytic bone lesions	66	27.3
Immobilization	8	3.3
Primary hyperparathyroidism	6	2.5
Tertiary hyperparathyroidism	2	0.8
Dehydration	2	0.8
Granulomatous disease	2	0.8
Thiazide diuretics	1	0.4
Calcium supplementation	1	0.4

Table 2
Demographics of patients with both elevated serum calcium and evidence of malignancy. Significance of age by Mann–Whitney U test. Significance of gender and race by Pearson chi-squared test. Age is in years. Gender and race values are total number of patients. HHM: humoral hypercalcemia of malignancy.

	HHM	Other etiology	*p*
Age (median)	59	60	0.528
Gender			
Male	55	93	0.859
Female	36	58	
Race			
Caucasian	59	98	0.96
African American	31	51	
Other	1	2	

2.4. Data analysis

All data analysis was performed in Microsoft Excel (ver 10, Microsoft) and SPSS Statistics (ver 22, IBM). Categorical variables were compared with Pearson chi-square or Fisher exact tests as appropriate. Association of individual laboratory values with etiology of hypercalcemia was assessed by Mann–Whitney U test. Laboratory results are presented as median values unless otherwise stated.

3. Results

3.1. PTHrP immunoassays

A total of 524 PTHrP immunoassays were performed through Barnes-Jewish Hospital from January 1, 2002 to December 31, 2013 (Fig. 1). Fifty-four PTHrP tests (10%) did not meet inclusion criteria as

Table 3
Site of primary malignancy among patients with both elevated serum calcium and evidence of malignancy. Three patients had multiple, concurrent cancer types. Significance by Fisher exact test or (*) for Pearson chi-squared test. HHM: humoral hypercalcemia of malignancy.

Site of primary malignancy	Total	HHM	Other etiology	*p*
Head and neck	61	27	34	0.214
Lung	46	22	24	0.112
Leukemia or lymphoma	23	4	19	0.035
Renal	21	6	15	0.371
Breast	17	5	12	0.47
Multiple myeloma	14	0	14	0.001*
Hepatocellular carcinoma	11	4	7	0.441
Bladder	8	6	2	0.056*
Colon	8	4	4	1*
Pancreatic	4	1	3	1*
Thyroid	4	0	4	0.3*
Cholangiocarcinoma	4	4	0	0.050*
Ovarian	3	2	1	0.558*
Other	21	7	14	0.672