



Is Breast Cancer Associated with Primary Hyperparathyroidism?

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Abstract

Introduction: Breast cancer is the most common cancer in women and the second leading cause of cancer-related deaths across the world. Hypercalcemia is known to occur in up to 20% to 30% of the patients with a cancer diagnosis at some point during the course of their illness. Breast cancer is one of the malignancies most commonly associated with hypercalcemia.

Primary Hyperparathyroidism (PHPT) has been associated with an increased risk of developing breast cancer compared with patients without PHPT. Little is known about the underlying risk factors. The aim of our study is to describe a cohort of patients with PHPT and breast cancer.

Methods: Retrospective study from a prospectively kept database of patients with PHPT treated by our group between January 2015 and July 2017 who had been diagnosed with breast cancer. The patients' characteristics were obtained and analysed from the electronic medical records. Patients without complete medical records were not included in our study. All data were collected in a non-identifiable fashion in accordance with the principles outlined in the Declaration of Helsinki and as required for our institutional review board approval.

Results and Discussion: A total of ten patients were included in this study, all patients were female; the mean age was 59.2 years. The mean preoperative calcium, PTH and vitamin D were 10.1 mg/dL, 99.6 pg/mL and 25.5 ng/dL, respectively. A significant decrease of intraoperative PTH and postoperative calcium and PTH were achieved after surgical treatment. Pathology reported that 50% of the cases were secondary to a single adenoma (five patients) and 50% (five patients) of the cases had parathyroid gland hyperplasia. Unilateral (70%), stages I or II (70%), invasive ductal breast carcinoma (90%) were the most common diagnosis. The immunohistochemical status reported that 80% of patients had hormone receptor positive breast cancer. The mean time between breast cancer and PHPT operations was 89.5 months.

Conclusion: Breast cancer and PHPT share several common characteristics, which has led to the postulation of common etiological pathways. However, the exact pathogenesis and the relationship between breast cancers and PHPT still remains unclear. PHPT should be considered as a possible cause of hypercalcemia in patients with non-aggressive breast cancer. We suggest that serum PTH should be determined in all breast cancer patients with increased serum calcium concentration, especially in those with no evidence of metastatic disease.

Introduction

Breast cancer is the third most common cancer in the world and in the United States of America it is the leading cause of cancer in women (except for skin cancer) and the second most common cause of cancer related deaths. Currently, the average risk of a woman born in the USA developing breast cancer at some point in her lifetime is approximately 12% [1]. Hypercalcemia is a known metabolic complication of several malignancies including breast cancer [2]. It occurs up to 30% to 40% in patients with breast cancer at some point during the course of their illness [3]. The detection of hypercalcemia in a patient with breast cancer generally signifies a poor prognosis, primarily because the presence of hypercalcemia usually indicates skeletal metastasis, but it can also be caused by Primary Hyperparathyroidism (PHPT) [4]. The most common etiologies of hypercalcemia are: PHPT and hypercalcemia of malignancy (bone metastases and humoral hypercalcemia of malignancy). The prevalence of PHPT is higher in postmenopausal women, 3% to 4%, and the origin is most often a single parathyroid adenoma [5]. It is associated with an increased risk of premature death in malignant disorders [3,4]. The differentiation between hypercalcemia caused by PHPT and

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other causes is usually easy because hypercalcemia caused by bone metastasis and humoral hypercalcemia of malignancy is associated with suppressed PTH levels [6]. PHPT has been associated with an increased risk of developing breast cancer compared with patients without it. Breast cancer is the most frequent malignant tumor diagnosed after parathyroidectomy in women, comprising 25% of all malignancies [4]. Also, an increased frequency of parathyroid adenoma and significantly higher serum calcium and parathyroid hormone levels have been documented in patients treated for breast cancer compared with healthy controls [4]. Although the association between PHPT and breast cancer is unclear, PHPT has been increasingly reported in breast cancer patients [7]. The aim of our study is to describe a cohort of patients with PHPT and breast cancer.

Materials and Methods

This is a retrospective study from a prospectively kept database of patients with PHPT treated by our group from January 2015 to July 2017 who had been diagnosed with breast adenocarcinoma at the American British Cowdray Medical Centre in Mexico City. The operations performed by our group (Sociedad Quirúrgica S.C.) consist of a bilateral neck exploration through a two-centimeter incision, and a radio-guided parathyroidectomy as described previously by various authors [7-15]. We continue to use intraoperative PTH levels (baseline, 10 minutes, 20 minutes and 30 minutes after a resection) [10,16]. The patient demographics that were obtained from our electronic medical records included age, gender, preoperative and postoperative serum calcium and PTH levels. The preoperative and postoperative vitamin D levels and the pathology results were also reviewed. Breast cancer laterality and pathology reports with immunohistochemical analysis were obtained. The pathologic stage grouping was determined according to the AJCC Staging Manual, Seventh Edition [17]. The data was analysed calculating the absolute and relative frequencies, measure of central tendency according to the variables. Patients without complete medical records were not included. All data were collected in a non-identifiable fashion in accordance with the principles outlined in the Declaration of Helsinki and as required for our institutional review board approval [18].

Results

A total of ten female patients with PHPT and breast cancer were included in this study, the mean age was 59.2 years. The mean preoperative calcium, PTH and vitamin D were 10.1 mg/dL, 99.6 pg/mL and 25.5 ng/dL, respectively. Intraoperative PTH at 10 minutes, 20 minutes and 30 minutes were 36.1, 29.6 and 24.2 pg/mL, respectively. Postoperative calcium and PTH were 8.4 mg/dL and 18 pg/mL respectively. Interestingly, pathology reported five cases with parathyroid gland hyperplasia and five cases with an adenoma. Right sided breast cancer was the most common presentation (40%), while left sided breast cancer and bilateral breast cancer was found in 30% of the cases. According to AJCC staging manual, eight patients were classified as stages I to stage II, one patient as stage III, and one patient as stage IV. The immunohistochemical status reported that eight patients had positive hormone receptors and one HER2/neu over expression. The mean time lapse between surgeries was 89.5 months (Table 1).

Discussion

The mechanisms underlying the coexistence of PHPT and certain malignancies, including breast cancer, are still unknown. The first question of interest is whether one disease clearly precedes the

Table 1: Clinical and Pathological Features.

Variable	N=10 (%/range)
Gender	
Female	10 (100)
Age (Y)	59.2 ± 9.3
Preoperative Serum Markers	
Calcium	10.1 ± 0.8
PTH	99.6 ± 15.5
Vitamin D	25.5 ± 7.9
Intraoperative PTH	
Basal	106.6 ± 41.4
Minutes	36.1 ± 22.6
Minutes	29.6 ± 18.1
30 Minutes	24.2 ± 11.6
Postoperative Serum Markers	
Calcium	8.4 ± 0.5
PTH	18 ± 15.4
Pathology Report	
Adenoma	5 (50)
Hyperplasia	5 (50)
Breast Cancer Laterality	
Bilateral	3 (30)
Unilateral	7 (70)
Right	4 (40)
Left	3 (30)
Stages	
I	4 (40)
II	4 (40)
III	1 (10)
IV	1 (10)
Immunohistochemistry	
ER	8 (80)
PR	8 (80)
HER2neu	1 (10)
Ki-67	3 (30)
Time lapse between Surgeries (months)	89.5 (1-264)

other and thus may contribute to the origin of the other. Established risk factors for breast cancer elucidate only 13% more than chance variation in breast cancer incidence among women in the United States [19]. More likely, the findings point toward the existence of a shared origin, between the two diseases, either genetic or environmental, possibly both.

Future studies may target the role of serum calcium and the association between hypercalcemia and mammographic density as well as possible gene-environmental interactions in the etiology of hyperparathyroidism and breast cancer.

Vitamin D may be a key factor, and there is evidence of potential links between vitamin D deficiency and the development and prognosis breast cancer, as well as aggravated clinical presentation of PHPT and increased parathyroid tumour growth.

Conclusion

Breast cancer and PHPT share several common characteristics, which has led to the postulation of common etiological pathways. However, the exact pathogenesis and the relationship between breast cancers and PHPT still remains obscure. PHPT should be considered as a possible cause of hypercalcemia in patients with non-aggressive breast cancer. We suggest that serum PTH should be determined in all breast cancer patients with increased serum calcium concentration, especially in those with no evidence of metastatic disease.

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