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Do Giant Parathyroid Adenomas Represent a Distinct Clinical Entity?

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Abstract

Background—The size of abnormal parathyroid glands in patients with primary hyperparathyroidism is highly variable, but the clinical significance of giant glands is unknown.

Methods—300 consecutive patients were reviewed following parathyroidectomy for primary hyperparathyroidism. We compared patients with giant parathyroid adenomas (weight ≥95th percentile) with the remaining patients.

Results—Giant adenomas were defined as weight ≥95th percentile or 3.5 grams (median 0.61 g, range 0.05–29.93). Patients with giant adenomas had a higher mean preoperative calcium level, higher mean parathyroid hormone level, and were less likely to have multiglandular or symptomatic disease. Giant adenomas were successfully localized on imaging in 87% of patients, which was not significantly increased over other patients (82%). There were no differences between the groups in age, gender, gland location, or the incidence of persistent or recurrent hyperparathyroidism. Finally, giant glands had an increased incidence of symptomatic post-operative hypocalcemia including one patient who required rehospitalization following removal of a giant gland.

Conclusions—Giant parathyroid adenomas have a distinct presentation characterized by single gland disease and lower incidence of symptoms despite increased levels of calcium and parathyroid hormone. Additionally, following resection of a giant adenoma, patients are more likely to develop symptomatic hypocalcemia.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disorder affecting over 100,000 individuals in the United States alone each year, and is the third most common endocrine disorder. PHPT is caused by autonomous secretion of parathyroid hormone from one or more of the parathyroid glands, with single gland adenomas accounting for the majority of cases [1–3]. Traditionally, patients have presented with the classic symptoms of fatigue, myalgias, bone pain, constipation, nephrolithiasis and bone demineralization [4, 5].

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However, with the advent of biochemical assays and increasing utilization of screening exams, patients are now often diagnosed with asymptomatic disease [6, 7].

Differences in presentation and management for patients with PHPT have been identified in younger patients, males, and African American patients [8–10]. It has long been observed that there exists a significant variation in the size of glands excised for PHPT. Although one study has shown a correlation with vitamin D deficiency and gland weight [11], the distinction of giant adenomas as a separate clinical entity has not been investigated. We sought to characterize the group of patients with giant parathyroid adenomas to determine whether these patients present with different preoperative symptomatology and biochemical tests. Additionally we characterized the correlation of preoperative imaging and intraoperative location, and postoperative course including differences in relative risk of persistent or recurrent hyperparathyroidism and clinically significant hypoparathyroidism compared to other patients with PHPT to determine if giant adenomas represent a clinical entity with distinct clinical characteristics.

METHODS

Patients

Following institutional review board approval, a retrospective chart review was performed on 300 consecutive patients who underwent an initial parathyroidectomy for primary hyperparathyroidism from March 2008 to September 2011 at our institution. Patients were excluded for prior parathyroidectomy, secondary or tertiary hyperparathyroidism, and other reasons for parathyroidectomy, including radical neck dissection and thyroidectomy. Parathyroidectomy was performed according to the most current guidelines from the National Institutes of Health at the time of surgery including any symptoms, age younger than 50 years, serum calcium > 1 mg/dl above the upper limit of normal, creatinine clearance of <60 ml/min, and bone density T score of less than –2.5 at any site and/or previous fragility fracture.

Data on laboratory studies, symptoms at diagnosis, imaging, gland weight, bone density, and postoperative course were retrospectively collected through review of the medical records. Asymptomatic disease was defined as patients without any of the following: kidney stones, osteoporosis, or diffuse muscle pains. Correct localization on imaging was defined as lateralization to the correct side with correct identification of single or multi-gland disease versus four gland hyperplasia. Ultrasound was performed at our institution by a radiologist and reviewed by the surgeon. Multi-glandular disease was defined as all patients with enlargement of more than one parathyroid gland. This included all patients who underwent 3.5 gland parathyroidectomy, as well as any patient who did not experience an adequate PTH drop after removal of one gland, underwent additional gland removal, and was found to have multiple hypercellular glands on pathology. Persistent hyperparathyroidism was defined as elevated calcium and parathyroid hormone at less than six months post parathyroidectomy, and recurrent hyperparathyroidism defined as HPT occurring after six months, as previously described [12, 13]. Elevated PTH with normal or low calcium was not characterized as recurrent or persistent disease in this study. Follow up is performed in accordance with surgeon preference, with one initial postoperative visit and a follow up visit at either six months or one year. Postoperative hypocalcemia was determined based on patients that presented to follow up with symptoms of hypocalcemia including perioral or extremity paresthesias, and tetany and were documented to have a low serum calcium.

Following the collection of data, patients were divided into two groups according to gland size. The 95th percentile of gland weight was greater than 3.5 grams and patients with glands at or above that weight were defined as the giant adenoma group while all other patients

were defined as the non-giant group. The 95th percentile was used as a statistical means of determining outliers and all analysis was performed according to stratification into these groups unless otherwise noted.

Statistical Analysis

Univariate statistical analysis was performed using a two-tailed Fisher's exact test for frequency association of categorical data and a two-tailed student's T test for continuous data points. Statistical calculations were performed using R (www.r-project.org). Significance was defined as $p < 0.05$ for all comparisons.

RESULTS

Three hundred patients who underwent parathyroidectomy for primary hyperparathyroidism were analyzed. Mean gland size was 1.17 grams with a standard deviation of 2.54 demonstrating the highly variable nature of gland size in PHPT. Median gland size was 0.61 g (range 0.05 g – 29.93 g) and giant glands were defined as greater than the 95th percentile, which included glands equal or greater than 3.5 g. Of the giant glands, the median size was 5.65 g (range 3.5 – 29.93 g), and the median size of the non-giant group was 0.56 g (range 0.05 – 3.2 g). There were no instances of parathyroid carcinoma in the study group. A summary of the demographics and preoperative symptoms of the study population is found in Table 1. Age and mean follow up did not differ between the two groups and there was a non-significant higher percentage of males in the giant group (33% versus 22%, $p=0.14$). Although patients with giant parathyroid adenomas had similar incidence of kidney stones (20% versus 16%, $p=0.67$), osteoporosis (45% versus 46%, $p=1.0$), and diffuse aches and pains (20% versus 28%, $p=0.77$) compared to the other group of patients, patients with giant adenomas were more likely to present with asymptomatic disease (53% versus 25%, $p=0.03$).

Preoperative laboratory and imaging studies are summarized in Table 2. Mean preoperative serum calcium (Ca) levels were higher in patients with giant adenomas (11.7 versus 10.9, $p<0.001$), as were mean preoperative serum parathyroid hormone (PTH) levels (227.6 versus 136.7, $p=0.002$), although there was no observed difference in preoperative phosphate (PO_4) (2.6 versus 2.5, $p=0.49$). Preoperative 25-OH vitamin D levels did not differ between the two groups (25.0 versus 26.6, $p=0.72$). Interestingly, increased size in the giant group did not increase the success of preoperative imaging. Independently, ultrasound accurately predicted adenoma location 79% (11/14) in giant adenomas and 76% (186/246) in the remaining population ($p=1.0$), 79% (11/14) versus 78% (213/274), $p=1.0$ for 99Tc-MIBI, and 100% (1/1) versus 64% (7/11), $p=1.0$, for 4D-CT. When all imaging modalities obtained for a given patient were used, giant adenomas were successfully localized 87% (13/15) of the time compared to 82% (235/285) for other patients ($p=0.94$). One of the incorrectly lateralized glands was located in normal anatomic right inferior gland location, and the other was located ectopically in the thymus. There was a similar incidence of ectopic glands in the giant (7%) and non-giant groups (3%, $p=0.31$).

The intraoperative findings and postoperative course are summarized in Table 3. Patients with giant adenomas were more likely to have single gland disease (93%) compared to other patients (69%), $p=0.04$. There was no difference between the two groups in the incidence of persistent (0% giant versus 2% other, $p=0.54$) or recurrent (0% versus 1%, $p=0.57$) hyperparathyroidism. Interestingly, there was a higher incidence of symptomatic postoperative hypocalcemia in the giant group (13%) compared to the non-giant patients (2%, $p=0.05$). Additionally, one patient was rehospitalized for severe symptomatic hypocalcemia following the removal of a giant adenoma.

Analysis was additionally performed according to stratification using definitions of a giant parathyroid gland as greater than the 90th percentile (2.2 g) and also of greater than 1.0 g (69th percentile). Using these stratifications for giant glands that are smaller than the definition of the 95th percentile, the following statistically significant associations with giant glands remain: patients with giant glands are more likely to present with asymptomatic disease, patients with giant glands presented with higher mean calcium and parathyroid hormone levels, and giant glands were not more likely to be correctly lateralized by individual or all imaging modalities combined. The incidence of multi-glandular disease was found to be lower in the giant group using the original 95th percentile definition as well as the 90th percentile definition, but not when giant glands were defined as larger than 1.0 g. The incidence of symptomatic postoperative hypocalcemia, which was significantly higher in giant glands using the 95th percentile definition, was not found to differ statistically between the giant and non-giant groups using either the 90th percentile or 1.0 g definition.

DISCUSSION

Although PHPT is one of the most common endocrine disorders with well documented high variability in gland size on resection, to our knowledge, no study has focused on the clinical differences for patients with giant parathyroid adenomas. In this study, which includes 300 patients from a single institution, we have identified several differences in presentation, intraoperative findings, and postoperative course in patients with giant parathyroid adenomas compared to other patients with PHPT.

As expected, patients with giant adenomas had higher mean preoperative calcium and parathyroid hormone levels, and significant correlations between gland weight, calcium, and PTH were observed. This indicates disease biology consistent with increased mass of hyperfunctioning parathyroid tissue, leading to increased autologous secretion of PTH resulting in higher calcium levels. Interestingly, patients with giant adenomas did not have a higher incidence of PHPT symptoms despite higher serum calcium and PTH, and actually were more likely to present with asymptomatic disease. One explanation is that patients with symptoms are more likely to present at an earlier disease stage and undergo parathyroidectomy before the gland could grow to the size criteria defined for a giant adenoma. Additionally, patients with giant adenomas had similar preoperative phosphate levels to the non-giant group. These results indicate that except for increased serum calcium, patients with giant adenomas appear more resistant to the physiologic effects of increased parathyroid hormone than patients with non-giant gland PHPT. It is not clear if this represents a distinct disease pathophysiology, or if patients with giant adenomas represent individuals with a different systemic response to the same disease process.

Previously, accuracy of 99Tc-MIBI scan has been shown to increase with larger gland size [14]. Our study, which was not designed to show increased accuracy over incremental changes in size, did not show a difference in accuracy in our defined giant group compared to the remaining patients and suggests that differences in localization due to gland size is due to difficult imaging for smaller adenomas. Our results of approximately 75–90% accuracy by imaging modalities are consistent with results in the published literature [15–17].

There are several limitations to this study. First, results are based on a retrospective review of 300 patients at a single institution. In this study, giant adenomas were defined by the 95th percentile of patients enrolled in the study. We performed analysis according to two additional definitions of giant glands (greater than 90th percentile and greater than 1.0 gram), but have discussed primarily the 95th percentile results because that was the definition of giant glands in our initial hypothesis, and we wanted to avoid the risk of type 1 error by over

emphasizing isolated statistically significant findings from multiple stratification points. However, there were largely similar findings at all stratification levels performed indicating a clinically distinct entity of giant adenomas. Although we were able to show several key differences between the giant and non-giant groups, it is possible that a more relevant pathophysiologic definition could be identified to better distinguish the groups. Finally, the data highlighted in this study are based on the 15 patients in the giant adenoma group, which poses selection bias due to the small number. Despite these limitations we did observe differences in patients with giant adenomas compared to the non-giant group, indicating that patients with giant adenomas have a distinct clinical presentation and potentially indicating a functionally distinct pathophysiology.

In summary, this study compares differences between patients with giant parathyroid adenomas and other patients with PHPT. Giant adenomas present with increased serum calcium and PTH levels and have a higher rate of asymptomatic disease. They are more likely to be single gland than other patients with PHPT, but are not more accurately localized by ultrasound, 4D-CT, or Tc99-MIBI scan. Finally, no differences were observed in persistent or recurrent PHPT, but patients having had a giant parathyroid adenoma removed should be followed closely, possibly with a lower threshold for calcium or vitamin D supplementation due to increased risk of symptomatic postoperative hypocalcemia.

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Table 1

Demographics and Symptoms

Parameter	Non-Giant (n=285)	Giant (n=15)	p-value
Age	59.7 +/- 13.9	59.3 +/- 9.8	0.90
Gender (Male)	63 (22%)	5 (33%)	0.14
Median Follow up (months)	6.6 +/- 9.2	7.2 +/- 8.8	0.82
Asymptomatic	71 (25%)	8 (53%)	0.03
Kidney Stones	46 (16%)	3 (20%)	0.67
Osteoporosis	131 (46%)	6 (45%)	1.0
Diffuse Pains	80 (28%)	3 (20%)	0.77

Table 2

Preoperative Laboratory Values and Imaging Results

Labs/Imaging	Non-Giant (n=285)	Giant (n=15)	p-value
Mean Ca (mg/dl)	10.9 +/- 0.8	11.7 +/- 1.0	<0.001
Mean PO ₄	2.5 +/- 0.5	2.6 +/- 0.6	0.49
Mean PTH (pg/ml)	136.7 +/- 111.3	227.6 +/- 238.6	0.002
Mean 25-OH Vit D (ng/ml)	26.6 +/- 5.3	25.0 +/- 2.6	0.72
Correct imaging (US)	186/246 (76%)	11/14 (79%)	1.0
Correct imaging (99Tc-MIBI)	213/274 (78%)	11/14 (79%)	1.0
Correct imaging (4D CT)	7/11 (64%)	1/1 (100%)	1.0
Correct imaging (All)	235/285 (82%)	13/15 (87%)	0.94

Table 3

Intraoperative Findings and Postoperative Course

Clinical Finding	Non-Giant (n=285)	Giant (n=15)	p-value
Multi-gland disease	88 (31%)	1 (7%)	0.04
Persistent HPT	5 (2%)	0 (0%)	0.54
Recurrent HPT	3 (1%)	0 (0%)	0.57
Post-OP Hypocalcemia	5 (2%)	2 (13%)	0.05