Giant Parathyroid Adenomas: Differential Aspects Compared to Atypical Parathyroid Adenomas

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ABSTRACT

Primary hyperparathyroidism is a common diagnosis, often caused by a parathyroid adenoma, which can be resolved with surgical excision. However, pre-operative diagnosis of the causative adenoma may be challenging given the overlapping presentations and laboratory findings in typical, giant, and atypical parathyroid adenomas. In this case series, we describe one of the largest giant parathyroid adenomas excised in the United States and compare its presentation to that of an atypical parathyroid adenoma. Using this comparison, we aim elucidate the diagnostic value of various presentation characteristics, such as adenoma size, mass effect, symptom burden, and biochemical derangements.

Keywords: Hyperparathyroidism; Parathyroid neoplasms; Parathyroid adenoma

INTRODUCTION

Primary hyperparathyroidism is most often caused by a parathyroid adenoma, which can be resolved with surgical excision. A typical parathyroid gland weighs 30–50 mg and measures 5 mm in its greatest dimension, while adenomas can weigh as much as 500–1,000 mg and measure 1 cm or larger. Giant parathyroid adenomas have been defined as those that weigh 3.5 g or greater (1). Giant parathyroid adenomas are often associated with more aberrant biochemical findings as compared to typical adenomas, including greater preoperative calcium and parathyroid hormone (PTH) levels as well as an increased incidence of postoperative hypocalcemia (2,3).

Primary hyperparathyroidism can also be caused by multiple gland disease/hyperplasia, atypical parathyroid adenomas, or parathyroid carcinomas. Atypical parathyroid adenomas account for around 1.2%–1.3% of primary hyperparathyroidism and consist of parathyroid neoplasms of uncertain malignant potential with atypical histological features (4). These adenomas commonly have thick fibrous bands, trabecular growth patterns, and mitotic activity (5). Like those with giant parathyroid adenomas, patients with atypical parathyroid adenomas tend to have higher serum calcium levels, higher PTH, and be larger in size and weight, when compared to typical adenomas (4). In fact, atypical parathyroid adenomas have been reported to be even larger than giant parathyroid adenomas, on average (5,6).
This case series describes one of the largest giant parathyroid adenomas excised in the United States and compares its presentation to that of an atypical parathyroid adenoma.

**CASE REPORT**

1. Giant parathyroid adenoma case presentation

Our patient is a male in his 80s with biochemically confirmed primary hyperparathyroidism with a PTH level of 140 and a calcium level of 11.1. He had a personal history of nephrolithiasis for which he underwent lithotripsy.

He underwent localization workup including a 4-dimensional computed tomography (4D CT) scan that revealed a 4.8×3.6×2.9 cm cystic lesion identified inferior to the right of the thyroid gland. He also underwent an ultrasound showing a 5.5×2.4×3.0 cm cystic lesion containing low level internal echoes abutting and inferior to the right thyroid lobe. The appearance did not seem typical of a parathyroid adenoma.

This patient case was selected given that it is one of the largest giant parathyroid adenomas excised in the United States.

Operative approach

We performed a minimally invasive parathyroidectomy targeted to the right paraesophageal location with resection of a large, paraesophageal right upper parathyroid adenoma.

A 5-cm transverse (Kocher) incision was created approximately 2 fingerbreadths above the clavicles, to lie parallel to the existing skin creases. Dissection was carried down through the subcutaneous tissue and the platysma using electrocautery. The strap muscles were divided vertically along the median raphe.

Attention was turned to the right side. The strap muscles were retracted laterally and the right lobe of the thyroid gland was retracted medially. The middle thyroid vein was divided. An enlarged parathyroid gland was identified in the right paratracheal position, extending deep into the posterior mediastinum, and extending below the right clavicle. It was dissected free from the surrounding tissue, its pedicle was divided, and it was removed.

Intraoperative PTH assay was utilized (reference range 10–65 pg/mL).

- Baseline prior to surgical manipulation=166 pg/mL
- At time 0 minutes following resection=63 pg/mL
- At time 5 minutes following resection=52 pg/mL
- At time 10 minutes following resection=43 pg/mL
- At time 15 minutes following resection=37 pg/mL

The specimen was aspirated ex vivo, and the aspirate demonstrated PTH levels greater than the assay scale, confirming that parathyroid tissue had been resected. The specimen was then sent to pathology for permanent section.

These results indicated biochemical cure of primary hyperparathyroidism; therefore, further exploration was not performed.
Hemostasis was achieved. The strap muscles were approximated in the midline using interrupted 3-0 Vicryl suture. The platysma was closed using interrupted 4-0 Vicryl suture. The skin was closed using 5-0 Biosyn subcuticular suture.

The patient was awakened from anesthesia and was found to have tolerated the procedure well. He was discharged on post operative day 1 and was doing well at this follow up visit.

Pathology
Final pathology revealed an enlarged cystic parathyroid gland measuring 5.2 cm in dimension and weighing 5,257 mg (Fig. 1).

2. Atypical parathyroid adenoma case presentation
Our second patient is a male in his 50s with a known history of schizophrenia for which he takes Lithium, hypothyroidism and hyperlipidemia, who presented to the hospital in the setting of worsening dizziness and nausea for 2 weeks. He had no personal history of kidney stones. A review of his previous laboratory studies suggested a slow increase in serum calcium over time.

During this urgent admission his laboratory values confirmed primary hyperparathyroidism with a hypercalcemic crisis with a calcium of 14.9 and a PTH of 243 (Fig. 2). To manage him expeditiously the patient was started in aggressive fluid hydration as well as Sensipar.
Further diagnostic workup included a thyroid ultrasound which showed a 4.3 cm mixed cystic and solid lesion abutting the lateral aspect of the left thyroid lobe. This structure was re-demonstrated on 4D CT scan showing a mixed solid and cystic enhancing soft tissue density posterior to the left thyroid lobe which measured 3.5×2.2×4.3 cm (Fig. 3).

Our patient was taken for a minimally invasive parathyroidectomy during his admission due to his hypercalcemic crisis.

Operative approach
The operation was completed as described above. An extremely large parathyroid mass was identified posterior to the lobe, and extending the full length of the left thyroid lobe. It was noted to have a distinct plane, separate from the thyroid and surrounding structures, including the trachea, esophagus and left recurrent laryngeal nerve. It was dissected free from the surrounding tissue, its pedicle was divided, and it was removed.

Intraoperative PTH assay was utilized (reference range 10–65 pg/mL).
- Baseline prior to surgical manipulation=291 pg/mL
- At time 0 minutes following resection=34 pg/mL
- At time 5 minutes following resection=34 pg/mL
- At time 10 minutes following resection=28 pg/mL

Pathology
Final pathology revealed an atypical parathyroid tumor measuring 5.3 cm in dimension and weighing 8,350 mg.

DISCUSSION

Primary hyperparathyroidism is one of the most common endocrine pathologies and is characterized by hypercalcemia and inappropriately normal or elevated PTH (7). It can be caused by excess hormone secretion secondary to a parathyroid adenoma or, more rarely, by an atypical adenoma, parathyroid hyperplasia, or carcinoma. Primary hyperparathyroidism
is usually diagnosed with clinical and laboratory findings, and patient history may include complaints of nephrolithiasis, polyuria, polydipsia, constipation, bone pain, and/or mental disturbances. The only definitive therapy for primary hyperparathyroidism is parathyroidectomy, typically of a singular, causative adenoma. While parathyroid adenomas often weigh 500–1,000 mg (more than 30 times the weight of an average parathyroid gland), giant parathyroid adenomas are even larger – defined as weighing 3.5 g or more (1).

In this case series, we first describe the presentation, excision, and pathology of one of the largest giant parathyroid adenomas excised in the United States. Our patient presented with isolated symptomatology consisting of nephrolithiasis, but denied other common complaints of primary hyperparathyroidism, such as bone pain or cognitive dysfunction. While patients with giant parathyroid adenomas tend to have similar incidence of symptoms when compared to those with non-giant parathyroid adenomas, those with giant parathyroid adenomas are more likely to present with asymptomatic disease (2). Regardless of adenoma size, the incidence of asymptomatic hyperparathyroidism has increased in recent years with more extensive laboratory testing identifying biochemical abnormalities early in the disease process (8,9). The greater likelihood of giant parathyroid adenomas presenting with asymptomatic disease has been attributed to both (1) the mass effect of the tumor leading patients to seek medical attention prior to symptom-onset and (2) symptomatic parathyroid adenomas resulting in earlier discovery and excision, before having an opportunity to grow to the size of a giant parathyroid adenoma (2,3). Our patient presented with symptomatic disease, had no complaints related to the mass effect of the tumor, and no masses were palpable on exam—leading to little suspicion of a giant parathyroid adenoma, absent pre-operative imaging findings.

In addition to presentation differences found between giant and non-giant parathyroid adenomas, there may be biochemical variations in disease manifestation. Giant parathyroid adenomas are associated with greater mean preoperative calcium levels and greater mean PTH, 11.7 mg/dL and 227.6 pg/mL respectively by one study (2). However, our patient was found to have a calcium of 11.1 and PTH level of 140 pg/mL, which fall within expected values for primary hyperparathyroidism, and closer to the reported mean biochemical values of non-giant parathyroid adenomas than those of giant parathyroid adenomas (2). Finally, our patient did not develop symptomatic post-operative hypocalcemia, which is reported more frequently in those with giant parathyroid adenomas (13% of giant parathyroid adenomas vs. 2% of non-giant parathyroid adenomas, by one study) (2).

While giant parathyroid adenomas may often present distinctly from non-giant parathyroid adenomas, our patient represents a somewhat typical presentation of primary hyperparathyroidism despite the extraordinarily large size of the mass. Biochemical and symptomatic characteristics may help one diagnose giant parathyroid adenomas as a distinct clinical entity, but the absence of these findings cannot rule out a giant parathyroid adenoma.

Clinical and biochemical characteristics can also help differentiate giant parathyroid adenomas from atypical parathyroid adenomas. Atypical parathyroid adenomas have been reported to be larger than giant parathyroid adenomas on average (5). One study found the median size of an atypical parathyroid adenoma to be 2.5 cm with a median weight of 4.15 g (5). With a weight cutoff for giant parathyroid adenomas of greater than 3.5 g, the median atypical thyroid adenoma would be heavier than many giant parathyroid adenomas, despite the nomenclature. In our case series we report an atypical parathyroid adenoma that weighs 158% more than its giant parathyroid adenoma counterpart.
Similar to giant parathyroid adenomas, atypical parathyroid adenomas tend to have more biochemically severe presentations when compared to typical adenomas. Atypical parathyroid adenomas tend to biochemically mimic parathyroid carcinomas, with moderate hypercalcemia and elevated PTH levels. In one study of atypical parathyroid adenomas, median calcium was 12.9 mg/dL and median serum PTH was 430 ng/L (5). Another reported pre-operative serum calcium of 13.6 mg/dL and preoperative intact PTH of 1,198.7 pg/mL (4). Therefore, serum calcium and PTH for atypical parathyroid adenomas are often even greater than those reported for giant parathyroid adenomas, indicating a utility of biochemical profiling in distinguishing typical vs. giant vs. atypical parathyroid adenomas. These differences can be appreciated in our case series, as our patient with an atypical parathyroid adenoma presented in hypercalcemic crisis (14.9 mg/dL) and was found to have a PTH of 243, as compared to a calcium of 11.1 and PTH of 140 in our patient with a giant parathyroid adenoma.

The symptomatic profile of atypical parathyroid adenomas is quite similar to that of a giant or typical parathyroid adenoma, including nephrolithiasis, fatigue, bone pain, and depression (5). However, unlike giant parathyroid adenomas which are more likely to present asymptomatically when compared to typical adenomas, atypical parathyroid adenomas are more likely to present with symptomatic hypercalcemia and fragility fractures at the time of diagnosis (5). Our patient with an atypical parathyroid adenoma was, in fact, more acutely symptomatic than the patient in our giant parathyroid adenoma case, presenting in hypercalcemic crisis.

Although giant and atypical parathyroid adenomas may be difficult to distinguish, the size, likelihood of symptomology, and degree of biochemical derangements may be valuable in elucidating the identity of a mass pre-operatively.

**CONCLUSION**

In this case series, we describe the presentation, excision, and pathology of one of the largest giant parathyroid adenomas excised in the United States and compare its presentation to that of typical and atypical parathyroid adenomas. Despite the anomalous size of the giant adenoma, the patient’s presentation, regarding symptom burden, lack of mass effect, and laboratory findings, was largely in line with primary hyperparathyroidism secondary to a typical parathyroid adenoma. Furthermore, our patient with an atypical parathyroid adenoma had a larger adenoma and more severe symptomatic and biochemical profile. While patient presentation and biochemical markers may help narrow the differential diagnosis of a mass precipitating primary hyperparathyroidism, final pathology may be still be needed to identify a typical vs. giant vs. atypical parathyroid adenoma, given overlapping presentations.

**REFERENCES**


