OCCULT PRIMARY HYPERPARATHYROIDISM: A CASE REPORT AND REVIEW OF PARATHYROID ULTRASONOGRAPHY

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ABSTRACT

Objective: To discuss the diagnosis and management of occult primary hyperparathyroidism.
Methods: We present the biochemical and radiologic evaluation, treatment, and outcome of a woman with occult primary hyperparathyroidism which presented as an unusual neck mass on ultrasound. We also present a relevant literature review.
Results: A 52-year-old female presented with Hashimoto thyroiditis and a 1.2-cm, hypoechoic oval nodule in the left upper lateral portion of the thyroid. She returned a decade later with a 2.2-cm, hypervascular mass on ultrasound. Parathyroid hormone was mildly elevated at 90 pg/mL (reference range is 15 to 65 pg/mL), but she had persistently normal levels of total serum calcium at 9.9 mg/dL (reference range is 8.7 to 10.3 mg/dL), phosphorus at 3.5 mg/dL (reference range is 2.1 to 4.5 mg/dL), and albumin at 4.4 g/dL (reference range is 3.6 to 4.8 g/dL). She had elevated ionized calcium of 5.9 mg/dL (reference range is 4.5 to 5.6 mg/dL). Computed tomography with contrast of the neck revealed an enhancing oval lesion abutting the superior pole of the left thyroid with attenuation characteristics similar though slightly different from the thyroid. 99mTc-Sestamibi scan showed increased uptake posterior to the superior aspect of the left thyroid. Bone densitometry showed osteoporosis of the left distal radius and osteopenia of the left femoral neck. Minimally invasive radio-guided parathyroidectomy was performed with normalization of parathyroid hormone. Pathology confirmed a 1.715-g parathyroid adenoma.

Conclusion: Despite normal total calcium levels, clinically significant primary hyperparathyroidism may present as a large adenoma which could appear as a hypervascular neck mass on ultrasound. A high index of suspicion based on ultrasound features and measurement of ionized calcium may be helpful in diagnosing occult, but clinically relevant primary hyperparathyroidism.

INTRODUCTION

Classically, primary hyperparathyroidism (PHPT) is characterized by hypercalcemia and hypophosphatemia secondary to increased production of parathyroid hormone (PTH) independent of calcium level. Hypercalcemia in otherwise healthy outpatients is usually due to PHPT (1). PHPT is a common clinical problem encountered in endocrinology practices, affecting 0.3% of the general population (2). Parathyroid adenomas are responsible for around 80% of cases, while diffuse 4-gland hyperplasia or malignancy is responsible for the balance of cases (3). Many patients with PHPT present with only modest elevations in serum calcium and PTH, often resulting in asymptomatic disease or mild symptoms (4). In fact, a majority of patients have no symptoms at the time of diagnosis. Those with clinical manifestations may present with arthralgias,
bone pain, paresthesia, cramps, weakness, irritability, polyuria, pruritus, and nephrolithiasis (5).

Normal parathyroid glands are shaped like small flattened disks, measuring approximately 6 mm in the cranio-caudal dimension and 3 mm in the transverse dimension (6). They are not usually identified on neck ultrasound (US), making a visible parathyroid gland suspicious for the presence of a pathological entity (7). Due to the increased use of high-resolution US, an increasing number of parathyroid incidentalomas are being detected (6). The frequency of observing incidental parathyroid tumors is <1% (8,9). The prognosis for future development of hyperparathyroidism in parathyroid incidentalomas is currently not known (10).

Our patient is a rare case of occult PHPT which caused osteoporosis but only had borderline biochemical abnormalities. The patient was found to have a large parathyroid adenoma after she presented with an atypical neck mass on US. To the best of our knowledge, this is the first description of a large parathyroid adenoma discovered incidentally as a neck mass on US and found to have adverse downstream effects in the form of osteoporosis while total calcium levels remained in the normal range.

CASE REPORT

A 52-year-old female initially presented with Hashimoto thyroiditis and a thyroid nodule. She had no local compressive symptoms. She had a past medical history of gastroesophageal reflux disease. Her medications included levothyroxine at 88 µg daily for the last 5 years and esomeprazole at 40 mg daily or omeprazole at 10 to 40 mg daily, taken intermittently for the last 5 years. Family history was non-contributory.

Thyroid-stimulating hormone was 2.59 mIU/mL (reference range is 0.29 to 5.10 mIU/mL) and total thyroxine was 5.2 µg/dL (reference range is 4.5 to 12.5 µg/dL). Thyroid US showed a hypoechoic, oval nodule in the left upper lateral portion of the thyroid immediately adjacent to the carotid artery measuring 1.2 × 0.9 × 0.7 cm. Doppler demonstrated prominent flow within this nodule. The rest of the thyroid was unremarkable.

The patient was subsequently lost to follow up and returned 10 years later. Her body mass index was 26.0 kg/m² and neck exam was benign with no appreciable masses or thyromegaly. Thyroid US now showed that the lesion had significantly increased in size to 2.2 × 1.1 × 1.0 cm. It was located superior and lateral to the left thyroid lobe. The lesion appeared hypoechoic as compared to the thyroid parenchyma and was markedly hypervascular (Fig. 1). Differential diagnoses included ectopic thyroid nodule, parathyroid lesion, lymph node, tumor, or vascular malformation. Of note, all previous serum calcium levels during the last decade were normal ranging 9.8 to 9.9 mg/dL (reference range is 8.5 to 10.2 mg/dL).

In order to better characterize the lesion a contrast-

![Fig. 1. Thyroid ultrasound showing a mass in the neck by left transverse and sagittal views with color doppler.](image-url)
enhanced computed tomography scan of the neck was performed which showed a corresponding 1.9 × 1.8 × 0.8-cm, oval enhancing lesion abutting the superior pole of the left thyroid lobe. A thin fat plane separated the lesion from the thyroid gland. The attenuation characteristics were similar though slightly different from the adjacent thyroid parenchyma, with the lesion measuring 145 Hounsfield units and the thyroid parenchyma measuring 177 Hounsfield units.

Biochemical workup revealed mildly elevated PTH of 85 pg/mL and 90 pg/mL (reference range is 15 to 65 pg/mL) checked roughly 6 months apart, with calcium of 9.9 mg/dL on both occasions (reference range is 8.7 to 10.3 mg/dL) and albumin of 4.4 g/dL (reference range is 3.6 to 4.8 g/dL). She had one elevated ionized calcium reading of 5.9 mg/dL (reference range is 4.5 to 5.6 mg/dL) followed by 2 normal repeat readings at 5.6 mg/dL and 5.4 mg/dL. Phosphorous was 3.3 mg/dL and 3.5 mg/dL (reference range is 2.5 to 4.5 mg/dL), 25-hydroxyvitamin D was 46.7 ng/mL (reference range is 30.0 to 100.0 ng/mL) and 24-hour urinary calcium excretion was elevated at 370.8 mg/day (reference range is 100 to 300 mg/day). Creatinine was 0.8 mg/dL (reference range is 0.57 to 1.00 mg/dL), glomerular filtration rate was 76 mL/min/1.73 (reference range is >59 mL/min/1.73), aspartate transaminase was 36 IU/L (reference range is 0 to 40 IU/L), alanine transaminase was 25 IU/L (reference range is 0 to 32 IU/L), and alkaline phosphatase was 78 IU/L (reference range is 39 to 117 IU/L).

A 99mTc-Sestamibi scan showed increased uptake posterior to the superior aspect of the left thyroid lobe which correlated to the lesion seen on US (Fig. 2). Dual-energy X-ray absorptiometry (DEXA) scan showed osteoporosis of the left distal radius (T score -2.9, bone mineral density (BMD) 0.700 g/cm²), left femoral neck osteopenia (T score -2.0, BMD 0.758 g/cm²) and normal BMD of the lumbar spine (T score -0.1, BMD 1.188 g/cm²). These findings were suggestive of cortical bone loss from hyperparathyroidism. A DEXA scan from 4 years prior showed osteopenia of the left femoral neck (T score -1.4, BMD 0.842 g/cm²) with normal BMD at the spine (T score -0.5, BMD 1.243 g/cm²). Retroperitoneal US showed no evidence of nephrolithiasis. A presumptive diagnosis of PHPT was made which met criteria for surgery due to the presence of osteoporosis (11). She underwent a minimally invasive, radio-guided parathyroidectomy of the left superior parathyroid gland (12). Pathology confirmed a 1.715-g left superior parathyroid adenoma measuring 2.5 × 1.7 × 0.8 cm.

Follow-up biochemical workup 1 month after surgery showed normalization of PTH levels to 47 mg/dL, calcium of 9.4 mg/dL, albumin of 5.5 g/dL, ionized calcium of 5.4 mg/dL, and 25-hydroxyvitamin D of 30.7 ng/mL (Table 1). Follow-up thyroid US confirmed that the previously noted nodule lateral to the left thyroid lobe was no longer visualized. A postoperative DEXA scan completed 1 year later showed improvement in BMD of the left distal radius (T score -1.7, BMD 0.729 g/cm²) and left femoral
neck (T score -1.9, BMD 0.781 g/cm²). This represented a 5% improvement in BMD in the left distal radius and 3% improvement in BMD in the left femoral neck.

**DISCUSSION**

Unlike the common clinical scenario where PHPT is diagnosed following laboratory tests showing mild hypercalcemia, our case presented as a large, hypervascular neck mass on thyroid US with normal serum calcium levels. PHPT may also be diagnosed during the workup of calcium nephrolithiasis or osteoporosis. Normocalcemic hyperparathyroidism is a form of PHPT with elevated PTH levels in the absence of hypercalcemia and these patients often come to medical attention during the evaluation for low BMD. However, to make a diagnosis of normocalcemic hyperparathyroidism, all secondary causes of elevated PTH should be ruled out and ionized calcium should be normal (13). One may consider normocalcemic hyperparathyroidism to be a milder variant of PHPT while noting that BMD can be low with preferential involvement of cortical sites (14). In one prospective study of 37 patients with normocalcemic hyperparathyroidism, evaluation for classical features of PHPT revealed a history of kidney stones in 5 (14%), fragility fractures in 4 (11%), and osteoporosis in 57% of patients (34% in spine, 38% in the hip, and 28% in the distal third of the radius) (15).

In our case, a complete workup revealed normal total calcium levels, but one elevated ionized calcium level in the setting of elevated PTH levels. Two repeat ionized calcium level readings were at the upper-limit of normal. While ionized calcium is not the easiest or cheapest to measure, it is the most physiologically relevant measure of calcium homeostasis (16). Several studies have concluded that total calcium or albumin-corrected calcium tend to misclassify a significant proportion of patients with derangements in calcium homeostasis when ionized calcium is used as the gold standard (16). In concordance with these findings, ionized calcium was crucial for diagnosing occult PHPT in our case. In addition, 24-hour urinary calcium excretion was found to be elevated. Thus, the patient’s overall clinical and biochemical picture was consistent with PHPT, for which she successfully underwent a minimally invasive, radio-guided parathyroidectomy.

Most parathyroid adenomas are juxtathyroid, located immediately posterior or inferior to the thyroid gland (17). Parathyroid adenomas are typically small, less than 1 cm in size, oblong nodules which are usually not hypervascular (18). The most typical imaging characteristic of parathyroid adenoma is the homogenously hypoechoic echogenicity in relation to the thyroid gland (19). Interestingly, they can change their contour due to pressure from surrounding anatomical structures and therefore have variable shapes on US (18). Parathyroid adenomas have an extrathyroidal polar artery as a feeding blood vessel in 83% of adenomas (18,19). Besides the polar artery, a vascular arc-like pattern of blood flow has been associated with high specificity for parathyroid adenomas (10,20). This appears as a continuous or discontinuous vascular arc surrounding the abnormal parathyroid gland from a minimum of 90 to 270 degrees. In one study, all patients with a positively identified arc had parathyroid adenomas (20). Color Doppler is not considered to be sensitive for initial detection of adenomas, but instead appears to be useful in improving diagnostic specificity once the mass is detected, with approximately 63% of cases showing demonstrable blood supply on sonogram (20).

The US appearance of the parathyroid adenoma in this case was highly unusual. The adenoma measured 2.2 cm, much larger than typical parathyroid adenomas, and was hypervascular with markedly increased central nodular blood flow. Due to its large size and unusual characteristics, the differential also included a mass of thyroid origin, abnormal lymph node, or vascular malformation. One would intuitively expect that elevated levels of serum calcium and PTH should positively correlate with parathyroid adenoma size, however the literature on this subject is equivocal (21,22). A predictive model using preoperative calcium and PTH has been studied to predict adenoma weight, size, and volume (21). Based on this predictive model, calcium and PTH levels were likely elevated in our case, indicating the presence of a parathyroid adenoma.

### Table 1

<table>
<thead>
<tr>
<th>Biochemical and Bone Density Measurements Before and After Parathyroidectomy</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td>90</td>
<td>47</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Ionized calcium (mg/dL)</td>
<td>5.9</td>
<td>5.4</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/mL)</td>
<td>46.7</td>
<td>30.7</td>
</tr>
<tr>
<td>BMD, left distal radius (g/cm²)</td>
<td>0.700</td>
<td>0.729</td>
</tr>
<tr>
<td>BMD, left femoral neck (g/cm²)</td>
<td>0.758</td>
<td>0.781</td>
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Abbreviation: BMD = bone mineral density.
model, our patient’s normal preoperative calcium levels and borderline-elevated PTH of 90 mg/dL would predict an adenoma measuring 0.85 g, 1.49 cm, and 0.99 cm³ (21). However, the actual size of the adenoma was 1.715 g, 2.5 cm, and 1.8 cm³, suggesting that our patient’s tumor possessed unusual characteristics. Correlation between biochemical variables and adenoma mass in a retrospective data analysis of 77 patients with PHPT showed that biochemical markers cannot accurately predict adenoma size (23). The presentation of a large parathyroid adenoma in association with minimally elevated PTH levels in our case is concordant with previous reports.

However, this case highlights an unusual path to the diagnosis of symptomatic PHPT. PHPT was discovered following an abnormal US finding of the adenoma itself versus elevated serum calcium levels as is the typical detection method for PHPT. This patient was found to have clinically significant osteoporosis with borderline-elevated PTH levels and normal total calcium and phosphorous levels. It is important to note that even in mild cases of PHPT, excess PTH can increase bone turnover leading to bone loss particularly at cortical sites as seen in our case (24). The DEXA scan one year after surgery showed marked improvement in BMD, decreasing lifetime risk of fracture in this patient with occult PHPT.

CONCLUSION

This case highlights that clinically significant PHPT may first be detected as an incidental finding of a large parathyroid adenoma with atypical features on US. The adenoma may measure >2 cm in size and may be hypervascular. These unusual parathyroid adenomas may produce significant downstream clinical effects such as osteoporosis, while calcium and phosphorous levels remain normal for years, making their diagnosis illusive. Measurement of ionized calcium may be helpful in the diagnosis of occult, yet clinically significant PHPT.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES