Clinicopathologic and therapeutic aspects of giant parathyroid adenomas – three case reports and short review of the literature

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Abstract
In the last decade, the clinical picture of primary hyperparathyroidism has changed, with the majority of patients being diagnosed while symptomatic and the “classical” clinical pattern characterized by bone disease, recurrent nephrolithiasis, peptic ulcer disease, neurological or psychiatric disorders being rarely encountered. In this context, most patients have minimal hypercalcemia and small parathyroid adenomas. Not surprisingly, giant parathyroid adenomas have seldom been described in the literature. We herein report three cases of giant parathyroid adenomas weighing more than 30 g and discuss their clinicopathological and therapeutic particularities. We also review the relevant literature, with the principal aim of outlining the rarity of these giant parathyroid adenomas and the issues concerning their diagnosis and treatment.

Keywords: giant parathyroid adenoma, parathyroid crisis, primary hyperparathyroidism.

Introduction
Primary hyperparathyroidism (pHPT) is a common disease, with an incidence of 25/100 000 in the general population [1] and up to 1:500 in postmenopausal women [2]. The disease is more frequent among older women (F:M ratio 3–4:1), with a peak of incidence between 50–60 years [3, 4]. It is generally caused by a solitary parathyroid adenoma (approximately 80–90% of cases) and few patients present with multigland hyperplasia (10–15%), double adenomas or carcinoma (1–4%) [3].

Though much larger than the normal parathyroid gland, whose weight is estimated to be 50–70 mg, majority of parathyroid adenomas generally remain relatively small in size and weigh no more than 1 g. There are very few giant adenomas described in the literature and weighing more than 30 g [5].

Nowadays, pHPT is commonly diagnosed in asymptomatic patients having routine calcium tests. Rarely, the diagnosis is suspected based on few unspecific clinical symptoms such as neuromuscular weakness, osteoarticular pains, vague abdominal complaints but the final diagnosis is established through laboratory tests [1, 5]. The “classical” clinical picture of pHPT including bone disease, recurrent nephrolithiasis, peptic ulcer disease along with the clinical picture of parathyroid crisis are seldom seen today.

Here we report three cases of giant parathyroid adenomas, which all have some interesting clinicopathologic and therapeutic particularities. We also review the relevant literature, with the principal aim of outlining the rarity of these giant parathyroid adenomas and the issues concerning their diagnosis and treatment.

Patients, Methods and Results
Case No. 1

A 57-year-old man was admitted for worsening osteoarticular pains, muscular weakness, nausea and intermittent abdominal pains. For the past 10 years, he had recurrent renal stones. The patient had osteoporosis with low bone mineral density (BMD) at spine level (L1–L4) (T-score -2.6 on dual-energy X-ray absorptiometry, DEXA). His medical history also revealed a longstanding ischemic and hypertensive heart disease, left leg post-thrombotic syndrome, prostate adenoma under medical treatment, dyslipidemia and grade 1 obesity. He reported no significant family history.

His body habitus was normal (body mass index 31.5 kg/m²). Physical examination revealed a painless lump in the lower part of the right thyroid lobe, relative firm and moving during swallowing.

The blood chemistry on admission is shown in Table 1 (Case No. 1). In the presence of very high serum intact parathormone level (iPTH), hypercalcemia and low serum phosphate, he was diagnosed with severe primary hyperparathyroidism.

Table 1 – Laboratory findings in three cases of giant parathyroid adenomas

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case No. 1</th>
<th>Case No. 2</th>
<th>Case No. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (nv: 9–11 mg/dL)</td>
<td>14.14</td>
<td>16.17</td>
<td>12.58</td>
</tr>
<tr>
<td>Phosphate (nv: 2.7–4.5 mg/dL)</td>
<td>2.1</td>
<td>1.58</td>
<td>1.14</td>
</tr>
<tr>
<td>Alkaline phosphatase (nv: 98–278 U/L)</td>
<td>845</td>
<td>425</td>
<td>1181</td>
</tr>
<tr>
<td>Vitamin D (nv: 50–125 nmol/L)</td>
<td>53</td>
<td>65</td>
<td>72</td>
</tr>
</tbody>
</table>
Variable | Case No. 1 | Case No. 2 | Case No. 3
--- | --- | --- | ---
TSH (nv: 0.34–4.31 UI/mL) | 0.413 | 0.094 | 1.278
FT4 (nv: 0.82–1.63 ng/dL) | 1.14 | 0.76 | 0.99
iPTH (nv: 15–68 pg/mL) | 1780 | 863 | 1174

nv – Normal values; TSH – Thyroid Stimulating Hormone; FT4 – Free Thyroxine; iPTH – Intact Parathormone.

Medical treatment with low calcium diet, diuretics and bisphosphonates was initiated while he had further investigations. Cervical ultrasonography revealed a hypoechoic mass, measuring 54×22×12 mm, with augmented vascular Doppler signal at the periphery, which appeared to correspond to the right inferior parathyroid gland (Figure 1A). Scintigraphy with technetium 99mTc Methoxyisobutylisonitrile (99mTc-MIBI) showed an uptake compatible with an adenoma of the right inferior parathyroid gland, concordant with the position corresponding to the mass revealed at ultrasonography (Figure 1B).

The patient underwent bilateral neck exploration. A giant right lower parathyroid adenoma (5×3×2 cm, weight 30.6 g) was identified and excised. It had no macroscopic signs of malignancy (no local invasion, no lymphadenopathy). Three normal parathyroids were also identified (Figure 2, A and B).

Intraoperative iPTH assay was not feasible but immediate (one hour) postoperative serum iPTH was 36.3 pg/mL (nv: 15–68 pg/mL). Histology revealed a parathyroid adenoma with mixed compact and pseudofollicular features, without any pathological features usually associated with malignancy, i.e., fibrous bands, infiltration of the thyroid or of the surrounding muscle tissue, nuclear pleomorphism, capsular or vascular invasion (Figure 3).

Postoperatively, the patient developed “hungry bones” syndrome and required strict serum calcium monitoring, with Calcium Gluconate infusion and Alfacalcidol supplementation. After the first two postoperative weeks, calcium infusions were gradually replaced with oral medication, the patient being discharged to home. After one year of follow-up, he is completely asymptomatic, with no renal stones recurrence, normal serum calcium, phosphorus and iPTH levels.

Case No. 2

A 60-year-old woman presented as an emergency with extreme fatigability, muscular weakness, nausea and vomiting and dehydration. She had a 20-years history of hypothyroidism on substitutive treatment with L-Thyroxine and 2-years history of acid peptic disease and recurrent renal colics.

Physical examination revealed moderate dehydration syndrome, tachycardia, non-specific abdominal pain. A painless lump in the lower part of the left thyroid lobe was also noted, the rest of the physical examination being unremarkable.

On admission, the blood chemistry showed severe hypercalcemia (16.17 mg/dL; nv: 9–11 mg/dL); the rest of laboratory data are noted in Table 1 (Case No. 2).

Given her clinical and biochemical profile, a para-
thyroid crisis was diagnosed and the patient underwent initial intensive medical treatment with intravenous fluids, loop diuretics, bisphosphonates. Cervical ultrasonography revealed a left isoechoic mass measuring 55×42×28 mm with strong perinodular vascular Doppler signal, which appeared to correspond to the left inferior parathyroid gland (Figure 4A). The scintigraphic study with $^{99m}$Tc-MIBI showed an extensive left uptake area corresponding to a left inferior hyperfunctional parathyroid adenoma (Figure 4B).

After one week of medical treatment, the clinical and biochemical profile gradually normalized and the patient underwent neck exploration. A giant left inferior parathyroid adenoma was excised (5.5×4×3 cm, weight 35.2 g). A left lobectomy for a left nodular goiter was also performed (Figure 5, A and B).

Case No. 3

A 33-year-old woman who showed hypercalcemia episodes starting in childhood, with multiple non-invasive interventions (extracorporeal shock wave lithotripsy, ESWL) for the recurrent renal stones in her medical history, was admitted in the Department of Endocrinology. Six months ago, a growing mass was discovered at the median level of the left tibia. The bone biopsy performed showed a histopathological aspect compatible with brown tumor, i.e., numerous giant cells with interstitial hemorrhage in a vascularized fibrous tissue (Figure 6A); in immunohistochemistry the giant cells expressed CD68 (Figure 6B). From her medical history, we also noted a prolactin-secreting pituitary microadenoma, diagnosed in 2004, and osteoporosis with low bone mineral density (BMD) at spine (L1–L4) and femoral level.

On admission, the patient was in a relatively good state, with the left inferior limb immobilized and showing significant mobility difficulties.

The laboratory examinations are noted in Table 1 (Case No. 3). The prolactin level on admission was 68 ng/mL; due to the presence of the pituitary microadenoma we initially suspected a MEN I syndrome but the pancreatic mass was not objectified.

Taking into consideration the increased values of the seric iPTH, hypercalcemia and low serum phosphorus levels, we further investigated the patient to diagnose a primary hyperparathyroidism. The echography revealed a cervical mass with a profoundly inhomogeneous echostucture, which extended from the inferior pole of the right thyroid lobe to the inferior pole of the left thyroid lobe, anterior to the trachea. The parathyroid scintigraphy confirms this partially cystic lesion, suggesting the presence of “two adenomas” under the inferior pole of both thyroid lobes (Figure 7).
Figure 7 – $^{99m}$Tc-MIBI scintigraphy showing uptake under the both thyroid lobes.

The patient underwent bilateral neck exploration. A huge, partially cystic right inferior parathyroid adenoma was excised (Figure 8, A and B). The mass was extended anterior to the trachea toward the left thyroid lobe, having a good dissection plane of the thyroid gland and without suspicious regional adenopathy.

Figure 8 – (A and B) Intraoperative image (a – right inferior parathyroid adenoma; b – right thyroid lobe) and operative specimen.

Histology revealed a parathyroid adenoma made mainly by chief cells, which were mixed with some clusters of oxyphil and clear cells. In the center, cystic areas could be seen; a “rim” of compressed and atrophic parathyroid tissue is present at the periphery of the lesion, confirming the diagnosis of adenoma (Figure 9).

Postoperatively our patient experienced mild hypocalcemia under calcium supplementation; five days after surgery, iPTH serum level was 15.26 pg/mL, calcium and serum phosphate was 8.6 mg/dL and 2.35 mg/dL, respectively. Three months after the surgery, the patient is in a generally good state, asymptomatic, with good mobility and normal calcium, phosphate and iPTH values.

Discussion

These three cases illustrate the clinical presentation of the rarely encountered giant parathyroid adenomas. Nowadays, the most common clinical presentation of pHPT is as an asymptomatic disease [3, 5], with only few of the patients still describing some of the “classical” symptoms: bone disease with osteitis fibrosa cystica or even brown tumors, recurrent nephrolithiasis, neurological symptoms and depression, gastrointestinal disease [6].

Our first patient described a longstanding history of nephrolithiasis and recurrent renal symptomatology, having been repeatedly treated for renal calculi until the pHPT diagnosis was established and he was submitted to parathyroidectomy. The second patient experienced a parathyroid crisis, which is considered a life-threatening emergency and is characterized by severe hypercalcemia (>14 mg/dL) frequently associated with signs and symptoms of multi-organ failure. The third case highlights the rare presentation of a huge, partially cystic macroadenoma, in a female patient who had also a long history of recurrent renal stones, the pHPT being diagnosed after a bone biopsy which revealed a brown tumor.

In the vast majority of the cases, we are confronted with “dwarf” solitary parathyroid adenomas, usually weighing less than 1 g [7, 8], associated with mildly
raised serum calcium and slightly elevated iPTH level. The biochemical diagnosis is followed by localization studies (neck ultrasonography and scintigraphy) and those with concordant imaging are operated using minimally invasive approaches [9–12].

Parathyroid adenomas weighing more than 3 g are defined as “giant adenomas”, but very few over 30 g are described in the literature [5]. In 2005, Power et al. described the largest one, measuring 8×5×3.5 cm and weighing 110 g [3]. Some authors advocated that adenoma’s weight has direct correlation with the functional status of the gland [13, 14] and the severity of biochemical abnormalities. In all our cases, this relationship was found to be true. Robert et al. showed that when parathyroid neoplasm weighs more than 4 g and serum iPTH along with calcium level are very high, one may encounter a malignant parathyroid disease [15].

In spite of this, there are several published cases where benign parathyroid neoplasms are associated with huge serum calcium and iPTH levels, along withpressive dimensions. These “giants” are more often seen in developing countries [16], being associated more frequently with similar clinical and biochemical profiles as parathyroid carcinomas. This is also the case of Romania where, at least in particular regions, we still encounter patients who had been treated for many years for bone, renal, abdominal or even psychiatric diseases and their complications, before reaching the accurate diagnosis of parathyroid disease. This situation is best illustrated by Cases No. 1 and No. 3.

The literature also presents cases with acute symptomaticity, characterized by extremely high serum calcium level (>14 mg/dL or 3.5 mM/L), associated with signs of multi-organ failure and requiring emergency treatment [17]. This clinical picture of parathyroid crisis, also known as acute hyperparathyroidism, parathyrtoxicosis, parathyroid hormone intoxication or hypercalcemic crisis, was first described by Dawson and Struthers and is considered a life-threatening endocrine emergency [17, 18]. Patients demonstrate gastrointestinal and neurological symptoms, acute renal failure, cardiac rhythm abnormalities.

Our second case demonstrates gastrointestinal and cardiovascular symptoms, high serum calcium levels (16.17 mg/dL) along with very high iPTH level (863 pg/mL) and a palpable mass in the left lower neck, all of these findings mimicking a parathyroid carcinoma. Patients in parathyroid crisis need an initial medical “bridge” therapy instead of emergency surgery; it is clearly demonstrated that this initial medical optimization with loop diuretics, low phosphorus diet, bisphosphonates reduces operative complications, before reaching the accurate diagnosis of parathyroid disease. This case is best illustrated by Cases No. 2 and No. 3.

The third case highlights the rare presentation of a huge, partially cystic parathyroid macroadenoma. The cystic parathyroid lesions are very uncommon, accounting for less than 0.01% of all neck masses [22]; these may be pure retention cysts or formed by degeneration of an adenoma or parathyroid carcinoma [23]. In our case, we have noted a partially cystic degeneration of the gland, probably due to the huge dimensions and long time evolution of the disease. Furthermore, the diagnosis was established after a bone biopsy, which revealed a brown tumor of the left tibia. Even if in these huge cystic lesions the possibility of a parathyroid cancer is a real concern, the histology in our case did not reveal any typical signs of carcinoma, i.e., capsular or vascular invasion, mitotic figures within tumor parenchymal cells.

We present herein three cases which have some interesting particularities: (i) a male patient with a long-standing history of nephrolithiasis and recurrent symptomatology without renal functional impairment, previously treated for this renal disease before reaching the diagnosis of parathyroid adenoma; (ii) a woman with an acute pHPT (parathyroid crisis) with very high calcium levels preoperatively, high iPTH level, mimicking a malignant disease, who required emergency admission and adequate preoperative preparation; (iii) a patient with a huge, partially cystic macroadenoma, also with a long history of hypercalcemia and recurrent renal stones, diagnosed after a bone biopsy which revealed a brown tumor. We highlight the importance of taking pHPT into consideration when we are dealing with patients who present long-standing symptoms of nephrolithiasis, “unexplained” osteoporosis or bone disease, neurological or psychiatric symptoms in the context of a raised serum calcium level.

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References


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