Review

Parathyromatosis: a rare yet problematic etiology of recurrent and persistent hyperparathyroidism

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ABSTRACT

Recurrent or persistent hyperparathyroidism is an uncommon yet challenging clinical problem, and parathyromatosis is one of its very rare causes. In this minireview, we review causes of recurrent hyperparathyroidism and all cases of parathyromatosis available in the literature. The clinical course of a case of parathyromatosis with the longest follow-up (1977-2011) is described. Similar cases reported between 1975 and the present are reviewed and analyzed to characterize the clinical presentation, course, and management of this rare condition. Parathyromatosis, which is benign parathyroid tissue seeding, has been detailed in 35 patients in the English literature. The majority were female subjects, with end-stage renal disease, in their fifth to sixth decade of life. In most cases, the diagnosis was made intraoperatively; and the condition was often refractory to surgery. A calcimimetic agent was used in 5 cases with end-stage renal disease; serum calcium and/or parathyroid hormone levels decreased in 4 subjects, but only one was reported to experience increments in bone density. Medical management combining a calcimimetic with a bisphosphonate may therefore be a preferred alternative.

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1. Causes of persistent or recurrent hyperparathyroidism

Primary hyperparathyroidism (PHPT) is defined as “the disease in which, in the absence of a known stimulus, one or more parathyroid glands secrete excess parathyroid hormone, producing hypercalcemia”[1]. It is most commonly caused by a single adenoma, and surgery is most often curative. Those not cured have either persistent or recurrent disease.

When hypercalcemia fails to resolve after parathyroidectomy (PTX), the disease is termed persistent, whereas recurrent HPT refers to reappearance of hypercalcemia after a normocalcemic period of at least 6 months post-PTX [2]. Several factors have been associated with initial treatment failure or recurrence of the disease including inexperience of the operating surgeon; ectopic or supernumerary glands; multiglandular disease; parathyroid carcinoma; and, rarely, parathyromatosis.
Successful parathyroid surgery for PHPT has been reported to exceed 95% in experienced hands [3]. The most common cause of initial treatment failure is surgeon inexperience. This is reflected by the fact that, in most of the patients reoperated for persistent or recurrent HPT, a missed parathyroid adenoma was found in the neck, suggesting inadequate exploration or resection [2,4,5]. Furthermore, persistent HPT was recently demonstrated by Mitchell et al [6] and Cheng et al [7] to be more common in low-volume as compared with high-volume hospitals.

Failure of initial surgery when performed by an experienced endocrine surgeon is most commonly due to an abnormal gland in an ectopic location. In a series of 102 patients undergoing reoperation for persistent or recurrent HPT, a parathyroid gland was described in an ectopic position in 53% of cases: 28% were found in the paraesophageal area; 26%, in the mediastinum; 24%, infrathyroid; 11%, intrathyroidal; 9%, in the carotid sheath; and 2%, in the high cervical position [8]. In another series of 167 patients with persistent or recurrent HPT, 155 parathyroid adenomas were found at reoperation, among which 66% were in ectopic locations. Ectopic sites included the tracheoesophageal groove (18%), the anterior mediastinum/thymus (23%), the carotid sheath (8%), the retroesophageal area (3%), and other mediastinal locations (3%), whereas 2% were intrathyroidal and 10% were undescended [9].

The majority of individuals, that is, around 85%, have 4 parathyroid glands, 2 superior and 2 inferior glands. Supernumerary glands have been reported to occur in up to 13% of subjects in autopsy studies [10]. Most patients with additional glands have 5 parathyroids, although the presence of up to 12 glands has been described [11]. The most frequent location for a supernumerary gland is within the cervical thymus or deep mediastinum [12]. Supernumerary parathyroid glands have been described in up to 39% of reoperative cases [5]. Thus, a sound knowledge of embryology and anatomy of parathyroid glands is essential to a surgeon for a successful neck exploration.

Another cause for a failed parathyroid surgery is the presence of unrecognized multiglandular disease, multiple adenomas, or hyperplasia. In a systematic literature review that included 20 225 cases of PHPT, double adenomas accounted for 4.14% of cases and multiple gland hyperplasia disease accounted for 5.74%. The vast majority of subjects (88.9%) had a single adenoma [13]. Patients with a familial syndrome associated with HPT are more likely to have multiglandular disease. In patients with multiple endocrine neoplasia (MEN) syndromes, multiple gland disease was found in 90% and 83% of patients with MEN1 and MEN2, respectively [14]. Whereas cure rates for single adenomas in PHPT exceed 95%, lower cure rates have been observed in patients with multiple gland disease. As an example, in a series of 50 patients with MEN1, persistent or recurrent HPT occurred in 66% of patients following subtotal PTX and in 20% of patients after total PTX. All patients had recurrence after single adenoma excision [15]. Therefore, failure to recognize that a patient has a familial syndrome may result in inadequate treatment of multiple gland disease and invariably leads to persistent or recurrent HPT.

Parathyroid carcinoma is a rare cause of PHPT, accounting for 0.4% to 5.2% of cases [16-21]. High recurrence rates, exceeding 50%, have been noted after surgical excision of parathyroid carcinoma, particularly in those diagnosed after initial surgery. Patients with an initial diagnosis before surgery and who have therefore undergone an en bloc resection showed a lower rate of recurrence and death [22]. Hence, to improve outcome and minimize recurrence rates, en bloc resection should be considered as the initial therapeutic step when suspecting parathyroid carcinoma [23].

Finally, parathyromatosis is a rare yet challenging etiology of recurrent or persistent HPT. It is described as multiple nodules of benign hyperfunctioning parathyroid tissue scattered throughout the neck and mediastinum. We report a case of recurrent and persistent HPT with an initial failed neck operation due to a supernumerary adenomatous gland and subsequent multiple unsuccessful reoperations due to disseminated parathyroid tissue at various sites in the neck and mediastinum, and review the relevant literature.

2. Parathyromatosis: the case report

A 60-year-old woman first presented at 23 years of age with complaints of generalized fatigue, muscle weakness, bone pain, nausea, vomiting, polyuria, and polydipsia. She had a 2-year history of recurrent renal colics and a duodenal ulcer diagnosed 4 years before presentation. Family history for MEN or familial HPT was negative. Biochemical assays revealed severe hypercalcemia and hypophosphatemia (Table 1). Skull radiographs showed a salt and pepper appearance, and radiograph of the hands revealed osteitis fibrosa cystica of the index finger of the left hand. A presumptive diagnosis of PHPT was made because parathyroid hormone (PTH) assays were not available then. At neck exploration, none of the 4 parathyroid glands appeared grossly abnormal except for a slight enlargement of the left upper parathyroid gland. Subsequently, a subtotal PTX was performed (3 1/2 glands removed) as well as a subtotal thyroidectomy for left lobe nodular disease. Calcium level remained elevated postoperatively. One week later, a mediastinal exploration revealed a paraesophageal mass of 6 × 3 × 2 cm with a histological diagnosis of parathyroid chief cell adenoma. Excision of the parathyroid adenoma and total thymectomy were performed. Postoperatively, the serum calcium dropped to 7 mg/dL, and she was discharged on per os (PO) calcium and large doses of vitamin D3. She developed hungry bone syndrome that persisted for 3 years, during which she was maintained on calcium and PO vitamin D supplements; these were eventually tapered and then stopped. She remained asymptomatic and normocalcemic for the following 11 years.

In 1991, that is, 14 years after her initial 2 consecutive surgeries, she presented with recurrence of the hypercalcemia. Ultrasound and computed tomography (CT) of the neck, cervical arteriography, and venous sampling all failed to localize the site of recurrence. The decision was made not to reoperate, and the patient was discharged on oral phosphate and furosemide therapy. She remained hypercalcemic for the next 5 years with severe hypertension requiring the use of multiple antihypertensive drugs. In 1996, CT of the neck failed...
<table>
<thead>
<tr>
<th>Year</th>
<th>Disease status</th>
<th>Serum Ca (mg/dL)</th>
<th>Serum PO₄ (mg/dL)</th>
<th>PTH (pg/mL)</th>
<th>24-h U Ca (mg/24 h)</th>
<th>Ancillary studies</th>
<th>Localization studies</th>
<th>Type of surgery</th>
<th>Operative findings</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 1977 | • Severe symptomatic hypercalcemia  
• Persistence of hypercalcemia | 19.6 | 1.3 | NA | NA | NA | NA | None | Cervical exploration  
SubPTx | LU PT gland hyperplasia | • Persistence of hypercalcemia |
| | | 16-19.2 | 1.4-2.2 | NA | NA | NA | NA | None | Mediastinal Exploration  
Excision of paraesophageal mass  
Total thymectomy | Paraesophageal mass  
6 × 3 × 2 cm with histological diagnosis of chief cell adenoma | • Hypocalcemia postop  
Hungry bone syndrome  
Discharged on PO Ca and vitamin D3 |
| 1991 | • Recurrence of hypercalcemia  
• Hypertension  
• Kidney stones | 11.6-12 | 1.6-2.8 | 93.1 | 339  
445 | NA | Left lower kidney pole stone | U/S neck (−)  
CT neck (−)  
Cervical arteriography and venous sampling (−)  
CT neck (−) | NA | NA | • Discharged on oral phosphate and furosemide |
| 1996 | • Persistence of hypercalcemia  
• Hypertension  
• Duodenal ulcer  
• Osteopenia  
• Early menopause  
• Persistence of hypercalcemia | 10.3-12.2 | 1.8-2.5 | 87.9-129 | 495 | FA: −2.35 | NA | Parathyroid Scan (+)  
Cervical exploration | Hyperplasia of RL PT gland  
Aggregates of intrathymic PT tissue  
Presence of PT tissue within mediastinal fibrofatty tissue | • Persistence of hypercalcemia  
• Started on weekly alendronate and conjugated estrogens  
• Shifted to pamidronate IV |
| 1997 | • Persistence of hypercalcemia  
• Kidney stones  
• Osteopenia | 12.1 | NA | NA | Parathyroid Scan (+)  
Cervical exploration | Hyperplasia of RL PT gland  
Aggregates of intrathymic PT tissue  
Presence of PT tissue within mediastinal fibrofatty tissue | • Persistence of hypercalcemia |
| 2001 | • Persistence of hypercalcemia | 12.2 | 2.1 | NA | NA | NA | Sestamibi (+)  
CT scan (+) | Mediastinal exploration | Presence of PT tissue within mediastinal fibrofatty tissue | • Persistence of hypercalcemia |
| 2005 | • Persistence of hypercalcemia  
• Kidney stones  
• Osteopenia | 12.8 | 2.3 | 120 | NA | FA: −1.6  
FN: −1.5  
AP spine: −0.1  
FT: −0.4 | Left kidney obstructive stone with hydronephrosis | NA | NA | • Transient mild drop in calcium after IV pamidronate  
Shifted to zoledronate |
| 2007 | • Persistence of hypercalcemia | 12-12.6 | 2-2.56 | 195 | NA | NA | MRI neck and med (+)  
Venous Sampling (+) | Mediastinal exploration | Mediastinal adenoma (800 g)  
Hyperplastic PT tissue nests | • Persistence of hypercalcemia |
<table>
<thead>
<tr>
<th>Year</th>
<th>Disease status</th>
<th>Serum Ca (mg/dL)</th>
<th>Serum PO₄ (mg/dL)</th>
<th>PTH (pg/mL)</th>
<th>24-h U Ca (mg/24 h)</th>
<th>Ancillary studies</th>
<th>Localization studies</th>
<th>Type of surgery</th>
<th>Operative findings</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 2008 | • Persistence of hypercalcemia  
• Osteopenia | 11.8 | 2.59 | 110 | 7.65 | NA | NA | NA | NA | • Started on vitamin D3  
• Kept on zoledronate  
• Discharged on cinacalcet |
| 2011 | • Persistence of hypercalcemia  
• Hypertension  
• Osteopenia | 11.9 | 2.9 | 218.3 | <4 | 232.3 | FA: −1.6  
FT: −0.5  
FN: −1.7  
AP spine: −0.3 | Tiny stones in right and left kidney | FDG-PET scan (−) | NA | NA | |
| 3 wk later | • Improvement of hypercalcemia | 10.6 | 2.7 | 118.8 | NA | NA | NA | NA | NA | • Marked biochemical improvement on cinacalcet |

24-h U Ca indicates 24-hour urine collection for calcium; 25OHD, 25-hydroxyvitamin D; AP, anteroposterior; Ca, calcium; FA, forearm; FN, femoral neck; FT, total femur; HF, hip fracture; LU, left upper; Med, mediastinum; MOF, major osteoporotic fracture; NA, data not available (either missing data or not done); PO₄, phosphorus; PT, parathyroid; RL, right lower; SubPTX, subtotal PTX.

* Reference range: Ca, 8.5-10.5 mg/dL; PO₄, 2.7-4.8 mg/dL; PTH, 15-75 pg/mL; 24-h U Ca, 0-300 mg.

* BMD was measured using Hologic 4500A densitometer (Hologic, Bedford, MA).

* FRAX: estimated 10-year fracture risk for major osteoporotic fracture and hip fracture based on FRAX Lebanon.
<table>
<thead>
<tr>
<th>Author, year [ref]</th>
<th>Age</th>
<th>Sex</th>
<th>Relevant medical history</th>
<th>Prior PT surgery</th>
<th>AutoTX of PT (site)</th>
<th>Initial PT surgery</th>
<th>Primary operative findings</th>
<th>Type</th>
<th>Outcome of disease</th>
<th>Interval to RO</th>
<th>N of ROs</th>
<th>F/U y after initial RO</th>
<th>Localizing imaging procedures (results)</th>
<th>Sites of parathyroid implants</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddick, 1977 [27]</td>
<td>49 M</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>3½ PTX</td>
<td>RS (150 mg) RI (280 mg) LS (45 mg) LI (30 mg) 5th gland in retrosternal adipose tissue Small collections of parathyroid cells in mediastinal fat</td>
<td>Remission</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3 y</td>
<td>None</td>
<td>RO (150 mg)</td>
<td>Retrosternal adipose tissue, mediastinal fat</td>
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<tr>
<td></td>
<td>22 M</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>3½ PTX</td>
<td>Hypercellular PT tissue Nests of PT cells in adipose tissue RI (1 cm)</td>
<td>Persistence of hypercalcemia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>11 y</td>
<td>None</td>
<td></td>
<td>Adipose tissue</td>
</tr>
<tr>
<td>Rattner, 1985 [53]</td>
<td>47 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>3½ PTX</td>
<td>10-cm cystic adenoma</td>
<td>Removal of cystic adenoma</td>
<td>Recurrence</td>
<td>23 y</td>
<td>1</td>
<td>3</td>
<td>None</td>
<td>Surface of thyroid</td>
<td>Adipose tissue</td>
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<tr>
<td></td>
<td>59 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>RI adenoma</td>
<td>Removal of RI adenoma and normal LI parathyroid gland</td>
<td>Persistence</td>
<td>19 y</td>
<td>1</td>
<td>NA</td>
<td>None</td>
<td>SVS (+) Angiography (+)</td>
<td>F/U = 8 y</td>
<td>• Documented cyst rupture at initial surgery • Normocalcemic for 3 y after RO then died from other causes • Remission after RO</td>
</tr>
<tr>
<td></td>
<td>62 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>RI hyperplasia</td>
<td>Removal of both inferior parathyroid glands LI hyperplasia</td>
<td>Persistence</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>SVS (+) Arteriography (+)</td>
<td>F/U = 14 y</td>
<td>• Remission after RO</td>
</tr>
<tr>
<td></td>
<td>37 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Adenoma</td>
<td>Removal of adenoma</td>
<td>Persistence</td>
<td>2 y</td>
<td>3</td>
<td>14 y</td>
<td>None</td>
<td>SVS (-)</td>
<td>Mediastinum</td>
<td>After last surgery, remained normocalcemic for 8 y then died.</td>
</tr>
<tr>
<td>Author, year [ref]</td>
<td>Age</td>
<td>Sex</td>
<td>Relevant medical history</td>
<td>Prior PT surgery</td>
<td>AutoTX of PT (site)</td>
<td>Initial PT surgery</td>
<td>RO</td>
<td>Localizing imaging procedures (results)</td>
<td>Sites of parathyroid implants</td>
<td>Comments</td>
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<tr>
<td>Akerstrom, 1988 [29]</td>
<td>37 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>Adenoma (570 mg)</td>
<td>Extirpation of parathyroid adenoma</td>
<td>Recurrence</td>
<td>6 y</td>
<td>1</td>
<td>5 y</td>
<td>Neck US (-) CT neck and med (-)</td>
<td>Fatty tissue along R LN, inferior and dorsolateral aspects of thyroid lobe, and pharyngeal wall</td>
<td>• Breakage of adenoma into 2 parts during initial surgery</td>
<td>Remission after RO</td>
<td></td>
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<tr>
<td>62 F</td>
<td>MEN1</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>2 hyperplastic glands</td>
<td>Excision of the 2 hyperplastic glands</td>
<td>Recurrence</td>
<td>13 y</td>
<td>2</td>
<td>6 y</td>
<td>US (-) CT (-) SVS (-)</td>
<td>Site of reoperation, thyroid, R LN, pharynx</td>
<td>• Documented rupture of capsule at 1st RO</td>
<td>Remission after last surgery</td>
<td>Rupture of adenoma during extirpation</td>
<td>Remained mildly hypercalcemic</td>
</tr>
<tr>
<td>18 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>Adenoma (260 mg)</td>
<td>Extirpation of adenoma</td>
<td>Recurrence</td>
<td>&lt;1.5 y</td>
<td>2</td>
<td>5 y</td>
<td>None</td>
<td>NA</td>
<td></td>
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<tr>
<td>Fitko, 1990 [54]</td>
<td>53 F</td>
<td>ESRD</td>
<td>Yes</td>
<td>No</td>
<td>RS adenoma (0.7g) RI adenoma (3.3g)</td>
<td>Removal of Rt glands + 1/2 of LU</td>
<td>Persistence of HPT</td>
<td>3 y</td>
<td>4</td>
<td>1.5 y</td>
<td>SVS inconclusive</td>
<td>Thyroid, left TE groove, soft tissue of neck</td>
<td>• Ruptured RS adenoma at initial surgery</td>
<td>Persistent hypercalcemia</td>
<td>Died 10 mo after last surgery</td>
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<td>Penington, 1990 [55]</td>
<td>47 M</td>
<td>ESRD</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>5 glands</td>
<td>SubPTX (small segment of the smallest gland left)</td>
<td>Recurrence of HPT</td>
<td>1 y</td>
<td>2</td>
<td>8 y</td>
<td>Subtraction scintigraphy with TI and Tc (-)</td>
<td>FA</td>
<td></td>
<td></td>
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<tr>
<td>Kessler, 1991 [56]</td>
<td>53 F</td>
<td>ESRD</td>
<td>Yes</td>
<td>No</td>
<td>Parathyroid gland cyst</td>
<td>3 1/2 gland PTX</td>
<td>Recurrence of hypercalcemia</td>
<td>6 y</td>
<td>3</td>
<td>&gt;0.75 y</td>
<td>NA</td>
<td>Muscle and surface of the thyroid</td>
<td>• Ruptured cyst at initial operation</td>
<td>Remission after last RO</td>
<td>(continued on next page)</td>
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<tr>
<td>Author, year [ref]</td>
<td>Age sex</td>
<td>Relevant medical history</td>
<td>Prior PT surgery</td>
<td>AutoTX of PT (site)</td>
<td>Initial PT surgery</td>
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<tr>
<td>Sokol, 1993 [57]</td>
<td>58 F</td>
<td>—</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>RI adenoma (4.2 × 2 × 1.3 cm)</td>
<td>Adenoma resection</td>
<td>NA</td>
<td>12 y 2 7.5 y</td>
<td>US neck (−) Tc 99 thyroid scintiscan (−) Arteriography (−) Tc Thallium scan (−) CT neck and mediastinum (−) MRI neck and mediastinum (−)</td>
<td>Thyroid, thymus, carotid sheath, TE groove</td>
<td>• Persistent hypercalcemia after last surgery stable on 0.625 mg conjugated estrogen daily</td>
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</tbody>
</table>
| Kollmorgen, 1994 [58] | 30 M | ESRD | Yes | Yes (Rt deltoide muscle) | Hyperplasia 4 glands | Removal of RS, LS, and LI glands | Persistence | 2 y 3 3 y | CT scan (+) Venous Sampling (+) Tc 99m sestamibi (+) | Mediastinal fat, left RLN, thyroid | • Remained normocalcemic after last surgery for a documented 4 mo \[\text{PT tissue spillage in the mediastinum and neck} \]
| Stehman-Breen, 1996 [62] | 35 M | ESRD | Yes | No | NA | SubPTX | Recurrence | 1.5 y 4 9 y | None | AutoTX site (shoulder), mediastinum, thymus | None | • Died shortly after last surgery (cardiopulmonary arrest) |
| Stehman-Breen, 1996 [62] | 38 M | ESRD | Yes | Yes (FA) | NA | TPTX | Recurrence | NA 3 NA | NA | AutoTX site at FA | None | • Hyperplasia of autotransplanted tissue in the FA | \[\text{Persistence of HPT}\]
| | 41 F | ESRD | Yes | No | Ectopic gland | SubPTX | Recurrence/persistence | NA 4 NA | None | PT scattered throughout neck AutoTX site at FA Auto Tx site at FA, thyroid, carotid sheath, trachea | None | \[\text{PT HPT normalized after last surgery}\]
| | 24 F | ESRD | Yes | Yes (FA) | NA | TPTX | Recurrence of symptoms Persistence | NA 4 4 y | None | None | None | None |
| | 46 M | ESRD | Yes | Yes (FA) | NA | TPTX | Recurrence of hypercalcemia | 4 y 1 NA | Sestamibi (+) U/S (-) FNA (+) | Fat, fibrous tissue, neck skeletal muscle, thyroid capsule | None | \[\text{No F/U provided after RO}\]
<p>| Baloch, 2001 [59] | 37 M | ESRD | Yes | No | NA | 3 1/2 PTX | None | None | None | None | None | None |</p>
<table>
<thead>
<tr>
<th>Author, year [ref]</th>
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<th>Sites of parathyroid implants</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Lee, 2001 [28]</td>
<td>36 F</td>
<td>ESRD</td>
<td>No</td>
<td>Yes (FA)</td>
<td>Nodular PT hyperplasia of excised glands intrathyroidal PT rest</td>
<td>3 1/2 PTX</td>
<td>Recurrence</td>
<td>15 mo</td>
<td>2</td>
<td>3.75 y</td>
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<tr>
<td>Lentsch, 2003 [60]</td>
<td>38 M</td>
<td>ESRD</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>SubPTX</td>
<td>NA</td>
<td>5 y</td>
<td>1</td>
<td>NA</td>
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<tr>
<td>Falvo, 2003 [63]</td>
<td>74 F</td>
<td>ESRD</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>NA</td>
<td>TPTX</td>
<td>NA</td>
<td>29 y</td>
<td>1</td>
<td>1 y</td>
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<tr>
<td>44 M</td>
<td>ESRD</td>
<td>Yes</td>
<td>Yes (LSCM)</td>
<td>NA</td>
<td>TPTX</td>
<td>Recurrence</td>
<td>3 y</td>
<td>2</td>
<td>5 y</td>
<td></td>
</tr>
<tr>
<td>58 F</td>
<td>ESRD</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>NA</td>
<td>TPTX</td>
<td>NA</td>
<td>3 y</td>
<td>1</td>
<td>8 mo</td>
<td>Scintigraphy (+)</td>
</tr>
<tr>
<td>75 F</td>
<td>ESRD</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>NA</td>
<td>TPTX</td>
<td>NA</td>
<td>6 y</td>
<td>1</td>
<td>1.5 y</td>
<td>Scintigraphy (+) US (+)</td>
</tr>
<tr>
<td>55 M</td>
<td>ESRD</td>
<td>Yes</td>
<td>Yes (FA)</td>
<td>NA</td>
<td>TPTX</td>
<td>NA</td>
<td>12 y</td>
<td>1</td>
<td>2 y</td>
<td>Scintigraphy (+)</td>
</tr>
<tr>
<td>Evans, 2005 [61]</td>
<td>62 F</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>Bilobed parathyroid adenoma (0.91 g, 11.6 g)</td>
<td>Removal of adenoma</td>
<td>Recurrence</td>
<td>14 y</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Daphnis, 2006 [48]</td>
<td>32 F</td>
<td>ESRD</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>SubPTX</td>
<td>Recurrence of HPT</td>
<td>3 y</td>
<td>1</td>
<td>6 y</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Author, year [ref]</th>
<th>Age sex</th>
<th>Relevant medical history</th>
<th>Prior PT surgery</th>
<th>AutoTX of PT (site)</th>
<th>Initial PT surgery</th>
<th>RO Type</th>
<th>Outcome of disease</th>
<th>Interval to RO</th>
<th>N of ROs</th>
<th>F/U y after initial RO</th>
<th>Localizing imaging procedures (results)</th>
<th>Sites of parathyroid implants</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Unbehaum, 2007 [49]</td>
<td>65 M ESRD Yes No</td>
<td>NA SubPTX</td>
<td>Recurrence of HPT</td>
<td>5 y</td>
<td>2</td>
<td>4 y</td>
<td>Tc 99m sestamibi (+) MRI med (+) SVS (+) CT (+) US (+) Tc 99m sestamibi SPECT (+)</td>
<td>Thyroid, mediastinum</td>
<td>HPT controlled with doxercalciferol, cinacalcet</td>
<td>HPT controlled with cinacalcet</td>
<td>Rupture of adenoma at initial surgery and during RO</td>
<td>Remission seen after RO</td>
<td>RS gland was found in the right fossa supravacularis</td>
</tr>
<tr>
<td>Tublin, 2007 [51]</td>
<td>29 F ESRD Yes No</td>
<td>NA 3 1/2 PTX</td>
<td>Persistence of HPT</td>
<td>6 y</td>
<td>1</td>
<td>6 mo</td>
<td>CT scan (+) Tc 99m sestamibi SPECT (+)</td>
<td>Left platysmus, below lower pole of right mandibular gland</td>
<td>Carotid sheath</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>73 F – Yes No</td>
<td>RS adenoma Right superior PTX NA</td>
<td>6 y</td>
<td>2</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriguchi, 2008 [50]</td>
<td>61 F ESRD Yes Yes (FA)</td>
<td>Nodular parathyroid hyperplasia LS gland in thyroid lobe RS gland missing NA SubPTX SubPTX</td>
<td>Persistence</td>
<td>1 y</td>
<td>4</td>
<td>5 y</td>
<td>Tc 99m sestamibi (+) CT scan (+) US (+) AutoTx site at FA Lower poles of thyroid lobes</td>
<td>Thyroid, pretracheal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindie, 2010 [52]</td>
<td>64 M ESRD Yes No</td>
<td>NA SubPTX</td>
<td>NA</td>
<td>5 y</td>
<td>3</td>
<td>9 y</td>
<td>99m Tc- sestamibi/123I (-)</td>
<td>Thyroid, pretracheal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data included in this table are detailed as reported in the original manuscript. F/U indicates follow up; FA, forearm; LI, left inferior; LS, left superior; LSCM, left sternocleidomastoid; LSH, left sternothyroid; Med, mediastinum; NA, data not available; PE, paraesophageal; PT, parathyroid; PTL, paratracheal; RI, right inferior; RLN, recurrent laryngeal nerve; RO, reoperation; RS, right superior; SubPTX, subtotal PTX; SVS, selective venous sampling; TE, tracheoesophageal; TPTX, total PTX; TX, transplantation.
to localize the site of suspected hyperplastic parathyroid tissue. Bone densitometry revealed osteopenia, and the patient was started on bisphosphonate therapy. One year later, a parathyroid scan revealed a 1-cm tumor mass in the right base of the neck; and the patient underwent her third surgical exploration. Intraoperative findings revealed a mildly enlarged right lower parathyroid gland as well as an additional gland in the upper mediastinum within the confines of the thymus that were removed. Histological examination revealed hyperplasia of right lower gland and aggregates of intrathymic parathyroid tissue. Thyroidectomy to the remnant right lobe was also performed. Serum calcium level and PTH levels remained elevated at subsequent follow-up visits, indicating the presence of residual parathyroid tissue (Table 1). In 2001, sestamibi scan and CT of the neck and chest revealed a 1-cm nodule in the base of the neck between the innominate artery and vein. Mediastinal exploration confirmed the presence of parathyroid tissue within fibrofatty tissue that was removed. However, serum calcium and PTH levels remained elevated (Table 1). In 2007, a search investigating the source of excess PTH was undertaken. Magnetic resonance imaging (MRI) of the neck mediastinum revealed a right mediastinal adenoma with multiple paratracheal nodules. Exploratory surgery was performed, and histological examination showed parathyroid tissue with nodular hyperplasia and multiple hyperplastic parathyroid tissue nests. These histological findings were consistent with the diagnosis of parathyromatosis. Attempt of removal of all parathyroid tissue again failed.

The patient presented again in 2011 with symptomatic hypercalcemia. In view of the previous 5 unsuccessful surgeries, further operation was not contemplated. It was then decided to start the patient on cinacalcet; and to minimize the deleterious effects of PTH on bone, a bisphosphonate was added. Intake of fluids was encouraged to minimize the risk of stone precipitation. The patient responded biochemically (Table 1), but subsequently discontinued the cinacalcet because of financial reasons, with elevations in her calcium and PTH levels to pretreatment values.

3. Literature search and statistical analyses

A PubMed search was conducted to identify published reports in the English literature from 1975 to the present using the following key words: parathyromatosis, recurrent hyperparathyroidism, persistent hyperparathyroidism, and cinacalcet. Reports of all cases reported were retrieved and summarized in Table 2. Five cases of parathyromatosis mentioned in 1 of 2 reported cases series were not included because of the lack of sufficient descriptive data [24,25].

Summary statistics on the retrieved case reports were implemented to characterize the clinical characteristics of the disease on presentation. Regression analyses investigating possible predictors of recurrence were also performed. All variables are presented as median (minimum-maximum), unless stated otherwise. Nonparametric tests were used because of the small sample size. Spearman correlation test was performed to assess the relationship between continuous variables such as age and time to reoperation. Mann-Whitney test was used to compare the median of continuous variables such as age and time to reoperation between groups (sex, kidney function status). Linear regression analysis was performed to assess the independent effect of age, sex, and kidney function status on the time to reoperation. The model was built with time to reoperation entered as outcome and age, sex, and kidney function as predictors, using the all-enter method. P values < .05 were considered significant. The statistical software SPSS, version 17 (Chicago, IL), was used.

4. Description and pathogenesis of parathyromatosis

This condition is a rare yet challenging etiology for recurrent or persistent HPT. It was initially described by Palmer et al [26] in 1975 in a review of 250 cases of failed parathyroid surgery. In 1977, Reddick et al [27] proposed 2 theories to explain the pathogenesis of parathyromatosis. The first speculates that parathyromatosis is a consequence of spillage and seeding of parathyroid tissue within the operative field during parathyroid surgery and accounts for most cases in the literature. The second proposes that preexisting parathyroid rests of embryological origin undergo hyperplasia under the influence of physiological stimuli. The latter theory is supported by 2 early reports describing a total of only 3 patients whose initial operation revealed multiple nodules of hyperfunctioning parathyroid tissue scattered throughout the neck [26,27]. Lee et al [28], in 2001, described the only case reported of a mixed form of ontogenous and postsurgical parathyromatosis. No cases of embryonal parathyromatosis have been reported since then. Reports detailing all 35 cases of parathyromatosis identified throughout the literature are summarized in Table 2.

5. Clinical characteristics of parathyromatosis

We identified 35 reported cases, 14 male (M) and 21 female (F) subjects. The median age at presentation was 47 years (range, 18-75). There was no age difference between the 2 sexes, and family history of hypercalcemia or HPT was not mentioned in any of the reports (Table 2). Twenty-two subjects had end-stage renal disease (ESRD) (M = 11, F = 11), 12 were otherwise healthy (M = 3, F = 9), and 1 male subject had MEN. There was no significant difference in age between ESRD subjects (median age, 45 years [24-75]) and non-ESRD subjects (median age, 53 years [18-73]; P = .6). There was no difference in median time to reoperation between sexes (M = 4.5 years [1-12] vs F = 6 years [0.3-29]; P = .5). Median time to reoperation was longer in otherwise healthy subjects (6 years [1.5-23]) as compared with those with ESRD (3 years [0.3-29]; P = .05), albeit with a very wide range in both conditions. The median number of reoperations was 2 (1-5), and 13 of 35 cases (8 ESRD) were only reoperated on once. Those either were followed up for a short period (<2 years, n = 5) and/or were on concomitant medical therapy (n = 2). There was a significant correlation...
between age and time to reoperation \( (r = 0.5, \ P = .01) \). Regression analysis showed that age was the only independent predictor for time to reoperation after adjustment for sex and kidney function status \( (\beta \ [SE], 0.19 \ [0.07]; \ P = .01) \). Rupture and spillage of parathyroid tissue in the surgical field were clearly documented in 9 patients.

In summary, parathyromatosis, as PHPT, is 1.5 times more prevalent in women than men, with a median age of 47 years at presentation. The disease is more commonly associated with secondary HPT, and the vitamin D status of reported patients was not mentioned. Patients with secondary HPT have an earlier recurrence of their disease after surgical intervention. The one patient described with MEN1 in whom a ruptured capsule was documented during reoperation for recurrent HPT had early recurrence of hypercalcemia within 2 years of reoperation \[29\]. The significant correlation between age and time to reoperation could be potentially explained by a higher threshold for surgical intervention in older subjects with HPT.

6. Localization and operative findings

Preoperative localization procedures may fail to localize and diagnose parathyromatosis. In a series by Matsuoka et al \[30\], only 4 of 10 patients were successfully diagnosed with parathyromatosis preoperatively; and ultrasound was more effective than sestamibi scan in suggesting the diagnosis. In our reviewed case series, localization of hyperfunctioning parathyroid tissue by noninvasive or invasive imaging modalities was achieved in only 16 patients. In these, hyperplastic parathyroid tissue had been found on fibrous scar tissue from previous surgery; in skeletal muscles and fat tissue within the neck; on the surface of the thyroid; and in the tracheoesophageal groove, carotid sheath, thymus, and mediastinal fat. Furthermore, in 11 of 22 ESRD patients, parathyromatosis involved the parathyroid autotransplantation sites, forearm, deltoid muscle, and left sternocleidomastoid muscle. Seven of these patients had parathyromatosis only at the transplantation site, whereas 4 others also had parathyromatosis at other surgical sites as well (Table 2). In a recent study conducted by Melck et al \[31\], forearm parathyromatosis was identified in 58% of patients reoperated after initial forearm autograft among a group of 12 patients with renal failure or MEN1 syndrome.

7. Treatment strategies

The successful treatment and control of parathyromatosis remains a challenge. Multiple attempts at surgical cure are most often unsuccessful. The major difficulty lies in accurately identifying and removing all the disseminated tiny nodules of parathyroid tissue. Furthermore, these nodules may be closely adherent to scar tissue or surrounding structures and subsequently difficult to excise. Therefore, surgical attempts to definitely control parathyromatosis are met with failure. In Table 2, 18 of 35 cases were reported to be in remission with relatively short follow-up periods (4 months to 2 years), with the exception of one case that remained in remission 8 years postoperatively.

Medical therapy has been attempted in few cases. One patient described by Sokol et al \[57\] had persistent disease and was maintained on conjugated estrogen. However, no further follow-up after treatment was provided. Data supporting the efficacy of hormone replacement therapy in reducing hypercalcemia in PHPT are from early uncontrolled trials \[32,33\]. In a 2-year randomized placebo-controlled trial of hormone replacement therapy in postmenopausal women with PHPT, no changes in ionized calcium or PTH were noted; but an improvement in bone mineral density (BMD) at multiple sites was described \[34\]. Raloxifene, as well, has been shown to lower serum calcium and bone remodeling markers in 18 postmenopausal women with PHPT in an 8-week study, with

<table>
<thead>
<tr>
<th>Table 3 – Use of cinacalcet in 5 cases of parathyromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author year [ref]</strong></td>
</tr>
<tr>
<td><strong>Age/sex</strong></td>
</tr>
<tr>
<td><strong>Dosage of cinacalcet</strong></td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
</tr>
<tr>
<td><strong>Concomitant drugs</strong></td>
</tr>
<tr>
<td><strong>Effect on Ca (mg/dL)</strong></td>
</tr>
<tr>
<td><strong>Effect on PTH (pg/mL)</strong></td>
</tr>
<tr>
<td><strong>Effect on Ca×PO(_4) product (mg(^2)/dL(^2))</strong></td>
</tr>
<tr>
<td><strong>Effect on BMD</strong></td>
</tr>
<tr>
<td><strong>Effects on end organs</strong></td>
</tr>
</tbody>
</table>

BID indicates twice daily; NA, data not available; PO\(_4\), phosphate; QD, once daily.

\( ^a \) All cases had ESRD except our reported case.

\( ^b \) Patient subsequently discontinued cinacalcet with elevation in calcium and PTH levels back to pretreatment values.
no drop, however, in PTH levels [35,36]. We are unaware of its use in parathyromatosis.

Several small studies have evaluated clodronate [37-39], pamidronate [40], and risedronate [41] in PHPT. However, alendronate remains the most extensively studied in this setting. These studies have consistently demonstrated that alendronate suppresses bone turnover and increases BMD at the hip and lumbar spine with no change at the forearm [42-45]. Nevertheless, the effects on serum calcium have been inconsistent and may have been affected by low vitamin D levels that were not measured in all studies. The efficacy and safety of zoledronate in PHPT have not been established in clinically controlled trials. None of the authors described the use of bisphosphonates in parathyromatosis probably because most of the patients described had ESRD and data on the use of bisphosphonates in ESRD are lacking [46]. In our patient, the use of a bisphosphate proved to be valuable in stabilizing BMD. Nevertheless, its calcium-reducing effect was mild and transient and was the reason for the addition of cinacalcet.

Cinacalcet is an oral calcimimetic that binds to calcium-sensing receptor, decreasing PTH secretion [47]. In the United States, it is approved by the Food and Drug Administration for the treatment of secondary HPT in chronic renal failure and for controlling HPT in parathyroid carcinoma, whereas in several countries of the European Union, it is also approved by the European Medicines Agency (EMEA) for use in PHPT. Four previous reports have described the successful use of cinacalcet in controlling parathyromatosis as detailed in Table 3 [48-51]. Successful therapy could be defined as a normalization of serum calcium levels, PTH levels, or both. The 4 patients described had ESRD, and cinacalcet was administered at a dose ranging between 30 and 180 mg/d for a total duration of 3 weeks to 22 months. All of the patients were on concomitant drugs, mainly vitamin D analogues. Effect of therapy on BMD was available for only one patient, with a reported increase of 11% at the forearm after 1.4 years. Only one case of parathyromatosis resistant to calcimimetics was recently reported in an elderly man on hemodialysis. However, the dose and duration of treatment were not specified [52]. Our patient was started on cinacalcet 30 mg twice daily and had a clear and rapid biochemical improvement within 3 weeks of treatment initiation (Table 1). In view of the short treatment duration and presence of nonspecific complaints, the impact of cinacalcet on her clinical symptoms could not be assessed.

We have therefore described the longest follow-up on a patient with parathyromatosis spanning over 30 years and presented a comprehensive review of this topic including all reported cases with sufficient details for analysis. Clinical characteristics and predictors of parathyromatosis were derived using appropriate statistical analyses. Limitations of this review stem from the inherent limitations of the cases reported to date. They include the limited number of cases due to the rarity of the disease and short-term follow-up, thus rendering the assessment of the long-term impact of calcimimetics on hypercalcemia and bone disease in this condition difficult. Finally, translational implications could not be drawn because of the lack of data relating genotype mutations and/or polymorphisms in key receptors involved in PTH synthesis/secretion to this condition (eg, vitamin D receptor or calcium-sensing receptor).

8. Conclusions

Parathyromatosis is a rare cause of persistent or recurrent HPT, with only 36 case reports detailing this condition, including ours. It is more prevalent in females and subjects with ESRD and is unlikely to have a familial or genetic cause. Median time to reoperation is 3 years in ESRD and 6 years in normal individuals, albeit with a very wide range in both conditions. This entity remains most often difficult to both diagnose preoperatively and to cure in a definitive manner surgically. Individuals with secondary HPT due to chronic kidney disease, and most likely vitamin D deficiency, may have an increased susceptibility to develop parathyroid tissue hypertrophy, tissue that may become particularly friable and likely to spill and seed intraoperatively. Care should be taken while handling parathyroid glands intraoperatively especially in the above-described populations to avoid inadvertent rupture and spillage. Because surgery is most often ineffective in curing parathyromatosis, medical treatment should be considered in an attempt to reduce the deleterious consequences of long-standing untreated HPT. The strategy could possibly include combining a calcimimetic to decrease serum calcium and PTH levels with a bisphosphonate to prevent bone loss, as was done in our patient. The efficacy of this combination in subjects with parathyromatosis, however, remains to be established.

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Conflicts of Interest

The authors declare no conflicts of interest.

REFERENCES


