Cystic Parathyroid Lesions

Functional and Nonfunctional Parathyroid Cysts

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Hypothesis: Functional parathyroid cysts (FPCs) and nonfunctional parathyroid cysts (NPCs) are 2 distinct clinical and histologic entities.

Design: Review of prospective clinical database records.

Setting: Tertiary academic center.


Intervention: Cervical exploration for primary hyperparathyroidism or cervical mass.

Main Outcome Measures: Age, sex, morbidity, imaging results, pathologic findings, cyst characteristics (size, location, and fluid), and perioperative calcium and parathyroid hormone levels.

Results: Cystic parathyroid lesions were found in 48 of 1769 patients (3%) studied. Functional parathyroid cysts were more common than NPCs, arising in 41 of 48 patients (85%), and showed no predisposition for sex or embryologic origin. Single-photon emission computed tomographic imaging failed to localize FPCs in 12 of 37 patients (32%). The fluid in FPCs was clear or colorless in 9 of 15 characterized specimens (60%). Rupture of cystic parathyroid lesions during resection was associated with prolonged elevation of intraoperative parathyroid hormone levels ($P=0.045$). Cystic parathyroid lesions weighing 4 g or more were associated with the development of postoperative symptomatic hypocalcemia ($P=0.03$). Functional parathyroid cysts occurred exclusively in adenomas with cystic change, whereas NPCs (with 1 exception) were without associated adenoma on final histologic examination.

Conclusions: Cystic parathyroid lesions often contain turbid or colored fluid, and FPCs are more common than NPCs. Neck cysts of uncertain origin should be diagnostic aspirated for parathyroid hormone content. During resection, cyst rupture should be avoided, and patients with large cysts should be managed expectantly to forestall the development of symptomatic hypocalcemia. Functional parathyroid cysts and NPCs are likely 2 separate clinical and histologic entities.

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Table. Characteristics of Functional Parathyroid Cysts (FPCs) and Nonfunctional Parathyroid Cysts (NPCs)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FPCs (n=41)</th>
<th>NPCs (n=7)</th>
<th>Total (N=48)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, No. (%)</td>
<td>12 (29)</td>
<td>0</td>
<td>12 (25)</td>
<td>.01a</td>
</tr>
<tr>
<td>Mass or compressive symptoms, No. (%)</td>
<td>6 (15)</td>
<td>5 (71)</td>
<td>11 (23)</td>
<td>.001a</td>
</tr>
<tr>
<td>Diagnosis by computed tomography or ultrasonography as a thyroid cyst, No./total No. (%)</td>
<td>1/20 (5)</td>
<td>4/6 (67)</td>
<td>5/26 (19)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Cyst diameter, cm²</td>
<td>Mean</td>
<td>3.0</td>
<td>3.2</td>
<td>.045a</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.3</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>(1.0-8.0)</td>
<td>(1.5-6.0)</td>
<td>(1.0-8.0)</td>
</tr>
<tr>
<td>Cyst fluid, No. (%)</td>
<td>Clear</td>
<td>9 (60)</td>
<td>13 (65)</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>Turbid</td>
<td>6 (40)</td>
<td>7 (35)</td>
<td>.41</td>
</tr>
<tr>
<td>Position, No. (%)</td>
<td>Superior</td>
<td>25 (61)</td>
<td>28 (58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inferior</td>
<td>16 (39)</td>
<td>20 (42)</td>
<td></td>
</tr>
</tbody>
</table>

a Statistically significant at P=.05.

b Functional parathyroid cyst measurements were based on cyst diameter for a solitary cyst or on overall diameter for a grossly cystic parathyroid gland when multiple cysts were present.

STUDY DEFINITIONS

Intraoperative PTH monitoring was conducted according to the technique previously described in detail by Carty et al. The mean clinical follow-up period was 21.4 months (range, 0.07-170 months). Cystic parathyroid lesions were defined as any parathyroid lesions that were grossly cystic with a predomi-
nant cystic component microscopically, whether lined by para-
thyroid cells or containing parathyroid tissue in its wall or tis-
sue containing significant fluid with an elevated PTH level.

Functional parathyroid cysts were considered present when bio-
chemical primary hyperparathyroidism was diagnosed before sur-
urgery. In contrast, NPCs were considered present in asympto-
matic patients who were eucalcemic before surgery (n=6) or who had no calcium level measured before resection (n=1).

One NPC was diagnosed by preoperative clinical aspiration of
cyst fluid rich in PTH (896 pg/mL) (to convert parathormone
level to nanograms per liter, multiply by 1.0). Single-photon
emission computed tomographic (SPECT) imaging with tech-
netium Tc 99m sulfur colloid was considered accurate when it
correctly lateralized CPLs before surgery. Postoperative sym-
ptomatic hypocalcemia was defined as characteristic symptoms
requiring an adjustment in oral calcium supplementation af-
after surgery. Operative cure was defined as normocalcemia at
more than 5 months of follow-up. Data were compared by χ²
or t test, with statistical significance defined as P.05.

RESULTS

The incidence of CPLs was high at 48 of 1769 patients
(3%). Among 48 patients with CPLs, 41 (85%) had FPCs
and 7 (15%) had NPCs. Although prior studies1,8-10 indi-
cate that NPCs account for 83% to 91% of PCs over-
all, we found that FPCs were much more likely to occur
than NPCs in our series of patients who underwent sur-
gical exploration (P.<.001). One patient with an FPC had
hyperparathyroidism in association with multiple endo-
ctrine neoplasia type 1 (MEN-1), while the other 47 pa-
thents had primary sporadic hyperparathyroidism. The
demographic and diagnostic characteristics of patients
with FPCs and NPCs are summarized in the Table. There
was no predominance of male sex for FPCs; in fact, there
was a trend toward female predominance, with a ratio
of female to male of 2.4:1 (P=.06).

Patients with FPCs had symptoms that included fa-
tigue (51%), arthritis (49%), osteoporosis or osteopenia
(38%), kidney stones (29%), nocturia (28%), depression
(27%), short-term memory loss (25%), gastrointestinal
reflux (15%), peptic ulcer disease (6%), compressive
symptoms (2%), and fracture (2%). Symptoms
suggestive of hyperparathyroidism occurred in 2 pa-
tients with NPCs, both with normal preoperative cal-
ium levels, and included fatigue, nocturia, reflux, oste-
oporosis, and arthritis in both patients and nephrolithiasis
in 1 patient. Overall, symptoms of pri-
mary hyperparathyroidism were present before surgery
in 39 of 41 patients (95%) with FPCs compared with 2
of 7 patients (29%) with NPCs (P.<.001). Compressive
neck symptoms (2 of 7 patients) and palpable neck mass
(5 of 7 patients) were more likely to occur in patients
with NPCs than in patients with FPCs (6 of 41 patients)
(P=.001).

For FPCs and NPCs, there was no correlation be-
 tween CPL weight and preoperative level of calcium or
PTH. As summarized in the Table, NPCs (median, 5.0
range, 1.0-8.0) (1.5-6.0) (1.0-8.0)

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the 97.4% accuracy rate reported for parathyroid lesions overall. With respect to anatomic embryologic origin, the literature describes a predominance of left-sided and inferior PCs. We observed 25 right CPLs (23 FPCs and 2 NPCs) and 23 left CPLs (18 FPCs and 5 NPCs), demonstrating no predominance with regard to laterality (P = .84). Both NPCs and FPCs were no more likely to arise from superior than from inferior parathyroid glands (Table). Histologically, 6 of 7 NPCs were described as benign cysts with an associated rim of normocellular parathyroid tissue, and 1 NPC was believed to have arisen from cystic degeneration of a hypercellular parathyroid gland. Histologically, all 41 FPCs were adenomas with cystic change. We found no patients with multiple cystic glands.

Fluid from CPLs was collected and characterized by aspiration (8 CPLs) or by intraoperative rupture (12 CPLs) in 20 of 48 patients. Although it is classically taught that fluid from an aspirated cervical cyst is clear and colorless in PCs, turbid fluid was present in 4 of 20 CPLs (20%), and straw-colored fluid was present in another 3 of 20 CPLs (15%) and in 1 NPC. Therefore, the “hallmark” clear colorless fluid was encountered in 9 of 15 patients (60%) with FPCs and in 4 of 5 patients (80%) with NPCs, representing only 13 of 20 patients (65%) with CPLs overall. The PTH content of cyst fluid ranged from 896 to 921 057 pg/mL (normal range, 10-65 mL). Cyst fluid was equally likely to be turbid in NPCs compared with FPCs (Table). In 1 patient with an NPC, a clear colorless fluid with a PTH level of 896 pg/mL was the basis for CPL diagnosis, as histologic examination of the resected 5-cm cyst failed to reveal an epithelial lining or discernible parathyroid tissue in the cyst wall.

Intraoperative PTH monitoring has been used at our institution since 1996 and was available for 34 patients with FPCs. Although all patients with FPCs having more than 5 months of follow-up after surgery (34 of 41 patients) were considered biochemically cured at the last follow-up (mean, 25.6 months [range, 5.5-170 months]), the initial postresection intraoperative PTH level met criteria for termination of surgical exploration in only 17 of 34 patients (50%). This proportion is substantially lower than the rate of 94% that our group previously described for concise parathyroidectomy among patients with sporadic primary hyperparathyroidism.7 Our established criteria to terminate parathyroid exploration require a PTH level drop to within the normal range and a drop to less than 50% of the baseline preresection PTH level.7 Among the patients with FPCs having an initial high postresection PTH level and after obtaining 1 to 4 additional postresection levels, an additional 8 of 34 patients had achieved an adequate drop in intraoperative PTH level, and surgery was ended. However, even with multiple postresection intraoperative PTH measurements, 9 of 34 patients with FPCs did not meet criteria for adequate resection at the time surgery was concluded. Great care was taken not to rupture CPLs during dissection and mobilization to facilitate complete resection and to avoid the complication of parathyromatosis. Despite this, rupture of these friable lesions occurred in 10 of 34 cases performed with intraoperative PTH monitoring. When FPCs were ruptured, the initial postresection intraoperative PTH level was more likely to remain elevated (8 of 10 patients [80%]) in contrast to the initial level of patients whose cyst remained intact (10 of 24 patients [42%]) (P = .04). Moreover, 5 of 10 ruptured cysts (50%) required at least 2 postresection PTH measurements or did not meet criteria for successful resection when surgery was terminated vs 4 of 24 cysts (17%) resected without rupture (P = .045).

In this series, there was no mortality, permanent hematoma, permanent hypoparathyroidism, or recurrent laryngeal nerve injury. In 12 patients, CPL resection required concurrent thyroidectomy because of anatomic configuration (7 patients) or for diagnosis (5 patients). Although no patient required intravenous calcium replacement after surgery, transient symptomatic hypocalcemia was common, occurring in 6 of 48 patients (13%). In patients having CPLs with symptomatic hypocalcemia, the median CPL weight was 4047 mg compared with 1666 mg in patients without symptomatic hypocalcemia (P = .03). When CPLs weighed 4 g or more, the rate of postoperative paresthesias was 43% compared with 10% when CPLs weighed less than 4 g (P = .03). Patients with ruptured cysts were not more likely to have postoperative paresthesias. At last follow-up, 1 patient with an FPC had normocalcemic hyperparathyromonemia (secondary hyperparathyroidism with vitamin D deficiency), and all patients having FPCs with more than 5 months of follow-up had durably normal calcium levels.

**COMMENT**

In case reports and small series, PCs have historically been observed during parathyroid exploration for goitrous masses and less often have been described during parathyroid exploration for hyperparathyroidism.8,10,12 The findings of our series based on prospective clinical data document a common incidence of 3% (48 of 1769 patients) for CPLs among patients undergoing parathyroidectomy.

Based on available retrospective biochemical evidence for hyperparathyroidism, it has been stated that NPCs must be distinguished from the rarer FPCs because presentation, evaluation, and management may differ.10 Functional parathyroid cysts have been reported to occur more commonly in men, and both PCs and FPCs were previously thought to arise from inferior parathyroid glands.2-5,10 Our series establishes that FPCs are much more common than NPCs, are not more common in men, and have an equal affinity for superior and inferior glands embryologically. Although other studies documented a disposition for left laterality for PCs, our series demonstrates that CPLs had an even distribution with regard to side.

It stands to reason that FPCs would be less likely than NPCs to result in compressive symptoms because the functional status of FPCs might be expected to lead to earlier clinical presentation. This concept is demonstrated by our results. The larger size of NPCs in general often leads to a more extensive imaging evaluation, including ultrasonography, computed tomography, and possible magnetic resonance imaging. It is less intuitive that SPECT imaging would be frequently nondiagnostic in lo-
calizing CPLs, but our observed accuracy rate of 68% (25 of 37 patients) differs greatly from the 97.4% previously reported for localization of parathyroid lesions in general.\(^7\) This confirms the observation in several prior studies\(^{13-15}\) of the difficulty in diagnosing PCs using imaging alone.

Only 1 FPC was associated with MEN-1 in our study. This contrasts with a prior postulate that NPCs are likely to have been previously functional and to have arisen in the setting of another hyperfunctioning gland.\(^6\) Clear colorless fluid on aspiration of a cystic neck mass is suggestive of PCs,\(^{2,5,6,11}\) but the findings of our study confirm the initial report by Layfield\(^{17}\) that CPL fluid is often turbid or colored. Therefore, the presence of turbid or colored fluid does not exclude the diagnosis of CPL. Before the use of aspiration and fluid analysis for PTH level, most PCs were discovered at the time of exploration for presumed thyroid disease, leading to the recommendation that thyroglobulin and PTH levels should be measured for all cystic neck masses of presumed thyroid origin with clear aspirates.\(^{18,19}\) We would adjust this recommendation to include aspiration of cystic neck masses for PTH analysis regardless of fluid character. An elevated PTH level in aspirated cyst fluid is diagnostic of PC,\(^{2,5,6,8}\) but it is important to measure the PTH level using an intact PTH assay, as false-negative results have been described using earlier N-terminal PTH assays.\(^6\)

In this study, we included cystic structures with normocellular parathyroid tissue (mostly NPCs) and cystic structures with parathyroid adenoma (all FPCs) not only because both are PCs by definition but also because they may be indistinguishable when encountered clinically, especially during preoperative imaging. This is in agreement with Rosenberg et al,\(^8\) who described PCs as arising in 2 different settings, (1) as the histologic degeneration of an adenoma or a hyperplastic gland or (2) as a true cyst with an epithelial lining. In contrast, Ippolito et al\(^{10}\) defined true PCs as being exclusively nonfunctional, as well as having an epithelial lining, an inferior embryologic origin, and clear water fluid. At the outset of our study, we observed that 3 of 7 (43%) of our confirmed NPCs were of superior embryologic origin and that 1 of 5 (20%) contained turbid or colored fluid. However, all of the FPCs in our series arose as histologic degeneration of an adenoma or a hyperplastic gland, while 6 of 7 NPCs had an epithelial lining. Based on histologic assessment in our study, it seems likely that true PCs as described by Ippolito et al\(^{10}\) are NPCs and that all FPCs are actually parathyroid adenomas with cystic degeneration. Therefore, we use the term cystic parathyroid lesion rather than parathyroid cyst when referring to both NPCs and FPCs to reflect this important distinction. If NPCs alone are considered PCs, they would indeed be rarer. We found a greater disposition for clear fluid in 4 of 5 patients with NPC (80%) and for left laterality in 5 of 7 patients (71%), but it is difficult to draw conclusions from these few patients.

Certainly, FPCs should be resected according to the established guidelines for patients with primary hyperparathyroidism.\(^{20}\) It has been suggested that the optimal treatment for NPCs is aspiration alone.\(^3\) Prinz et al\(^5\) recommended initial treatment with aspiration and pos-

When defined as parathyroid lesions that are grossly cystic with a predominant cystic component microscopically, CLPs are common and are seen more often with symptoms of hyperparathyroidism than with compression or visible mass. Demographically, CPLs have no predominance of sex, left-sidedness, or inferior position. When a CPL is cystic, SPECT imaging does not reliably identify the laterality of the culprit parathyroid gland. Fluid in CPLs can be turbid or colored and should be aspirated for PTH content to facilitate diagnosis and to guide management. Functional parathyroid cysts and NPCs are likely to 2 separate clinical entities, as FPCs occur in the setting of adenomas with cystic degeneration, while NPCs may be histologically true PCs. Cystic parathyroid lesions should be surgically resected, and cyst rupture should be avoided to prevent skewed elevation of intraoperative PTH levels. Patients with large cysts are at higher risk of symptomatic hypocalcemia after surgery and should be managed expectantly.

CONCLUSIONS

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Author Contributions: Dr McCoy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: McCoy, Yim, Zuckerbraun, and Carty. Acquisition of data: McCoy, Zuckerbraun, and Carty. Analysis and interpretation of data: McCoy, Yim, Peel, and Carty. Drafting of the manuscript: McCoy, Yim, and Carty. Critical revision of the manuscript for important intellectual content: McCoy, Yim, Ogilvie, Peel, and Carty. Statistical analysis: McCoy, Yim, and Carty. Administrative, technical, and material support: McCoy, Yim, Ogilvie, and Carty. Study supervision: Carty.
McCoy and colleagues report their findings in 48 patients who had FPCs (n = 41) or NPCs (n = 7). As they mention in their article, finding more FPCs than NPCs differs from most other articles in the literature. This is obviously because patients were referred to this excellent group of endocrine surgeons for their expertise in treating patients who have primary hyperparathyroidism.

What is the usual presentation of patients with parathyroid cysts? Patients with NPCs usually have a large cystic mass (median, 5.0-cm diameter in this series) as observed by physical examination or ultrasonography or at operation. Fine-needle aspiration usually (65%) [13 of 20 patients] in this series] reveals clear colorless fluid. Such fluid is virtually pathognomonic for parathyroid cysts. Parathyroid hormone assay of the cyst fluid can confirm the diagnosis, although it is probably unnecessary when the fluid of a cyst is clear and colorless. When cyst fluid is yellow or turbid, however, assaying for PTH level certainly can establish the correct diagnosis. Most articles in the literature suggest using a midregional or C-terminal assay rather than an N-terminal PTH assay, because midregional assays are more likely to confirm the diagnosis.

Patients who have primary hyperparathyroidism and cystic parathyroid tumors should be treated in a similar fashion as those who have noncystic parathyroid tumors. Although the authors had no patients with multiple parathyroid cysts, patients with multiple cystic parathyroid tumors have been described.

The authors report that 10 of 34 patients who had intraoperative PTH level monitoring had the cysts rupture during their parathyroid operation. This finding documents the difficult nature of removing these cystic lesions without perforating the cyst. Rupturing of any parathyroid tumor should be avoided because it can cause parathyromatosis, as the authors mention. The authors also report that intraoperative PTH assay results failed to drop by 50% in 8 of 10 such patients who had parathyroid cysts. It would be interesting to know whether they have any technical advice about how to avoid cyst rupture and whether the high intraoperative PTH assay results led to a prolonged search for other abnormal parathyroid glands. How would they manage such a patient today since intraoperative PTH level monitoring is obviously misleading?

How should patients with NPCs be managed? Aspiration usually eliminates the cystic mass, but these lesions often reaccumulate fluid. Tetracycline or alcohol could be injected into these cysts because they are almost always benign, but for upper cysts one must be concerned about injury to the adjacent recurrent laryngeal nerve. Patients with large parathyroid cysts sometimes also have pressure symptoms, so surgical removal should be considered if a large cyst recurs.

In conclusion, the authors provide useful information about parathyroid cysts and their management. Certainly in response to their initial question, FPCs and NPCs differ.

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