ORIGINAL ARTICLE

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.

Patients: Patients enrolled in a prospective surgical database between January 1, 1990, and May 31, 2007.

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=.045). Cystic parathyroid lesions weighing 4 g or more were associated with the development of postoperative symptomatic hypocalcemia (P=.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 diagnostically 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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PARATHYROID CYSTS (PCs) ARE intriguing entities that are thought to be encountered rarely in endocrine surgery. Their etiology has been pondered since the first case was described in 1905 by Goris.[1] Since then, only about 300 cases have been reported in the world literature as case reports and small series. It has historically been taught that nonfunctional parathyroid cysts (NPCs) are more common,[2-5] that NPCs are generally located in the inferior position anatomically,[2-5] and that functional parathyroid cysts (FPCs) are more likely to arise in men.[2] Management strategies for PCs differ in the literature.[2-4,6] Using the definition of cystic parathyroid lesions (CPLs) as parathyroid glands that were grossly cystic with a predominant cystic component microscopically, we describe herein a series of CPLs managed using current imaging and intraoperative parathyroid hormone (PTH) monitoring techniques, with the aim of clarifying the incidence, characteristics, and best clinical management of these lesions.

See Invited Critique at end of article

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METHODS

PATIENT POPULATION AND CLINICAL DATABASE

Under a protocol approved by the University of Pittsburgh Institutional Review Board, Pittsburgh, Pennsylvania, the prospectively entered clinical data of 1769 consecutive patients undergoing parathyroidectomy for primary hyperparathyroidism diagnosed be-

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

Characteristic	FPCs (n=41)	NPCs (n=7)	Total (N=48)	*P* Value
Male sex, No. (%)	12 (29)	0	**12** (25)	.01[a]
Mass or compressive symptoms, No. (%)	6 (15)	5 (71)	**11** (23)	.001[a]
Diagnosis by computed tomography or ultrasonography as a thyroid cyst, No./total No. (%)	1/20 (5)	4/6 (67)	**5/26** (19)	<.001[a]
Cyst diameter, cm[b]				.045[a]
Mean	3.0	4.4	3.2	
Median	2.3	5.0	2.5	
Range	(1.0-8.0)	(1.5-6.0)	(1.0-8.0)	
Cyst fluid, No. (%)				.42
Clear	9 (60)	4 (80)	**13** (65)	
Turbid	6 (40)	1 (20)	**7** (35)	
Position, No. (%)				.41
Superior	25 (61)	3 (43)	**28** (58)	
Inferior	16 (39)	4 (57)	**20** (42)	

[a] Statistically significant at $P \leq .05$.
[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.

fore surgery and intraoperative or postoperative diagnosis of a PC or cystic parathyroid gland between January 1, 1990, and May 31, 2007, were queried using the term *parathyroid cyst*. The deidentified data of 48 patients found to have CPLs, including 6 patients diagnosed at resection of a presumed thyroid mass or cyst, were then examined for presentation, morbidity, demographics, pathologic findings, history of irradiation, preoperative imaging results, perioperative calcium and PTH levels, cyst characteristics (size, location, and fluid), and operative approach (including intraoperative PTH monitoring).

STUDY DEFINITIONS

Intraoperative PTH monitoring was conducted according to the technique previously described in detail by Carty et al.[7] 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 predominant cystic component microscopically, whether lined by parathyroid cells or containing parathyroid tissue in its wall or tissue containing significant fluid with an elevated PTH level. Functional parathyroid cysts were considered present when biochemical primary hyperparathyroidism was diagnosed before surgery. In contrast, NPCs were considered present in asymptomatic 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 technetium Tc 99m sulfur colloid was considered accurate when it correctly lateralized CPLs before surgery. Postoperative symptomatic hypocalcemia was defined as characteristic symptoms requiring an adjustment in oral calcium supplementation after surgery. Operative cure was defined as normocalcemia at more than 5 months of follow-up. Data were compared by χ^2 or *t* test, with statistical significance defined as $P \leq .05$.

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 studies[2,4,8-10] indicate that NPCs account for 83% to 91% of PCs overall, we found that FPCs were much more likely to occur than NPCs in our series of patients who underwent surgical exploration ($P<.001$). One patient with an FPC had hyperparathyroidism in association with multiple endocrine neoplasia type 1 (MEN-1), while the other 47 patients 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 fatigue (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 patients with NPCs, both with normal preoperative calcium levels, and included fatigue, nocturia, reflux, osteoporosis, and arthritis in both patients and nephrolithiasis in 1 patient. Overall, symptoms of primary 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 between CPL weight and preoperative level of calcium or PTH. As summarized in the Table, NPCs (median, 5.0 cm) were larger in diameter than FPCs (median, 2.3 cm) ($P=.045$). Patients with NPCs were more likely (6 of 7 patients [86%]) than patients with FPCs (18 of 41 patients [44%]) to have undergone preoperative computed tomography or ultrasonography ($P=.04$) and to have been misdiagnosed before surgery as having a thyroid mass or cyst ($P<.001$). In patients with FPCs, preoperative SPECT imaging was lateralized correctly in 25 of 37 patients so imaged (68%), which is considerably lower than

the 97.4% accuracy rate reported for parathyroid lesions overall.[7] With respect to anatomic embryologic origin, the literature describes a predominance of left-sided and inferior PCs.[2,4,5,9] 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,[2,6,11] 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[7] 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 hyperparathormonemia (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.[8,11,12] 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,[2,8] 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[2-5] 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.[16]

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,[2,3,6,8] 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.[4]

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[11] recommended initial treatment with aspiration and possible tetracycline sclerosis after a second recurrence, but they suggested consideration of surgical management when cyst aspiration or sclerosis failed and for patients with compressive symptoms. Ujiki et al[5] concluded that most cysts recurred after aspiration and that surgical management is beneficial. Although unusual, at least 2 cases of FPC carcinoma have been reported in the literature.[21,22] No carcinoma within NPCs was found in our series; one NPC was described as having hyperplastic parathyroid tissue and may have been a subclinical parathyroid adenoma. We recommend surgical treatment of all CPLs regardless of functional status, as the morbidity of surgery in expert hands is low.

Larger CPLs (≥4 g) are associated with a higher likelihood of postoperative symptomatic hypocalcemia. However, larger cysts are more likely to be biochemically nonfunctional. Therefore, it behooves the careful surgeon to consider the diagnosis of CPL before surgery by aspirating cyst fluid for intact PTH assay. When CPLs are ruptured during resection, intraoperative PTH concentrations can remain elevated, prolonging surgery, so it is prudent to use meticulous dissection to avoid cyst rupture.

CONCLUSIONS

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 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.

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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.

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INVITED CRITIQUE

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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