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A single-institution 25-year review of true parathyroid cysts

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Abstract *Background:* Parathyroid cysts (PCs) are rare, and their origin is a subject of debate. They have been described as either functional, causing hyperparathyroidism, or non-functional in eucalcaemic patients. *Patients and methods:* We have performed a 25-year departmental review of PCs. Features studied included the clinical presentation and intra-operative findings, and a histological review was performed. Cases of cystic degeneration of parathyroid adenomas and pseudocystic change were excluded. *Results:* Over 25 years, 22,009 thyroidectomies and 2,505 parathyroidectomies were performed in our department. Amongst these, 38 non-functional PCs were documented in 37 patients. The mode of presentation included incidental findings on routine chest x-ray, compressive symptoms or an asymptomatic palpable neck mass. Aspiration was the initial treatment in 14 patients and was curative in 10 of these. Four out of 14 patients underwent surgical procedures for recurrence of the cyst that occurred 6 to 48 months after aspiration. In 27 patients, surgery was performed and all identified PCs were localized in the inferior parathyroid glands. Histologically, the cyst wall consisted in associations of lymphoid, muscular, thymic, salivary, adipose and mesenchymal tissues. *Conclusions:* PCs are rare but should be included within the differential diagnosis of a neck lump. True PCs are non-functional. Pathological and immunohistochemical findings are suggestive of a branchial origin. Fine-needle aspiration may be curative and is diagnostic due to the characteristic appearance of the fluid and high PTH levels on assay.

Keywords Parathyroid cysts

Introduction

Parathyroid cysts (PCs) are rare lesions of the neck and superior mediastinum that were first described by Sandstrom in 1880 [1]. They typically present as a palpable neck mass or as an incidental finding during neck surgery. In 1905, Goris performed the first resection of a cervical PC [2], and less than 300 cases have been reported in the literature since. Less than 10% of PCs are associated with hyperparathyroidism, the first such case being reported in 1952 [3]. This review documents our 25-year experience with PCs.

Patients and methods

We have performed a review of patients found to have PCs in our department during the last 25 years. We have excluded cases of cystic degeneration of parathyroid ad-

Table 1 Parathyroid cysts documented over 25 years at La Timone, Marseille

Age (year)/ sex (M/F)	Clinical presentation	Imaging findings; fine-needle aspiration	Serum PTH (1–84); serum calcium (Mmol/l); intracystic PTH	Treatment
52/M	Asymptomatic thyroid nodule	NA	NA/2.30/NA	Surgery, 20 mm R PIII
28/F	Asymptomatic thyroid nodule	Cold nodule	NA/2.25/NA	Surgery, 10 mm R and 50 mm L PIII
38/F	Asymptomatic thyroid nodule	30-mm cystic nodule	NA/2.32/NA	Surgery, L PIII
34/F	Asymptomatic thyroid nodule	NA	NA/2.13/NA	Surgery, 15 mm L PIII
29/F	Asymptomatic thyroid nodule	40-mm cyst	40/2.40/1,060[a]	Surgery, R PIII
57/F	Asymptomatic mediastinal mass on MRI	40-mm cyst + tracheal deviation+ oesophageal compression	31/2.45/1,300[a]	Surgery, L PIII
26/F	Mediastinal mass on chest x-ray in dyspnoic patient	60-mm cyst+tracheal deviation	15/2.44/380[a]	Surgery, L PIII
70/F	Mediastinal mass on chest x-ray in dyspnoic patient	55-mm cyst+tracheal deviation	42/2.30/2,300[b]	Surgery, R PIII
51/F	Asymptomatic mediastinal mass on routine chest x-ray	47-mm cyst+tracheal deviation	25/2.44/175[a]	Surgery, R PIII PC fluid
35/F	Asymptomatic thyroid nodule	24-mm cyst; FNA: 10 cc of water-clear fluid	25/2.20/3,000[b]	Aspiration, recurrence 6/12; surgery, 20 mm intrathyroidal
30/F	Asymptomatic thyroid nodule	50-mm cyst	30/2.48/400[a]	Surgery, L PIII
30/F	Asymptomatic thyroid nodule	Cold nodule	NA/2.23/2,500[b]	Surgery, 15 mm R PIII
17/M	Asymptomatic thyroid nodule	Cold nodule+tracheal deviation	27/2.20/NA	Surgery, L PIII 40 mm
39/F	Asymptomatic thyroid nodule	Cold nodule	41/2.32/720[a]	Surgery, R PIII 60 mm
70/F	Cervical mediastinal mass on CT scan in dyspnoic patient	40-mm cyst+tracheal deviation; FNA: 25 cc of water-clear fluid	41/2.20/130[a]	Aspiration, recurrence 15/12; surgery, 13 mm R PIII
46/F	Asymptomatic thyroid nodule	30-mm cyst; FNA: 15 cc of water-clear fluid	24/2.30/500[a]	Aspiration, recurrence 14/12; surgery, R PIII 20 mm
64/M	Cervico-mediastinal thyroid nodule on CT in dyspnoic patient	60-mm cyst+tracheal deviation; FNA: 18 cc of water-clear fluid	26/2.30/97[a]	Surgery, L PIII
62/F	Thyroid nodule + compressive symptoms	60-mm cyst+tracheal deviation	NA/NA/NA	Surgery, L PIII
59/F	Asymptomatic thyroid nodule	28-mm cyst	NA/2.27/1,150[a]	Surgery, L PIII
44/F	Asymptomatic thyroid nodule	20-mm cyst	NA/NA/NA	Surgery, L PIII
58/M	Asymptomatic thyroid nodule	Cold nodule	NA/2.24/960[b]	Surgery, L PIII 30 mm PC
24/F	Asymptomatic goiter	Cold nodule	NA/2.10/NA	Surgery, L PIII 20 mm
39/M	Cervical-mediastinal goiter+ hoarseness	Cold nodule+tracheal deviation	34/2.27/1260[b]	Surgery, L PIII 40 mm
51/F	Asymptomatic goiter	34-mm cyst	25/2.31/1,300[a]; 1,400[b]	Surgery, L PIII
35/F	Asymptomatic thyroid nodule	30-mm cyst; FNA: 20 cc water-clear fluid	24/2.25/1,200[a]	Aspiration, recurrence 48/12; aspiration, recurrence 6/12; surgery, endoscopic L PIII
24/F	Asymptomatic mediastinal mass on RX	Cold nodule+tracheal deviation	NA/NA/NA	Surgery, L PIII 40 mm
46/M	Asymptomatic thyroid nodule	NA	NA/2.50/NA	Surgery, L PIII PC
31/M	Asymptomatic mediastinal mass on routine chest x-ray	40-mm cervical and antero-mediastinal cyst; FNA: 20 cc water-clear fluid	14/2.32/240[a]	Aspiration, no recurrence 24/12
68/F	Asymptomatic thyroid nodule	32-mm cervical cyst; FNA: 13 cc water-clear fluid	20/2.36/198[a]	Aspiration, no recurrence 96/12

Table 1 (continued)

Age (year)/ sex (M/F)	Clinical presentation	Imaging findings; fine-needle aspiration	Serum PTH (1–84); serum calcium (Mmol/l); intracystic PTH	Treatment
53/F	Asymptomatic thyroid nodule	47-mm cervical cyst; FNA: 40 cc water-clear fluid	26/2.41/245[a]	Aspiration, no recurrence 60/12
40/F	Asymptomatic thyroid nodule	35-mm cervical cyst; FNA: 22 cc water-clear fluid	38/2.21/202[a]	Aspiration, no recurrence 12/12
30/F	Asymptomatic thyroid nodule	42-mm cervical cyst; FNA: 20 cc water-clear fluid	40/2.26/170[a]	Aspiration, no recurrence 172/12
40/F	Asymptomatic thyroid nodule	40-mm cervical cyst; FNA: 30 cc water-clear fluid	16/2.36/82[a]	Aspiration, no recurrence 12/12
33/F	Asymptomatic thyroid nodule	15-mm cervical cyst lesion; FNA: 5 cc water-clear fluid	28/2.26/2,000[a]	Aspiration, no recurrence 12/12
38/F	Asymptomatic thyroid nodule	35-mm cervical cyst; FNA: 21 cc water-clear fluid	22/2.35/364[a]	Aspiration, no recurrence 12/12
29/F	Asymptomatic thyroid nodule	33-mm cervical cyst; FNA: 10 cc water-clear fluid	NA/NA/150[a]	Aspiration, no recurrence 60/12
34/F	Asymptomatic thyroid nodule	34-mm cervical cyst lesion; FNA: 12 cc water-clear fluid	37/2.25/81[a]	Aspiration, recurrence 6/12; aspiration, no recurrence 6/12

FNA Fine-needle aspiration, *NA* not assessed, *L PIII* left inferior parathyroid gland, *R PIII* right inferior parathyroid gland, */12* follow-up in months
[a]Intact PTH (normal<65 pg/ml)
[b]C-terminal/mid-region (normal<105 pg/ml)

enomas and pseudocystic change where no identifiable lining was found at histology. The mode of presentation of the cyst and all data including preoperative imaging, fine-needle aspiration cytology, serum calcium, serum and intracystic parathyroid hormone level, operation notes and pathology have been documented (Table 1). In one PC, an immunohistochemical study of the wall was also performed.

Results

Between 1979 and 2004, 22,009 thyroidectomies and 2,505 parathyroidectomies were performed in our department. Thirty-eight PCs were identified in 37 patients. They included 7 men and 30 women, with a mean age of 42 years (range 17–70 years).

The mode of presentation was: discovery on a routine chest x-ray in 2 patients; compressive symptoms—dyspnoea or dysphagia—in 6 patients; asymptomatic palpable mass in 29 patients. None of the patients presented with hyperparathyroidism.

PCs presented clinically as smooth, non-tender, soft, solitary lumps. Depending on the circumstances and availability, a variety of radiological investigations were performed to further define the nature and anatomical position of the lesion. When performed, radioiodine thyroid scanning showed an area of no uptake. Ultrasound, CT or MRI scans localized the lesion, revealed the cystic nature and, in nine patients, demonstrated tracheal deviation or compression.

Fourteen patients underwent fine-needle aspiration as an out-patient, and this was diagnostic in all cases. The intracystic fluid ranged from 10 to 40 cc and was water-clear. The intact PTH measurement in the cyst fluid ranged from 81 to 2000 pg/ml. In one patient, the cyst fluid also contained 3,000 pg/ml of C-terminal/mid-region PTH. Serum calcium, phosphorus and/or intact PTH levels were consistently normal in 34 patients. In three patients, the data were not available.

The preoperative diagnosis was non-functional PC in 14 patients and a possible thyroid lesion in 23. In the former group, curative percutaneous aspiration of the cyst fluid was performed, with definitive resolution of the cyst confirmed by imaging in ten of the 14 patients, nine requiring a single aspiration and one a second aspiration. Four of 14 patients underwent surgical procedures for recurrence of the cyst after a single unsuccessful aspiration in three cases and a second aspiration in another. Recurrences occurred from 6 months to 48 months after the initial aspiration. The latter group underwent surgery. An open procedure was performed in 26 out of 27 patients, with one patient undergoing an endoscopic parathyroidectomy via a lateral approach as favoured by our unit. All cervical–mediastinal PCs were removed by a cervical incision.

At operation, all cysts had a well-defined plane of dissection, with the exception of one cyst that was intrathyroidal. All three other parathyroid glands were examined during open surgery and microbiopsy of normal appearing glands was performed in six patients. One patient presented with two PCs. The origin of the cyst was from an inferior (PIII) gland in all operated cases, 16 in the left gland and 12 in the right. In patients who did not undergo surgery, eight PCs were clearly located in the left, and two in the right inferior parathyroid glands.

Intra-operatively, the cysts were thin-walled, translucent and unilocular, with diameters ranging from 10 to 60 mm (mean 34.5 mm). In 13 patients, fluid withdrawn intra-operatively was water-clear, with a mean intracystic C-terminal/mid-region PTH of 1,900 pg/ml (range 960 to 2,000 pg/ml) and a mean intact PTH level of 552 pg/ml (range 97 to 1,300 pg/ml).

Microscopic examination showed the cyst to be composed of a connective tissue wall lined by a single thin layer of cuboidal cells. Nests of parathyroid cells were found embedded deeply or compressed around the cyst wall without signs of acute and chronic organisation. Beneath the epithelium, various combinations of mesenchymal cells; thymic remnants; salivary gland heteropia; and adipose, muscular and lymphoid tissue were also noted. PCs were on occasion also found to be situated within an otherwise normal parathyroid gland. In the patient with an intrathyroidal cyst, parathyroid tissue could not be identified in the specimen. Given the elevated cyst PTH level and no identification of the inferior parathyroid gland, we presume that the cyst originated from a P III gland. In one non-functional PC, an immunohistochemical study of the wall was performed, which demonstrated that the lining stained positively for low-molecular-weight keratins (AE1–AE3, CK7, pan-keratin) and mesenchymal markers (HBME1, vimentin). The wall stained negatively for high-molecular-weight keratins (CK 19), chromogranin and NSE. A nest of parathyroid cells stained positively for chromogranin.

In all patients pre- and postoperative laryngoscopy evaluation was performed. Days 1, 2 and 8 calcium, phosphorus and parathyroid hormone levels were obtained in all patients who underwent surgery. No recurrent nerve palsies or temporary and definitive hypoparathyroidism was reported. In non-operated patients, a follow-up ranging from 1 to 14 years (mean 3.9 years) was available, which documented the resolution of the cysts by ultrasonography or CT scan, with normal serum calcium, phosphorus and parathyroid hormone level in all patients.

Discussion

Parathyroid cysts are rare clinical and pathologic entities, with less than 300 cases reported in the world literature. This series represents the largest single-institution experience of true non-functional PCs published to date. They are reported to occur in 0.5% of parathyroid diseases [4] and represent 1% of all cystic lesions of the neck [5]. Mediastinal localization has been reported in up to 30% of cases [6]. PCs have been previously divided in two groups, functional, which cause hyperparathyroidism and non-functional, which do not. This view may be challenged since embryological and histological data suggest that functional cysts appear to be a different entity [7–10].

True PCs present most commonly in middle-aged women, with a female to male ratio of 2.5:1. They are usually asymptomatic and may be discovered on a routine chest x-ray or on routine clinical examination, where it may be mistaken for a goiter, especially when the PC is partially descended into the antero-superior mediastinum. Such cases represent 60% of all mediastinal PCs and are mainly associated with an inferior parathyroid [11].

The most common presentation of a PC is a cystic lesion during cervicotomy for a thyroid nodule. Such cysts may occasionally cause compressive symptoms such as dysphagia, dyspnoea, hoarseness or pain, especially when localized in the mediastinum [12–14]. Cases complicated by massive haemorrhage into the cervical tissue and the mediastinum have also been reported [15–17], but these hematomas are more usually related to the cystic degeneration of an adenoma than with a true non-functional cyst.

At physical examination, PCs tend to be soft, mobile, non-tender masses, usually located in the lower part of the neck but can arise in any site between the jaw and the mediastinum [18, 19].

On radio-iodine thyroid scans, PCs appear as an area of absent uptake. Tl-201-Tc-99m pertechnetate subtraction or sestamibi scintigraphy rarely yields positive results, and current imaging techniques like sonography, CT scan and MRI may demonstrate the cystic nature of these lesions but are usually not able to determine the exact aetiology [20]. Defects of the branchial apparatus, thyroid cysts and lymphatic-vascular anomalies may be included within the differential diagnosis [21].

Fine-needle aspiration is the main diagnostic tool in the management of non-functioning PC. In 1953, Crile and Perryman were the first to correctly diagnose a PC preoperatively by aspirating parathyroid oxyphil cells [22]. When intracystic fluid is water-clear and colourless, it is very suggestive of a parathyroid origin [23]. In 1963, Chimènes first commented on the high levels of PTH on aspirated material, and this now represents a universally accepted criterion for the diagnosis of a PC [24]. The PTH concentrations in the cyst fluid are elevated many times above serum parathyroid levels, and thyroglobulin and calcitonin levels should be undetectable, in contrast with a thyroid cyst which has higher thyroglobulin concentration, with undetectable or low PTH levels [25]. However, detection of high PTH levels does not indicate that the cyst is functioning [8, 13]. Indeed, all patients who had hormone measurements on aspirated cystic fluid had elevated

C-terminal/mid-region and intact parathyroid hormone levels but normal serum calcium and PTH levels. Some authors have stated that C-terminal/mid-region parathyroid hormone determination should be the assay of choice since the intact-specific assay could be normal or only slightly increased [5] because the cyst may contain breakdown products rather than the intact PTH molecule itself [26]. Indeed, intracystic PTH assay may be useful when histological diagnosis is doubtful in PCs discovered during cervicotomy [27]. We also have one experience where a PTH assay yielded correct diagnosis in a case of intrathyroidal localization of a cyst where parathyroid tissue could not be identified histologically.

The management of non-functioning PCs is a matter of debate. Following the first therapeutic needle aspiration by Clark [22] in 1978, other successful outcomes of this procedure have followed [28, 29]. However, PCs can recur after conservative treatment, and, although repeated aspirations may be performed, the effectiveness of this approach is variable [30, 31]. Intracystic tetracycline injection may also be used in patients with a recurrence [32–34]. However, this has been associated with neck pain, neurotoxicity and recurrent nerve palsy due to leakage of the sclerosing agents through a disrupted thin cyst wall [35, 36]. Overall, fine-needle aspiration under ultrasound guidance with PTH fluid assay represents the approach of choice for both diagnosis and initial treatment since this is safe, easy and repeatable. Repeated recurrence may be treated surgically, but this is not imperative since non-functioning PCs are virtually never cancer [37, 38]. The effectiveness of this approach clearly requires long-term follow-up.

There are several theories concerning the origin of PC that may be summarized as follows:

1. Some PCs arise from a pre-existing parathyroid adenoma or an hyperplastic gland [22, 39, 40] in patients presenting with hyperparathyroidism. However, these are not true cysts [8–10], but represent cystic degeneration of a parathyroid adenoma or pseudocystic change in a hyperplastic gland.
2. The microcyst theory suggests that PCs originate from an accumulation or retention of secretions, with a gradual enlargement or coalescence of the cysts [41]. In autoptic series, microcysts are common, increase with age and may be detected in 50% of otherwise normal parathyroid glands [42]. Whilst it is conceivable that they could become grossly visible, it remains to be explained why PCs are rare and occur in young patients and microcysts are so common particularly in older patients.
3. PCs may be persistent embryological remnants [43]. The inferior parathyroid originates from the third branchial pouch with the thymus from which it normally separates. A variable number of small epithelial tubules, canals of Kürsteiner, arise intimately related to the thymic tissue [44] and extend into surrounding connective tissue, possibly persisting into postnatal life as vesicular, canalicular or gland-like rudiments, giving origin to a PC. This theory is compatible with our series of 38 true PCs, given that all were located in the inferior parathyroid glands. Furthermore, various combinations of lymphoid, muscular, thymic, salivary, adipose and mesenchymal tissues were found in the cyst wall at light microscopy, findings that are highly suggestive of a branchial origin [45].

Conclusion

Parathyroid cysts are rare but must be included within the differential diagnosis of a neck lump. True PCs are non-functional and are probably of branchial origin. Fine-needle aspiration is diagnostic and may be curative.

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