Small nonfunctional parathyroid cysts: single institution experience

Ljubica Fustar Preradovic¹, Davorin Danic², ³ and Radan Dzodic⁴, ⁵

¹ Department of Pathology and Cytology, Dr. Josip Bencevic General Hospital, Slavonski Brod, Croatia
² Department of Otorhinolaryngology and Head and Neck Surgery, Dr. Josip Bencevic General Hospital, Slavonski Brod, Croatia
³ Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
⁴ School of Medicine, University of Belgrade, Belgrade, Serbia
⁵ Institut of oncology and radiology of Serbia, Belgrade, Serbia

Abstract. Parathyroid cysts (PCs) account for less than 1% of all parathyroid lesions and are most commonly located along thyroid lobes, rarely at ectopic sites. PCs are important because they can pose a differential diagnostic challenge against other cystic formations of the neck. PCs can be functional (elevated serum parathyroid hormone level) and nonfunctional. Four cases of nonfunctional PCs are presented. All four female patients underwent physical examination and ultrasonography of the neck with ultrasound-guided fine-needle aspiration biopsy (UG-FNA). The material thus obtained was stained by the standard May-Grünwald-Giemsa method. Parathyroid hormone level was determined in aspirate and serum, along with serum levels of total calcium, inorganic phosphates. In two asymptomatic patients, remission occurred after initial aspiration biopsy; one patient had compression syndrome with vocal cord paresis that required surgical treatment; and one patient had cyst recurrence that was surgically removed. Cystic neck masses can pose a major differential diagnostic problem considering different approach, treatment method, and preoperative and postoperative follow up. Surgical treatment is necessary in case of functional and large nonfunctional PCs (due to compression syndrome), whereas individualized therapeutic approach is used in case of small nonfunctional PCs. Ultrasonography with UG-FNA, cytologic analysis of the material obtained, and determination of parathyroid hormone level in aspirate and serum are crucial for making an accurate diagnosis.

Key words: Parathyroid hormone, Cyst, Ultrasonography, Cytology

PARATHYROID CYSTS (PCs) are rare pathologic masses that pose a diagnostic and therapeutic challenge. To date, around 300 PC cases have been described in the literature [1]. Sandström, a Swedish anatomist, was the first to describe parathyroid glands (PG) in 1880. Goris, a Belgian surgeon, was the first to perform and describe surgical extirpation of PC in 1905. In 1953, Crile reported the first case of PC diagnosed by fine-needle aspiration (FNA) [2].

PCs are mostly found on the neck, can involve any PG, but may also occur at ectopic sites, from mandibular angle to sternum edge, or in mediastinum [3, 4].

The etiopathogenesis of PC development remains unclear. Microscopically, connective and adipose tissue lined by a single layer of cuboidal or cylindrical epithelial cells is found in the wall. Some cysts contain PG tissue or smooth muscle segments; occasionally, mediastinal cysts may also contain thymus tissue, thus being called third pharyngeal pouch cysts. They may also occur as a reflection of persistent Kürsteiner canals that are associated with PG development. Occasionally, PCs may develop due to cystic-degenerative lesions, e.g., adenoma, hyperplasia, or rarely PG carcinoma (less than 1%) [3, 5, 6]. According to functional status, PCs are classified into two categories, functional cysts and nonfunctional cysts. Functional cysts are found in less than 20% of cases and develop due to cystic-degen-erative lesions of adenoma, hyperplasia, or PG carcinoma. They are more common in male individuals. Serum parathormone (PTH) level exceeds the upper reference value, while disease symptoms are associated with hyperparathyroidism [7-9]. Nonfunctional cysts are found in 80% of cases [10]. Serum levels of PTH and calcium are within the reference values. These
cysts can be asymptomatic. In some cases, they can be accompanied by symptoms generated by pressure against adjacent structures, such as dysphagia, dyspnea, dysphonia, or pain. Being asymptomatic or associated with nonspecific symptoms, differentiation from other cystic neck masses is necessary [7].

Cystic neck masses of variable origin may pose a considerable differential diagnostic challenge, primarily due to different approach, treatment modalities and patient follow up.

We describe four cases of nonfunctional PCs with review of the literature considering clinical symptomatology, etiopathology, diagnostic workup and therapeutic approach to this relatively rare clinical entity.

**Material and Methods**

This retrospective study was carried out at General Hospital in Slavonski Brod, Croatia. Study material was obtained by ultrasound-guided fine-needle aspiration biopsy (UG-FNA) performed by a clinical cytologist (interventional cytologist) [11], who also performed cytomorphological analysis of the material obtained.

PCs were detected in four patients. Each patient signed an informed consent form, while the study protocol was approved by the Hospital Ethics Committee and by the Zagreb School of Medicine Ethics Committee.

All patients underwent ultrasonography (US) of the neck. US examinations were performed on an ACUSON X300 (Siemens, Erlangen, Germany) US device with 8.9 MHz and 11 MHz superficial tissue probes. UG-FNA was carried out by the free-hand technique [12].

Slides for cytomorphological analysis were stained using the standard May-Grünwald-Giemsa method, and analyzed on a light microscope [13].

Aspirate and serum PTH levels, and serum total calcium and inorganic phosphate levels were determined in patients with a neck mass suspect of PC. PTH level in aspirate and serum was determined on a Cobas e411 analyzer (Roche, Mannheim, Germany).

**Case Reports**

**Case 1**

A 51-year-old female patient was aware of the cyst of the thyroid gland, diagnosed at another institution. She was symptom-free. US examination revealed an anechoic mass measuring 1.8×2.1×1.5 cm along the lower pole of the left thyroid lobe. UG-FNA was performed and the mass drained by aspiration of 2.5 cc. of clear, colorless, fluid content. Aspirate PTH was 240.1 pg/mL (16-65) and serum PTH 35.43 pg/mL (16-65). Serum total calcium and inorganic phosphate levels were within the reference range. Cytologically, a crumbly pink substance and occasional red blood cells were found in biopsy sediment. No nucleated cells were observed (Fig. 1). The diagnosis was nonfunctional PC. In this case of nonfunctional PC of small dimensions, we opted for follow up strategy. Follow up US, serum PTH and calcium levels were determined once a year. There was no cyst refilling in three years of initial FNA, indicating remission.

**Case 2**

A 54-year-old female patient was referred from ENT clinic, where she was examined for persistent dry cough. US examination showed an anechoic mass measuring 1.3×1.6×0.9 cm at the lower pole of the left thyroid lobe. The mass was drained on UG-FNA, yielding 1 cc. of clear, colorless, fluid content. Aspirate PTH was 498.0 pg/mL (16-65) and serum PTH 29.22 pg/mL (16-65). Serum total calcium and inorganic phosphate levels were within the reference range. Cytologically, a crumbly pink substance and occasional red blood cells were found in biopsy sediment. No nucleated cells were observed. The diagnosis was nonfunctional PC. In this case of nonfunctional PC of small dimensions, we opted for follow up strategy. Follow up US, serum PTH and calcium levels were determined once a year. Three years after the initial diagnosis, the cyst measured 2.4×1.3×0.9 cm. Serum PTH and calcium levels were within the reference values (Table 1). The patient was operated on due to PC enlargement.

**Case 3**

A 52-year-old man was referred from ENT clinic, where he was examined for a 1.5 cm mass located at the lower pole of the left thyroid lobe. US examination revealed an anechoic mass measuring 2.5×1.8×1.5 cm along the lower pole of the left thyroid lobe. UG-FNA was performed and the mass drained by aspiration of 2.5 cc. of clear, colorless, fluid content. Aspirate PTH was 220.5 pg/mL (16-65) and serum PTH 25.37 pg/mL (16-65). Serum total calcium and inorganic phosphate levels were within the reference range. Cytologically, a crumbly pink substance and occasional red blood cells were found in biopsy sediment. No nucleated cells were observed. The diagnosis was nonfunctional PC. In this case of nonfunctional PC of small dimensions, we opted for follow up strategy. Follow up US, serum PTH and calcium levels were determined once a year. There was no cyst refilling in two years of initial FNA, indicating remission.

**Case 4**

A 56-year-old woman was referred from ENT clinic, where she was examined for persistent dry cough. US examination showed an anechoic mass measuring 1.5×1.8×1.2 cm at the lower pole of the left thyroid lobe. The mass was drained on UG-FNA, yielding 0.5 cc. of clear, colorless, fluid content. Aspirate PTH was 360.0 pg/mL (16-65) and serum PTH 40.22 pg/mL (16-65). Serum total calcium and inorganic phosphate levels were within the reference range. Cytologically, a crumbly pink substance and occasional red blood cells were found in biopsy sediment. No nucleated cells were observed. The diagnosis was nonfunctional PC. In this case of nonfunctional PC of small dimensions, we opted for follow up strategy. Follow up US, serum PTH and calcium levels were determined once a year. There was no cyst refilling in three years of initial FNA, indicating remission.
Small nonfunctional parathyroid cysts

Table 1  Patient characteristics and results of investigations

| Parameter                      | Case 1                  | Case 2                  | Case 3                  | Case 4                  |
|--------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Age (yrs/sex)                  | 51/F                    | 54/F                    | 76/F                    | 44/F                    |
| Clinical presentation          | Asymptomatic            | Asymptomatic            | Hoarseness, left cord paresis | Asymptomatic            |
| US imaging                     | Anechoic mass under lower pole of the left thyroid lobe; 1.8×2.1×1.5 cm | Anechoic mass under lower pole of the left thyroid lobe; 2.4×1.3×0.9 cm | Anechoic mass under lower pole of the left thyroid lobe; 2.2×1.4×1.3 cm | Anechoic mass under lower pole of the right thyroid lobe; 1.7×1.5×1.3 cm |
| Cytology                       | Acellular               | Acellular               | Acellular               | Occasial macrophages    |
| Aspirate PTH (pg/mL)           | 240.1                   | 498.0                   | 389.50                  | 21,770.0                |
| Serum PTH (16-65 pg/mL)        | 35.43                   | 29.22                   | 30.31                   | 64.3                    |
| Serum calcium (2.14-2.53 mmol/L)| 2.32                    | 2.46                    | 2.54                    | 2.20                    |
| Serum inorganic phosphates (0.79-1.42 mmol/L) | 1.35                    | 1.24                    | 1.44                    | 1.20                    |
| Histopathology                 | Not operated on         | Parathyroid cyst        | Parathyroid cyst        | Not operated on         |

US, ultrasonography; PTH, parathyroid hormone.

Histopathologically, it was a partially transparent and partially golden-brown cystic mass measuring 2.2×0.8×0.8 cm. Histologically, the inner surface of the cyst was lined with a layer of flat epithelial cells, with parathyroid tissue found along the cyst connective wall. Immunohistochemistry reaction was positive for chromogranin A and negative for thyroglobulin.

Case 3

A 76-year-old female patient was referred from ENT clinic for long-term hoarseness and left vocal cord paresis. Ultrasonography revealed an anechoic mass measuring 2.2×1.4×1.3 cm in the left cervical region VI (Fig. 2). On UG-FNA, 0.5 cc. of clear, colorless, fluid content was obtained, while a hypoechoic mass measuring 0.8×1.1×0.5 cm remained at the FNA site. Aspirate PTH was 389.50 pg/mL (16-65) and serum PTH 30.31 pg/mL (16-65). Serum levels of total calcium and inorganic phosphates were within the reference range. Cytologically, a crumbly pink substance and occasional red blood cells were found in biopsy sediment. No nucleated cells were observed (Fig. 1). The diagnosis was nonfunctional PC.

In this case of nonfunctional PC of small dimensions, we opted for follow up strategy. At six months of the initial diagnosis, US examination revealed an anechoic mass measuring 2.0×1.7×1.0 cm in the left cervical region VI. Native and post-contrast computerized tomography of the neck showed an oval hypodense lesion, 1.4×1.0 cm in size, absorption value around 5 HU, was observed at the lower left thyroid lobe. The patient was operated on due to persisting hoarseness and left cord paresis. Histopathology report described a cystic mass, 1.7×0.8×0.8 cm in size, of thin wall, partly transparent and partly golden-brown. Histologically, the inner cyst surface was lined with a layer of flat epithelial cells, with parathyroid tissue found at the connective wall. Immunohistochemistry showed positive reaction for chromogranin A and negative for thyroglobulin (Fig. 3a, 3b).
154

Fustar Preradovic et al.

Dominantly for thyroid disease evaluation, and 29,321 UG-FNA procedures for suspect cervical nodes. Pathologic parathyroid lesions were recorded in 137 cervical mass UG-FNA cases, including four PCs. In the group of pathologically altered PGs, PCs accounted for 2.9% of pathologic PG lesions. All four nonfunctional PCs were detected in female patients, mean age 56 (range 44-76) years. According to literature data, PCs are most commonly diagnosed in the fourth and fifth decades of life [15].

PCs are mostly solitary and unilocular, more frequently found under lower thyroid lobes on the left [16]. In our patients, PCs were located under the lower pole of the left thyroid lobes in three cases, and

**Case 4**

A 44-year-old female patient. Two years before, the patient had undergone left thyroid lobectomy with isthmectomy for nodular goiter. Follow up US examination revealed an anechoic mass, 1.7×1.5×1.3 cm in size, under the right thyroid lobe (Fig. 4). The mass was drained on UG-FNA, which yielded 2 cc of clear, colorless, fluid content. Aspirate PTH was 21,770.0 pg/mL (16-65) and serum PTH 64.3 pg/mL (16-65). Serum levels of total calcium and inorganic phosphates were within the reference range. Cytologically, occasional macrophages were found on the crumbly pink substance. No epithelial cells were found. The diagnosis was nonfunctional PC. In this case of nonfunctional PC of small dimensions, we opted for follow up strategy. On three-month follow up, there was no cyst refilling, while serum levels of total calcium and inorganic phosphates were within the reference range.

**Discussion**

PCs are rarely encountered, accounting for 0.8%-3.41% of all parathyroid lesions. McCoy et al. report the incidence of PC lesions to be 3% in a cohort of 1,789 patients treated for primary hyperparathyroidism [10]. In retrospective study including 6,621 patients that underwent cervical US examination, Capelli et al. found the incidence of PCs to be 0.075% in an unselected population [14].

During the 2005-2014 period, our clinical cytologist performed 18,200 US examinations of the neck, predominantly for thyroid disease evaluation, and 29,321 UG-FNA procedures for suspect cervical nodes. Pathologic parathyroid lesions were recorded in 137 cervical mass UG-FNA cases, including four PCs. In the group of pathologically altered PGs, PCs accounted for 2.9% of pathologic PG lesions. All four nonfunctional PCs were detected in female patients, mean age 56 (range 44-76) years. According to literature data, PCs are most commonly diagnosed in the fourth and fifth decades of life [15].

PCs are mostly solitary and unilocular, more frequently found under lower thyroid lobes on the left [16]. In our patients, PCs were located under the lower pole of the left thyroid lobes in three cases, and

**Fig. 3** Histopathology: inner cyst surface lined with a layer of flat epithelial cells; parathyroid gland tissue along the cyst connective wall (hematoxylin-eosin stain; ×40) (a); parathyroid gland tissue positive for chromogranin A along the cyst connective wall (chromogranin A stain; ×40) (b).

**Fig. 4** Parathyroid cyst under the right thyroid lobe.
under the lower pole of the right thyroid lobe in one case (Table 1).

Technetium sestamibi scintigraphy is not used in the diagnosis of these pathologic parathyroid lesions because it shows cold node even in cases of functional PC [16].

On US imaging, PCs are visualized as anechoic masses with posterior enhancement. Only masses located in the neck and up to the sternum edge can be visualized on US imaging. It is necessary to examine the entire cervical region. Thyroid disorders and other diseases may be visualized as PCs, e.g., cysts and hypoechoic nodes at the posterior thyroid edge, in particular multinodular goiter, branchial cysts, thyroglossal cysts, other neck tumors, and metastases from other tumors, which can also develop cystic-degenerative lesions. Pathologically altered PGs, and occasionally PCs, may be located within the thyroid and therefore cannot be differentiated from thyroid nodes [1, 17-24].

Ultrasonography is a very sensitive but less specific method due to many variations in PC visualization in terms of PC shape, size and location. Therefore, a suspect US finding should be confirmed by UG-FNA. Occasionally, it may be necessary to perform FNA of more than one suspect mass, frequently from several sites. Parathyroid cyst FNA generally yields clear, colorless, water-like or golden-brown fluid [1, 2, 7, 11, 13, 25-27]. Aspirate sediment should be examined on a microscope, along with determination of aspirate PTH. A high PTH level indicates PC, as this test has a high specificity for PC [2, 5, 12, 19]. In our hospital, aspirate PTH is not routinely determined for each cystic neck mass because it increases the cost of treatment, but only in cases suspect of PC according to US finding and macroscopic appearance of the aspirate. The cytomorphological sample is mostly poorly cellular or containing no cells at all (Fig. 2).

According to our experience, a combination of US examination with UG-FNA, aspirate cytomorphology, when necessary, specific immunocytochemistry staining for chromogranin and thyroglobulin, determination of aspirate PTH level and determination of serum levels of PTH, calcium and inorganic phosphates help clinicians in differentiating PCs from malignant and benign cervical cystic masses, primarily in the thyroid, as well as in differentiating functional from nonfunctional PCs.

Clark et al. were the first to describe PC FNA in 1978 [4]. Since then, a number of literature reports have described diagnostic FNA of nonfunctional cysts, which was at the same time therapeutic biopsy in 33% to 92% of cases [7, 8]. Some cases of simple nonfunctional cysts require only UG-FNA with cyst draining [7]. Such an approach was also applied in our cases 1 and 4.

A small nonfunctional asymptomatic cyst (case 2) relapsing after initial biopsy requires US follow up with determination of serum PTH level twice a year. In such cases, tetracycline or ethanol sclerotherapy can be performed. We did not decide to use it in our case 2 due to small dimensions of the PC, which was asymptomatic and located at the lower pole of the left thyroid lobe. Different authors vary in their opinions concerning possible complications that may accompany such an intervention, e.g., fibrosis and/or recurrent nerve paresis. Literature data indicate that complications are more common in case of inferior gland pathology [7, 28]. In our case 2, the cyst increased three years of the diagnosis and the patient underwent minimally invasive operative procedure.

In case 3, a nonfunctional PC was associated with left cord paresis. Initial FNA yielded unsatisfactory result, followed by cyst refilling and persistent cord paresis. In such cases, therapeutic approach can vary, including repeat UG-FNA, cyst ablation with a sclerosing agent [7], or surgical extirpation [8, 13, 29]. We opted for surgical extirpation and the patient underwent minimally invasive operative procedure. The minimally invasive surgery requires precise preoperative diagnosis identifying the type and localization of the PG pathologic lesion.

**Conclusion**

PCs are rarely encountered in clinical practice. Operative procedure is necessary for functional PCs and large nonfunctional PCs due to compression syndrome, whereas conservative therapeutic approach is used in small nonfunctional PCs.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.
References

1. Dutta D, Selvan C, Kumar M, Datta S, Das RN, et al. (2013) Needle aspirate PTH in diagnosis of primary hyperparathyroidism due to intrathyroidal parathyroid cyst. Endocrinol Diabetes Metab Case Rep 2013: 130019.

2. Ghervan C, Goel P (2011) Parathyroid cyst, a rare case of cystic cervical lesion. Case report. Med Ultrason 13: 157-160.

3. Apel RL, Asa S (2002) The Parathyroid Glands. In: LiVoltsi VA (ed) Endocrine Pathology. Churchill Livingstone, Philadelphia: 103-147.

4. Clark OH (1978) Parathyroid cysts. Am J Surg 135: 395-402.

5. Halbauer M, Šarčević B, Tomić Brzac H (2000) Doštitne žlijezde. In: Sarcevic B, Halbauer M, Tomic Brzac H (ed) Citološko-patohistološki atlas bolesti štitne žlijezde s ultrazvučnim slikama. Nakladni zavod Globus, Zagreb: 185-229 (In Croatian).

6. McCullagge, Russell CF, Toner PG (1995) Parathyroid cyst of the thymus. Thorax 50: 913-914.

7. Sung JY, Baek JH, Kim KS, Lee D, Ha EJ, et al. (2013) Symptomatic nonfunctioning parathyroid cysts: role of simple aspiration and ethanol ablation. Eur J Radiol 82: 316-320.

8. Ippolito G, Palazzo FF, Segab F, Sierra M, De Micco C, et al. (2006) A single-institution-25-year review of true parathyroid cysts. Langenbecks Arch Surg 391: 13-18.

9. De la Garza S, Flores de la Garza E, Hernández Batres F (1985) Functional parathyroid carcinoma. Cytology, histology, and ultrastructure of a case. Diagn Cytopathol 1: 232-235.

10. McCoy KL, Yim JH, Zuckerbraun BS, Ogilvie JB, Peel RL, et al. (2009) Cystic parathyroid lesions: functional and nonfunctional parathyroid cysts. Arch Surg 144: 52-56.

11. Lieu D (2010) Cytopathologist-performed ultrasound-guided fine-needle aspiration of parathyroid lesions. Diagn Cytopathol 38: 327-332.

12. Tomić Brzac H, Bence-Žigman Z, Dodig D (2002) Ultrasound of thyroid, parathyroid glands and neck lymph nodes. Eur Radiol 11: 2411-2424.

13. Keebler CM, Facic M (2008) Cytopreparatory techniques. In: Bibbo M, Wilbur DC (ed) Comprehensive Cytopathology (3rd). WB Saunders, Philadelphia: 977-1003.

14. Cappelli C, Rotondi M, Pirola I, De Martino E, Leporati P, et al. (2009) Prevalence of parathyroid cysts by neck ultrasound scan in unselected patients. J Endocrinol Invest 32: 357-359.

15. Sreeramulu PN, Borappa K, Girish Gowda SL (2010) Parathyroid cyst: a rare case report. Indian J Surg 72: 71-73.

16. Misjak M, Pavlović D, Petric V, Tomić Brzac H (2005) Dijagnostika i liječenje bolesti došitnih žlijezda. Zagreb: Klinička bolnica “Sestre milosrdnice” (In Croatian).

17. Gooding GAW, Duh QY (1997) Primary hyperparathyroidism: functioning hemorrhagic parathyroid cyst. J Clin Ultrasound 25: 82-84.

18. Layfield LJ (1991) Fine needle aspiration cytology of cystic parathyroid lesions. A cytomorphicologic overlap with cystic lesions of the thyroid. Acta Cytol 35: 447-450.

19. Löwhagen T, Sprenger E (1974) Cytologic presentation of thyroid tumors in aspiration biopsy smear. A review of 60 cases. Acta Cytol 18: 192-197.

20. Abraham D, Sharma PK, Benz J, Gault PM, Neumayer L, et al. (2007) Utility of ultrasound-guided fine-needle aspiration of parathyroid adenomas for localization before minimally invasive parathyroidectomy. Endocr Pract 13: 333-337.

21. Sawady J, Mendelsohn G, Sirota RL, Taxy JB (1989) The intrathyroidal hyperfunctioning parathyroid gland. Mod Pathol 2: 652-657.

22. Ing SW, Pelliteri PK (2008) Diagnostic fine-needle aspiration biopsy of an intrathyroidal parathyroid cyst and subsequent eucalcemia in a patient with primary hyperparathyroidism. Endocr Pract 14: 80-86.

23. Solbiati L, Osti V, Cova L, Tonolini M (2001) Ultrasound of thyroid, parathyroid glands and neck lymph nodes. Eur Radiol 11: 2411-2424.

24. Karstrup S, Glenthøj A, Torp-Pedersen S, Nielsen L, Hagedøs L (1986) Ultrasonically guided fine-needle biopsy for histological sampling of suspect parathyroid tissue. Br J Radiol 59: 507-509.

25. Pontikides N, Kaprara A, Cheva A, Doumas A, et al. (2012) Diagnostic and therapeutic review of cystic parathyroid lesions. Hormones (Athens) 11: 410-418.

26. Loo EK, Simo R, Conn B, Connor SE (2008) Vocal cord paralysis secondary to a benign parathyroid cyst: a case report with clinical, imaging and pathological findings. Eur Radiol 18: 2015-2018.