Purpose: The preoperative diagnosis of parathyroid cancer (PC) is challenging. The purpose of this study was to identify the differences between PC and benign primary hyperparathyroidism.

Methods: The medical records of 85 hyperparathyroidism patients that underwent surgery between 2001 and 2017 were retrospectively reviewed.

Results: Seven of the 85 were diagnosed with PC. Mean age was 53.0±13.0 years and 66 (77.6%) were women. Follow-up duration was 52.9±44.4 months. Tumors were larger (3.50±1.26 cm vs. 2.10±0.84 cm, P=0.002), and intact parathyroid hormone (iPTH) (1,142.8±524.5 pg/mL vs. 461.2±513.5 pg/mL, P=0.002) and alkaline phosphatase (ALP) (398.6±493.6 U/L vs. 166.7±181.1 U/L, P=0.01) levels were higher in cancer patients than in benign primary hyperparathyroidism. Intraoperatively, adhesion to surrounding soft tissue or the thyroid gland was detected more frequently in cancer (85.7% vs. 12.8%, P<0.001). Two patients experienced recurrences and one of them died from PC.

Conclusion: PC patients had larger tumors size, and higher serum iPTH and ALP levels. Intraoperative detection of adhesion to surrounding soft tissue/thyroid importantly raised suspicion of PC. Surgeons operating for hyperparathyroidism should be prepared to perform an appropriate en bloc resection initially upon suspicion of PC.

Keywords: Parathyroid neoplasms; Hyperparathyroidism; Parathyroid cancer

INTRODUCTION

Parathyroid cancer (PC) is an exceptionally rare malignancy. It constitutes only 0.005% of all malignancies and 1%–5% of cases of primary hyperparathyroidism (1). In Korea, 21 cases of PC (7 male and 14 female patients) were found among 214,701 malignancies treated in 2015 (2).

The clinical presentation of PC is hypercalcemia accompanied with a high serum level of parathyroid hormone, which is like that of benign primary hyperparathyroidism. Both diseases can present with nephrolithiasis, osteopenia, or general weakness. The definitive diagnosis of PC is made by pathologic examination for lesions displaying vascular invasion, perineural space invasion, capsular penetration with growth into adjacent tissues, and/or metastasis. Therefore, preoperative fine needle aspiration cytology is not suitable for
characteristics of parathyroid cancer

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differentiating between benign and malignant tumors (3), and thus, it is nearly impossible to diagnose PC preoperatively. For that reason, most patients undergo operation under the presumption of parathyroid adenoma and suspicion of PC is only raised during surgery.

Likewise, differentiating PC from benign primary hyperparathyroidism intraoperatively is also challenging. PCs are firm, densely scarred, obliterate normal tissue planes and often adhere to the thyroid glands. Although atypical adenomas may similarly be large and exhibit considerable adherence to surrounding structures, they do not direct invade surrounding tissues such as in cases of malignancies (1).

The treatment of choice for PC is complete surgical resection — en bloc resection including the tumor along and any involved adjacent structure (4,5). Resection of the ipsilateral thyroid gland and the central compartment lymph node is important for disease-free survival (6,7).

Because it is difficult to determine whether a parathyroid lesion is malignant or not, many surgeons are perplexed with a postoperative pathologic confirmation of PC. Therefore, we analyzed the clinicopathologic characteristics of the patients of PC to identify diagnostically useful differences between PC and benign primary hyperparathyroidism.

MATERIALS AND METHODS

A total of 157 parathyroid operations were performed at our institute between 2001 and 2017, and 83 of these were conducted in primary hyperparathyroidism patients (the other 74 were 65 secondary hyperparathyroidism and 9 parathyroid cysts). These 83 patients were diagnosed as having primary hyperparathyroidism. In addition, 2 patients with secondary hyperparathyroidism diagnosed postoperatively to have PC were also enrolled in the study.

Medical records were reviewed retrospectively for clinical information including age, sex, symptoms, physical findings, major cause of hyperparathyroidism diagnosis, and preoperative biochemical test results. Symptoms or signs including nephrolithiasis, palpable neck mass, osteopenia/osteoporosis, and more were reviewed. Biochemical tests included serum calcium, phosphorus, alkaline phosphatase (ALP), and intact parathyroid hormone (iPTH). Preoperative imaging studies, operative records, and pathologic results were also analyzed. Preoperative imaging study included neck ultrasonography (USG) and a 99mTc-myocardial perfusion (MIBI) parathyroid scan, and if needed, neck computed tomography (CT) or magnetic resonance imaging (MRI). Medical records of USG findings were evaluated when images were unavailable. Operative records were searched for mention of parathyroid tumor adhesion to surrounding thyroid/soft tissue.

PC was diagnosed pathologically based on the presence of vascular invasion, perineural space invasion, capsular invasion with growth into adjacent tissue, and/or metastasis, in accordance to the criteria detailed in the fourth edition of the World Health Organization classification of endocrine tumors (3). Vascular invasion was described as tumor cells invading through vessel walls and endothelium and/or thrombus adherent to an intravascular tumor. Extra-parathyroidal invasion was defined as having features of cancer extending into surrounding structures, including extension into soft tissue, muscle and/or thyroid. Mitotic counts per 50 high power fields (HPFs) were evaluated by microscopy of tumor sections.
During follow-up, serum calcium, phosphorus, and iPTH were examined every 3 months. When hypercalcemia (>10.8 mg/dL) and elevated iPTH (>65 pg/mL) were confirmed biochemically, neck USG, $^{99m}$Tc-MIBI parathyroid scan, neck CT or MRI, chest CT, and positron emission tomography (PET)-CT were conducted to locate and evaluate distant metastasis. Disease recurrence and survival were evaluated in the PC patients. Persistent PC was defined as biochemically confirmed hypercalcemia (>10.8 mg/dL) within 6 months of initial surgical intervention, and recurrent PC was defined as normocalcemia persisting longer than 6 months after initial surgery by eventually followed by recurring hypercalcemia.

Our Institutional Review Board of Gil Medical Center approved this retrospective study before the patient list was retrieved from the hospital database (GCIRB 2017-379).

1. Statistical analysis

Statistical analysis was performed using IBM SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Pearson’s $\chi^2$ test and independent t-test were used to evaluate the significances of differences between PC and benign primary hyperparathyroidism. Fisher’s exact test, McNemar’s test and the Mann-Whitney U test were used for nonparametric analysis. Statistical significance was accepted for P values <0.05.

RESULTS

The clinicopathologic characteristics of the 85 study subjects are summarized in Table 1. Eighty-three patients were diagnosed as primary hyperparathyroidism and 2 patients were initially diagnosed as secondary hyperparathyroidism but were revealed as PC after operation. PC was diagnosed in 7 patients (8.2%). Incidence of PC among primary hyperparathyroidism in our institution was 6.02% (5/83). Follow-up duration was 52.9±44.4 months (range: 0–154).

| Table 1. Clinicopathologic characteristics of 85 hyperparathyroidism patients |
|-----------------------------|-------------------|
| Variables                   | Results           |
| Mean age at diagnosis       | 53.0±13.0         |
| Sex (F/M)                   | 66/19             |
| Tumor size (cm)             | 2.2±0.95          |
| Calcium (mg/dL)             | 12.2±2.1          |
| Phosphorus (mg/dL)          | 2.7±0.9           |
| iPTH (pg/mL)                | 515.8±543.6       |
| ALP (U/L)                   | 185.8±227.1       |
| Creatinine (mg/dL)          | 1.2±1.5           |
| Histology                   |                   |
| Parathyroid adenoma         | 72 (84.7)         |
| Parathyroid cancer          | 7 (8.2)           |
| Parathyroid hyperplasia     | 6 (7.1)           |
| Site of lesion              |                   |
| Right lower                 | 27 (31.8)         |
| Left lower                  | 25 (29.4)         |
| Right upper                 | 15 (17.6)         |
| Left upper                  | 15 (17.6)         |
| Mediastinum                 | 2 (2.4)           |
| Multiple                    | 1 (1.2)           |

Values are presented as mean±standard deviation or number (%). Normal range: Calcium, 8.2–10.8 mg/dL; Phosphorus, 2.5–4.7 mg/dL; iPTH, 10–65 pg/mL; ALP, 35–123 U/L; Creatinine: 0.6–1.2 mg/dL. iPTH = intact parathyroid hormone; ALP = alkaline phosphatase.
Symptoms and signs accompanying hyperparathyroidism varied in 85 patients. The mean number of symptoms and signs was 2.9±1.7 (range: 1–11). Osteopenia/osteoporosis was present in 54 patients (63.5%), hypertension in 26 (30.6%), nephrolithiasis in 21 (24.7%), general weakness/fatigue in 13 (15.3%), gall bladder stone in 8 (9.4%), weight loss, abdominal pain, and vomiting in 6 each (7.1%), bone pain, nausea, and polydipsia/polyuria in 5 each (5.9%), anorexia, palpable neck mass, neck discomfort, and headache in 4 each (4.7%), tingling sensation, dizziness, and depression in 3 each (3.5%), hypoglycemia, chest pain, lethargy, and syncope in 2 each (2.6%), and bone fracture, and recurrent pancreatitis in one each (1.2%) were noted. Incidental hypercalcemia was observed in 20 patients (23.5%), incidental neck mass by USG in 16 (18.8%), incidental findings during thyroid surgery in 11 (12.9%), and incidental ALP elevation was found in one (1.2%). The most common chief complaint to make patient to be treated was an incidental finding of hypercalcemia (18/85, 21.2%), and the second was incidental finding of neck mass by USG (15/85, 17.6%).

Differences between PC and benign primary hyperparathyroidism are summarized in Table 2. Tumors were larger in cancer patients than in patients with benign disease (P=0.002). Preoperative serum iPTH (P=0.002) and ALP (P=0.01) were higher, and adhesion to surrounding soft tissue or the thyroid gland (P<0.001) (Fig. 1) was observed more frequently in cancer patients compared to the benign counterpart. No study subject showed calcification in USG. Tumors of one cancer patients (14.3%, case 1; Table 3) and two parathyroid adenoma patient (2.6%) infiltrated thyroid tissue (P=0.230) in USG. In these 3 patients, adhesion to thyroid was recognized during surgery. One (14.3%) PC and three (3.8%) benign disease cases presented with a palpable neck mass (P=0.296). Nephrolithiasis was present in 1 (14.3%) cancer and 21 (26.9%) benign cases (P=0.671), while osteopenia/osteoporosis was observed in 4 (57.1%) in cancer and 52 (66.7%) benign patients (P=0.686).

According to histopathologic results, the cut surface margin of the PC had an infiltrative margin (Fig. 2). All PCs exhibited capsular invasion, 6 (85.7%) exhibited vascular invasion, and 6 (85.7%) exhibited capsular penetration with growth into adjacent tissues (Fig. 3). The mean number of capsular invasion foci was 4.1±3.3 (range: 1–11) and the mean number of vascular invasion foci was 1.6±0.8 (range: 0–2). Three patients had thyroid parenchyma invasion pathologically (cases 2, 5, and 6). Mean mitotic count (1.0±1.8 vs. 0.8±4.3, P=0.046) were significantly higher in PC than in benign cases.

| Variables | Parathyroid cancer (n=7) | Benign primary hyperparathyroidism (n=78) | P |
|-----------|-------------------------|------------------------------------------|---|
| Sex (F/M) | 6/1 (85.7) | 60/18 (76.9) | 0.690 |
| Mean age at diagnosis | 53.1±9.2 | 53.0±13.3 | 0.489 |
| Tumor size (cm) | 3.50±1.26 | 2.10±0.84 | 0.002 |
| Calcium (mg/dL) | 13.2±2.4 | 12.1±2.0 | 0.081 |
| Phosphorus (mg/dL) | 3.4±1.7 | 2.7±0.8 | 0.128 |
| iPTH (pg/mL) | 1342.8±524.5 | 461.2±513.5 | 0.002 |
| ALP (U/L) | 398.6±493.6 | 166.7±181.1 | 0.010 |
| Creatinine (mg/dL)* | 1.0±0.5 | 1.1±1.0 | 0.637 |
| No. of symptom and sign | 3.0±1.7 | 2.9±1.7 | 0.412 |
| Intraoperative detection of adhesion | 6/1 (85.7) | 10/68 (12.8) | 0.001 |
| Mitotic count | 1.0±1.8 | 0.8±4.3 | 0.046 |
| Follow-up duration (mon) | 61.7±53.2 | 52.1±43.8 | 0.373 |

Values are presented as mean±standard deviation or number (%). Normal range: Calcium, 8.2–10.8 mg/dL; Phosphorus, 2.5–4.7 mg/dL; iPTH, 10–65 pg/mL; ALP, 35–123 U/L; Creatinine: 0.6–1.2 mg/dL.

*Analysis excluding patients under hemodialysis.
Tumor adhesion to surrounding soft tissue or the thyroid gland was observed in 10 (12.8%) of the 78 benign cases, among which all were parathyroid adenomas. Their tumor size was larger (3.20±0.95 cm vs. 1.94±0.69 cm, P<0.001), and their serum calcium (14.0±3.5 mg/dL vs. 11.8±1.6 mg/dL, P=0.009) and iPTH (1,291.6±713.7 pg/mL vs. 367.5±394.7 pg/mL, P<0.001).

Table 3. Seven cases of parathyroid cancer

| Case number | Age | Sex | Chief complain          | Site                        | Type of operation                                                                 | Intraoperative detection of adhesion | Size (cm) | LNM | Calcium (mg/dL) | iPTH (pg/mL) | ALP (U/L) | Follow-up duration (mon) | Outcome | Disease associated with diagnosis |
|------------|-----|-----|--------------------------|-----------------------------|----------------------------------------------------------------------------------|-------------------------------------|-----------|-----|-----------------|--------------|-----------|-----------------------------|---------|----------------------------------|
| 1          | 58  | F   | Incidental finding       | Right upper parathyroidectomy | Right upper parathyroidectomy, total thyroidectomy, and central lymphadenectomy | +                                   | 2.0       | (-) | 11.4            | -            | 206.0     | 39                          | Recurrence | (-)                              | PTC     |
| 2          | 45  | F   | Incidental finding       | Left lower parathyroidectomy | Subtotal parathyroidectomy and central lymphadenectomy                            | -                                   | 2.2       | (-) | 11.1            | 1,255.5      | 68.0      | 18                          | Recurrence | (-)                              | CKD     |
| 3          | 42  | F   | Incidental finding       | Left upper parathyroidectomy | En bloc resection with the ipsilateral lobe, central lymph node, and subtotal parathyroidectomy | +                                   | 3.0       | (-) | 12.0            | 1,473.8      | 350.0     | 11                          | Recurrence | (-)                              | CKD     |
| 4          | 46  | F   | Fatigue                  | Left upper parathyroidectomy | En bloc resection with the ipsilateral lobe and central lymph node                 | +                                   | 4.5       | (-) | 14.3            | 1,751.0      | 223.0     | 57                          | Recurrence | (-)                              | (-)     |
| 5          | 63  | M   | Palpable neck mass       | Left lower parathyroidectomy | En bloc resection with the ipsilateral lobe and central lymph node                 | +                                   | 5.5       | (-) | 14.6            | 1,354.7      | 1,501.0   | 139                         | Recurrence | 3 times Local recurrence | Lung/bone metastasis | Death |
| 6          | 65  | F   | Poor oral intake         | Left lower parathyroidectomy | En bloc resection with the ipsilateral lobe and central lymph node                 | +                                   | 3.3       | (-) | 17.6            | 898.7        | 176.0     | 34                          | Local recurrence | 2 times | Recurrence | (-) |
| 7          | 53  | F   | Hypercalcemia on medical check-up | Left lower parathyroidectomy | En bloc resection with the ipsilateral lobe and central lymph node                 | +                                   | 4.0       | (-) | 11.5            | 253.2        | 266.0     | 134                         | Recurrence | (-)                              | (-)     |

Normal range: Calcium, 8.2–10.8 mg/dL; iPTH, 10–65 pg/mL; ALP, 35–123 U/L.
LNM = lymph node metastasis; ALP = alkaline phosphatase; PTC = papillary thyroid cancer; CKD = chronic kidney disease; iPTH = intact parathyroid hormone.
levels were higher than the non-adherent cases in 78 benign patients. Furthermore, their serum ALP level (309.3±255.7 U/L vs. 145.7±159.5 U/L, P<0.001) and mean mitotic count (4.90±11.56 vs. 0.15±0.68, P=0.003) were significantly higher.

Details of the 7 cases are provided in Table 3. We had begun operation with suspicion of parathyroid adenoma in most patients. When the adhesion to the thyroid gland or surrounding soft tissue was detected intraoperatively, however, en bloc resection including the ipsilateral thyroid lobe and central lymphadenectomy was performed under suspicion of PC. Three patients had obvious symptom to make them to be treated (42.9%, cases 4–6). One patient (case 7) were diagnosed as PC after having medical check-up. Case 1 of female patient was diagnosed as PC after thyroid operation for papillary thyroid cancer. There was no symptom and sign related to hyperparathyroidism. Her preoperative thyroid USG showed a heterogeneous solid nodule with an unclear border at the posterior side of the thyroid. It looked to be a thyroid mass unrelated to thyroid cancer. However, the mass was adhesive to the right thyroid, which led to en bloc resection with total thyroidectomy. Cases 2 and 3 patients in their
forties had been under hemodialysis for 15 and 14 years respectively, during which secondary hyperparathyroidism occurred. Osteoporosis was detected in these patients. Preoperative neck USG in case 2 revealed a 1.0 cm sized, smooth, oval, hypoechoic nodule in the posterior portion of the right mid pole, and 0.9 cm and 0.7 cm lesions at left gland with similar characteristics. Intraoperatively, the left lower parathyroid gland resembled a 2 cm sized kidney-shaped mass. Despite conducting central neck dissection to identify remaining parathyroid tissue, the right lower parathyroid gland could not be found. Pathology report revealed the left lower gland to be a PC. In case 3, preoperative neck USG displayed a 2.0 cm sized hypoechoic lesion in the upper area of the left thyroid lobe suggestive of a parathyroid tumor. As the adhesion to the left thyroid was noted intraoperatively, en bloc resection was performed with excision of right upper and left lower parathyroid glands. Despite through central neck dissection, we could not find the right lower parathyroid gland. The left upper parathyroid gland was diagnosed to contain PC postoperatively. These patients were alive with a low-normal calcium level and mild iPTH elevation at 18 and 11 months after operation, respectively. Case 4 patient had suffered from fatigue and bone pain. Gall bladder stone and osteoporosis were discovered during evaluation. She showed serum iPTH elevation with a normal calcium level after the operation, a whole body \(^{99m}\text{Te-MIBI}\) scan and PET-CT were performed. Pelvic MRI depicted multiple brown tumors, which were later pathologically confirmed. Serum iPTH was normalized after neck radiotherapy (30 fractions at 5,400 cGy). Case 5 patient visited with palpable neck mass and neck discomfort accompanied with weight loss and nephrolithiasis. Case 6 patient complained poor oral intake, weight loss, fatigue, and tingling sense. She showed gall bladder stone and osteoporosis. Case 4–7 patients underwent en bloc resection with the ipsilateral lobe and central lymph node under suspicion of PC due to detection of adherence to surrounding soft tissue and thyroid gland.

There was no persistent PC in 7 patients. However, two patients (Cases 5 and 6) suffered from disease recurrence. Case 5 patient was followed-up irregularly and experienced recurrence three times; in operative bed soft tissue at 27 months postoperatively, in the operative bed and mediastinum at 39 months, and in mediastinum at 54 months. Serum iPTH and calcium levels were normal after reoperations. At 77 months, hypercalcemia was aggravated, and lung metastasis was detected on CT. However, he did not visit outpatient clinic regularly and bone metastasis was detected at 131 months, and he died of hypercalcemia associated cardiac arrest at 139 months postoperatively. In case 6 patient, local recurrences occurred in operative bed soft tissue at 15 and 20 months postoperatively.

**DISCUSSION**

In this study, we analyzed the characteristics of PC patients and evaluated differences between PC and benign primary hyperparathyroidism. Tumor size was larger, and preoperative serum iPTH and ALP were significantly higher in cancer patients than in those with benign disease. Intraoperative findings of the severe adhesion between parathyroid lesion and surrounding thyroid gland or soft tissue were observed in cancer patients.

Several clinical, laboratory, and radiologic findings raised suspicion of PC. In general, PC was more common in younger patients and in men. Average age at presentation was 48 for cancer and 55 for those with benign disease. In cancer patients, the male/female ratio was around 1:1 but 3–4 times more women than men had benign disease (8). In a report conducted in Korea in 2015, 7 males and 14 females of PC patients were found and the disease was most common in the sixth decade of life regardless of sex (42.9%) (2).
In previous reports, severe hypercalcemia (>14 mg/dL), iPTH elevation to 3–15 times the normal upper limit, serious renal and skeletal disease, and the presence of a palpable neck mass were found to be features of PC (4,9,10). Furthermore, some patients with PC exhibit ALP elevation than in those with primary hyperparathyroidism, in whom levels were generally near the upper limit of normal (4,11). Ultrasonographic evidence of infiltration, calcification, suspicious vascularity, and the presence of a thick capsule have also been reported to be strongly associated with parathyroid malignancy (4,12).

Intraoperative suspicion of local invasion or regional metastasis was critical (9,12), and findings of a lobulated firm mass, surrounded by a fibrous grayish-white capsule that adheres persistently to the ipsilateral thyroid lobe or adjacent cervical tissues raised suspicion of PC.

In the present study, no difference was detected between the gender ratios or ages between the malignant and benign patient groups at diagnosis. The presence of a palpable neck mass at presentation and co-existing renal or skeletal disease were no different between the two groups. Preoperative imaging studies revealed no calcification in any malignant lesions, though one patient showed infiltration into the thyroid lobe. Analyzing preoperative USG was difficult because ultrasonographic images were not available in some cases due to the retrospective nature of the study. In these cases, we evaluated medical records of USG findings, but these were inadequate for evaluating the presence of infiltration, calcification, suspicious vascularity, or a thick capsule.

Interestingly, two patients with a diagnosis of secondary hyperparathyroidism were found to have PC. The etiology of PC has not been determined, and no established predisposing factors have been identified. However, several etiologic factors are associated with PC including history of neck radiation, a hyperplastic parathyroid gland, and secondary/tertiary hyperparathyroidism caused by chronic kidney disease (despite no evidence that PC arises from malignant transformation of preexisting parathyroid lesions) (4,11). Several case reports have described PC occurring in secondary/tertiary hyperparathyroidism (13-17). Our seven cases of PC did not have history of neck radiation.

Mitotic status does not distinguish PC from adenomas (3,18). Mitosis can be observed in 80% of parathyroid adenomas (usually at <1 per 10 HPFs), and also 80% of PC (19). However, it has been reported that mitoses of >5 per 50 HPFs in PC is a poor prognostic factor (18). Although the atypical mitotic figure is exclusively observed in PC, it was not observed in our series. Although the number of mitosis was not big, in this study, mitotic count was higher in PC patients than benign cases significantly. We did find that a high mitotic index was associated with adhesion to surrounding tissue in benign group. We suggest it is worth considering the possibility that parathyroid adenoma with severe adhesion is an atypical parathyroid adenoma entity. Atypical parathyroid adenoma is a controversial entity, which displays various atypical features (adhesion to surrounding tissues, banding fibrosis, nuclear atypia, and mitosis) without meeting the diagnostic criteria of PC (3). It is difficult to differentiate atypical parathyroid adenoma and PC in the operative field due to the adhesive feature (20). However, most atypical parathyroid adenomas are clinically benign (21), and no genetic or pathological link has been demonstrated between parathyroid adenoma, atypical parathyroid adenoma and PC (22,23).

Several reports have been published on the detection of synchronous thyroid cancer and PC (24-26). Some suggest coincidence, while others have proposed association based on
their similarities, which include increased endogenous calcium levels, growth factors, and goitrogenic factors (24). In our series, 17 patients (20%) received combined thyroid surgery because of concomitant thyroid disease (14 thyroid cancer and 3 benign disease). Because we did not routinely evaluate preoperative iPTH for thyroid operations, the true incidence of concomitant thyroid and parathyroid lesions from our institution could not be calculated.

The incidence of PC among primary hyperparathyroidism in our institution was 6.02% (5/83), although in the literature it is reported to be around 1%–5% (1). A reason for this inconsistency is the low annual incidence of primary hyperparathyroidism in Korea (0.007%–0.014%) (27) compared to annual incidence from western countries ranging from 0.04% to 0.3% (28-30).

As this series was conducted using a retrospective design, it was limited in terms of incomplete preoperative USG data and follow-up loss. Although we searched medical records meticulously, accompanying symptoms, signs, and diseases would have been analyzed more thoroughly had this been a prospective study.

In conclusion, PC patients had larger tumors and higher preoperative serum iPTH and ALP values. The intraoperative detection of adhesion to surrounding thyroid gland or soft tissue was found to be essential for raising suspicions of PC. Notably, PC also developed from secondary hyperparathyroidism patients and found on occasion to be accompanied by thyroid cancer. Surgeons who explore patients with hyperparathyroidism or perform thyroid surgery should be prepared to undertake initial, appropriate en bloc resection upon suspicion of potential PC.

REFERENCES

1. Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL. Sabiston Textbook of Surgery: the Biological Basis of Modern Surgical Practice. 20th ed. Philadelphia (PA): Elsevier Saunders; 2017.
2. Korea Central Cancer Registry; National Cancer Center (KR); Ministry of Health and Welfare (KR). Annual Report of Cancer Statistics in Korea in 2015. Goyang: Korea Central Cancer Registry; 2017.
3. Lloyd RV, Osamura RY, Klöppel G, Rosai J; World Health Organization; International Agency for Research on Cancer. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017.
4. Al-Kurd A, Mekel M, Maze H. Parathyroid carcinoma. Surg Oncol 2014;23:107-14.
5. Owen RP, Silver CE, Pellitteri PK, Shahe AR, Devaney KO, Werner JA, et al. Parathyroid carcinoma: a review. Head Neck 2011;33:429-36.
6. Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. Ann Surg Oncol 2010;17:2156-74.
7. Schulte KM, Talat N, Galata G, Gilbert J, Miell J, Hofbauer LC, et al. Oncologic resection achieving R0 margins improves disease-free survival in parathyroid cancer. Ann Surg Oncol 2014;21:1891-7.
8. Givi B, Shah JP. Parathyroid carcinoma. Clin Oncol (R Coll Radiol) 2010;22:498-507.
9. Ricci G, Assenza M, Barreca M, Liotta G, Paganelli L, Serao A, et al. Parathyroid carcinoma: the importance of high clinical suspicion for a correct management. Int J Surg Oncol 2012;2012:649148.
10. Shane E. Clinical review 122: parathyroid carcinoma. J Clin Endocrinol Metab 2001;86:485-93.

https://jes-online.org
https://doi.org/10.16956/jes.2019.19.2.35
11. Kassahun WT, Jonas S. Focus on parathyroid carcinoma. Int J Surg 2011;9:13-9.

12. Duan K, Mete Ö. Parathyroid carcinoma: diagnosis and clinical implications. Turk Patoloji Derg 2015;31 Suppl 1:80-97.

13. Kim BS, Ryu HS, Kang KH, Park SL. Parathyroid carcinoma in tertiary hyperparathyroidism. Asian J Surg 2016;39:285-9.

14. Takada D, Tsukamoto T, Fuse M, Kada S, Yanagita M. The use of cinacalcet hinders the diagnosis of parathyroid carcinoma in a chronic dialysis patient: a case report. BMC Nephrol 2017;18:315.

15. Bossola M, Tazza L, Ferrante A, Giungi S, Carbone A, Gui D, et al. Parathyroid carcinoma in a chronic hemodialysis patient: case report and review of the literature. Tumori 2005;91:558-62.

16. Falvo L, Catania A, Palermo S, Sorrenti S, Bonifazi AP, De Stefano M, et al. Bilateral synchronous parathyroid carcinoma in a patient on long-term hemodialysis: presentation of a rare clinical case and review literature. Int Surg 2005;90:18-22.

17. Zivaljevic V, Krgovic K, Tatic S, Havelka M, Dimitrijevic Z, Diklic A, et al. Parathyroid cancer in a hemodialysis patient: a case report. Tumori 2002;88:430-2.

18. Bondeson L, Sandelin K, Grimelius L. Histopathological variables and DNA cytometry in parathyroid carcinoma. Am J Surg Pathol 1993;17:820-9.

19. Snover DC, Foucar K. Mitotic activity in benign parathyroid disease. Am J Clin Pathol 1981;75:345-7.

20. Ippolito G, Palazzo FF, Sebag F, De Micco C, Henry JF. Intraoperative diagnosis and treatment of parathyroid cancer and atypical parathyroid adenoma. Br J Surg 2007;94:566-70.

21. DelLellis RA. Parathyroid tumors and related disorders. Mod Pathol 2011;24 Suppl 2:S78-93.

22. Stojadinovic A, Hoos A, Nissan A, Dudas ME, Cordon-Cardo C, Shaha AR, et al. Parathyroid neoplasms: clinical, histopathological, and tissue microarray-based molecular analysis. Hum Pathol 2003;34:54-64.

23. Fernandez-Ranvier GG, Khanafshar E, Tacha D, Wong M, Kebebew E, Duh QY, et al. Defining a molecular phenotype for benign and malignant parathyroid tumors. Cancer 2009;115:334-44.

24. Baek CO, Kim KH, Song SK. Synchronous parathyroid carcinoma and papillary thyroid carcinoma in a patient with long-standing schizophrenia. Korean J Intern Med 2017;32:1104-7.

25. Chaychi L, Belbruno K, Golding A, Memoli V. Unusual manifestation of parathyroid carcinoma in the setting of papillary thyroid cancer. Endocr Pract 2010;16:664-8.

26. Savil H, Sevina A, Sari R, Ozen S, Buyukberber S, Ertas E. Occult parathyroid carcinoma in a patient with papillary thyroid carcinoma and Hashimoto's thyroiditis. J Endocrinol Invest 2001;24:42-4.

27. Kim JK, Chai VJ, Chung JK, Hwang KT, Heo SC, Kim SI, et al. The prevalence of primary hyperparathyroidism in Korea: a population-based analysis from patient medical records. Ann Surg Treat Res 2018;94:235-9.

28. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. J Bone Miner Res 2006;21:171-7.

29. Adami S, Marcocci C, Gatti D. Epidemiology of primary hyperparathyroidism in Europe. J Bone Miner Res 2002;17 Suppl 2:N18-23.

30. Yu N, Donnan PT, Murphy MJ, Leese GP. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. Clin Endocrinol (Oxf) 2009;71:485-93.