Journal of Cardiothoracic Surgery

CASE REPORT

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Metastatic parathyroid carcinoma diagnosed after five surgical attempts: a case report and review of the literature

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Abstract

Background Diagnosis of parathyroid carcinoma as a rare cause of primary hyperparathyroidism is usually very challenging, even after surgical resection.

Case presentation A 45-year-old woman with a diagnosis of primary hyperparathyroidism underwent surgery three years ago. Parathyroid adenoma resection and total thyroidectomy, due to incidental intraoperative finding of papillary thyroid carcinoma, were performed. She had been asymptomatic for 2.5 years before her PTH and calcium levels rose. The second surgery was performed based on parathyroid hyperplasia diagnosis, but the patient did not recover. She was then referred to us. Imaging modalities could not localize the PTH source. Sequential bilateral neck explorations were unsuccessful. As a last attempt, mediastinal exploration was performed. By confirming no parathyroid tissue in the mediastinum, excision of some tiny pulmonary nodules (previously considered as PTC metastasis) was done, which was confirmed to be parathyroid cancer metastasis.

Conclusions Diagnosing parathyroid carcinoma is difficult because of unreliable diagnostic criteria. The correct diagnosis may be determined through the follow-up for recurrent hyperparathyroidism in a previously diagnosed case of parathyroid adenoma.

Keywords Metastatic parathyroid carcinoma, Papillary thyroid carcinoma, Parathyroid adenoma, Parathyroid carcinoma, Primary hyperparathyroidism

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Introduction

Parathyroid carcinoma (PC) is a rare malignancy responsible for less than 1% of primary hyperparathyroidism cases [1]. PC coexistence with papillary thyroid carcinoma is extremely rare; to the best of our knowledge, there are only 15 cases in the international literature [2]. Differentiating between benign causes of primary hyperparathyroidism and PC, before surgery, is not always easy. Even after surgical resection, PC may be misdiagnosed as parathyroid adenoma (PTA) [3]. Sometimes, only post-operative rise of serum calcium and PTH levels lead to the proper diagnosis.

Case presentation

A 45-year-old woman was referred to us for recurrent hypercalcemia. Three years prior, she had been admitted to an outside hospital for chronic dry cough with no underlying disease or notable family history. Past medical history was negative for nephrolithiasis or fracture. Serum calcium, 24-h urinary calcium, and PTH levels were 10.6 mg/dl (8.6–10.3), 462 mg (100–300), and 249 pg/ml (10.4–66.5), respectively. Neck ultrasound showed a 21 mm hypoechoic lesion suggestive of a right-inferior parathyroid adenoma.

On first surgical attempt, a 25 mm right-inferior parathyroid adenoma was resected and confirmed by frozen section examination (FSE). Intraoperative PTH assay was not performed. The surgeon incidentally found a suspicious right lobe thyroid nodule (based on its appearance, size, and palpation) and excised it, suspected it to be malignant. FSE confirmed a 13 mm papillary thyroid carcinoma (PTC). Total thyroidectomy and central lymphadenectomy were subsequently performed. In the permanent pathological examination (PPE) the left-superior parathyroid gland was incidentally found inside the left thyroid lobe. The resected lymph nodes (LN) were reported as reactive. Of note, resection of the right-superior parathyroid gland was also (mistakenly?) mentioned in the operative report; however, this was not reported in the PPE. The patient received radioactive iodine therapy and was given 150 micrograms daily of levothyroxine.

Table 1 Patient's laboratory data at the time of admission in our hospital

Parameter (normal range)	Result
Na (135–145 mEq/L)	139
K (3.5–5.3 mEq/L)	3.7
Ca (8.6–10.3 mg/dL)	13.2*
P (2.5-5 mg/dL)	1.5*
Mg (1.5–2.6 mg/dL)	1.5
iPTH-ELISA (10.4–66.5 pg/mL)	2131*
Vitamin D3 (30–100 ng/mL)	31
Albumin (3.8–5.1 g/dL)	4.1
Creatinine (0.6–1.1 mg/dL)	0.8
Urea (10–50 mg/dL)	32
WBC (4–11 × 10^3 cells/μL)	8.3
Hb (12.3–15.3 g/dL)	12.5
PLT (150–450 × 10^3/μL)	314
Amylase (28–100 unit/L)	35
TSH (0.35–4.9 μlu/mL)	0.26*
Thyroglobulin (3.5–56 ng/mL)	0.04*
Antithyroglobulin antibody (up to 115 IU/mL)	12.6

iPTH = Intact parathyroid hormone; WBC = White blood cells; Hb = Hemoglobin; PLT = Platelets; TSH = Thyroid stimulating hormone

* Abnormal

Post-operatively, the patient no longer had a dry cough. Serial serum calcium levels were around 9.5 mg/dl. PTH levels were not measured. Around three years later, she was readmitted to the same hospital for weakness, lethargy, hypercalcemia (11.7 mg/dl) and elevated PTH (224 pg/ml). With a diagnosis of parathyroid hyperplasia, the same surgeon, believing he had previously removed three parathyroid glands, only excised the left-inferior parathyroid gland. Half was confirmed to be normal parathyroid tissue. The second half was then implanted in the patient's forearm. Intraoperative PTH assay was not performed. Post-operatively, the patient's calcium and PTH levels remained high (13.7 mg/dl and 425 pg/ml, respectively).

Six months later, the patient was referred to us for epigastric pain, constipation, weakness, and lethargy. Physical examination was unremarkable. Table 1 contains admission laboratory data. Of note, thyroglobulin was 0.04 ng/ml (3.5–56) and antithyroglobulin antibody was 12.6 (up to 115 IU/mL). Thoracic-abdominopelvic CT scans, with and without contrast, showed several small nodules in both lung upper lobes. Considering the history of PTC, these nodules were assumed to be PTC metastases. ^{99m}Tc-MIBI SPECT/CT parathyroid scan and parathyroid 4D CT-scan did not show PTA in the neck or mediastinum. Neck ultrasound did not show remaining thyroid tissue or PTA. However, an 8×3×5 mm hypoechoic tissue with minimal vascularity was seen on the innominate artery, which was suspected to be a fibrotic nodule or parathyroid tissue. Given that the prior pathology report did not mention right-superior parathyroid gland removal, we performed an exploratory neck surgery, the patient's third surgery, to find possible remaining parathyroid gland or any aberrant parathyroid tissue.

The right-superior parathyroid gland was found, excised, and confirmed by FSE to be a normal parathyroid gland. However, intraoperative PTH did not decrease. The nodule on the innominate artery was then resected and found to be a reactive LN. The neck and carotid sheath were dissected, revealing several more suspicious nodules sent for FSE; all were shown to be reactive LNs or fibro-adipose tissues. Thymectomy was then performed. FSE did not reveal parathyroid tissue

inside the thymus. Lastly, the implanted parathyroid in the forearm was excised but PTH did not decrease. Ultimately, we ended the procedure for the following two reasons. First, the surgery had already taken nine hours. Second, although we believed that the right recurrent laryngeal nerve (RLN) had not been cut, we could not be sure (intraoperative neuromonitoring was unavailable in our hospital). Given this was the third surgery, we did not want to risk exploring the left side of the neck and injuring the left RLN which would have resulted in tracheostomy. In the PPE, the removed parathyroid gland and parathyroid tissues embedded in the forearm were reported as normal parathyroid tissues. Post-operatively, the patient had hypercalcemia (15 mg/dL).

Two weeks later, the patient underwent laryngoscopy, which was normal. The left side of the neck was then explored for any aberrant or remaining parathyroid gland. Several suspicious nodules were excised. FSE and subsequent PPE found no evidence of parathyroid tissue. The post-operative course was complicated by a husky voice and a hypercalcemia crisis, which were managed conservatively.

After two weeks, we performed the fifth surgery to explore the mediastinum as the last possible place to find aberrant PTA and take a biopsy from the pulmonary nodules (due to the small size of the nodules, our interventional radiologist did not accept to perform a CT-guided needle biopsy, and superDimension™ navigation system is not available in our country as well). First, a laryngoscopy examination was performed, which did not demonstrate any abnormalities (and the patient's voice returned to normal before discharge). Then, via an upper-partial sternotomy extended to the left anterior thoracotomy, multiple specimens were taken from the mediastinum. FSE did not show any evidence of parathyroid tissue. Ultimately, two nodules of the left upper lobe were excised. FSE revealed carcinomatous infiltration in favor of parathyroid carcinoma (Fig. 1A and B). The operation was terminated. As expected, PTH remained elevated. PPE confirmed metastatic parathyroid carcinoma. The neoplastic cells were immunoreactive for GATA-3, PTH (Fig. 1C and D), CK, synaptophysin, and chromogranin while revealing negative reactions for TTF-1, PAX-8, ER, and GCDFP15.

Search strategy for literature review

In PubMed, we searched for articles between January 2005 and December 2023 containing the phrases "parathyroid cancer" or "parathyroid carcinoma" and "metastatic" or "metastasis". We then reviewed all relevant studies without language restriction.

Discussion

Diagnosing PC is difficult because of non-specific diagnostic criteria. Moreover, the correct diagnosis might not be made until metastases are present as in our case (Table 2) [4–9]. The overall 5-year survival rate for PC is 82.7% [10]. However, it is 16% for patients who develop distant metastases in the first five years [1].

Although PC is rare, it must be considered on differential diagnoses of primary hyperparathyroidism. Some features (Table 3) increase the likelihood of PTH-dependent hypercalcemia due to PC etiology, although our patient had none of them until the second surgery [10].

The surgery for PC should include parathyroidectomy or *en bloc* resection of the whole mass in case it invades the surrounding tissues. *En block* resection in the neck may include the ipsilateral thyroid lobe, paratracheal and upper mediastinal lymphatic tissue, part of the neck muscles, or even RLN. Additionally, some surgeons suggest ipsilateral lymph node dissection [10].

In this patient, intraoperative PTH measurement helped us determine whether the removed parathyroid tissues were responsible for PTH secretion. Initial imaging guides the starting point of the surgery, while intraoperative PTH monitoring determines when the surgery should end. It is recommended that if a patient is a candidate for re-operative parathyroidectomy due to primary hyperparathyroidism, intraoperative PTH monitoring should be performed. Surgeries that rely solely on imaging and do not include intraoperative PTH monitoring may fail, especially in cases where multi-gland disease is present [11].

Certain aspects make our case noteworthy. First, multiple neck surgeries revealed no evidence of PC. Second, relying only on the normal level of calcium can lead to a delay in the early detection of metastatic PC. Third, the presence of PTC led us to attribute the lung nodules to it. However, this issue was very unlikely considering the absence of local spreading of PTC and the patient's thyroglobulin and antithyroglobulin antibody levels. Fourth, the coincidence of PTC and PC is extremely rare and has been reported only in a few cases [2].

The metastatic source was the right-inferior parathyroid gland, which was reported as PTA. Although pathological features such as trabecular arrangement, thick fibrous bands, and frequent mitotic figures are strongly suggestive of PC, the definitive diagnosis is made by the presence of parathyroid tissue in an abnormal location [12]. In a study of over 1000 patients with primary hyperparathyroidism who underwent surgery, 29 were diagnosed with PC. Interestingly, about one-third of them had preliminary histopathological findings in favor of PTA [13]. Upon retrospective pathological examination of the parathyroid gland in our patient, no definitive histopathological features of PC were found, such

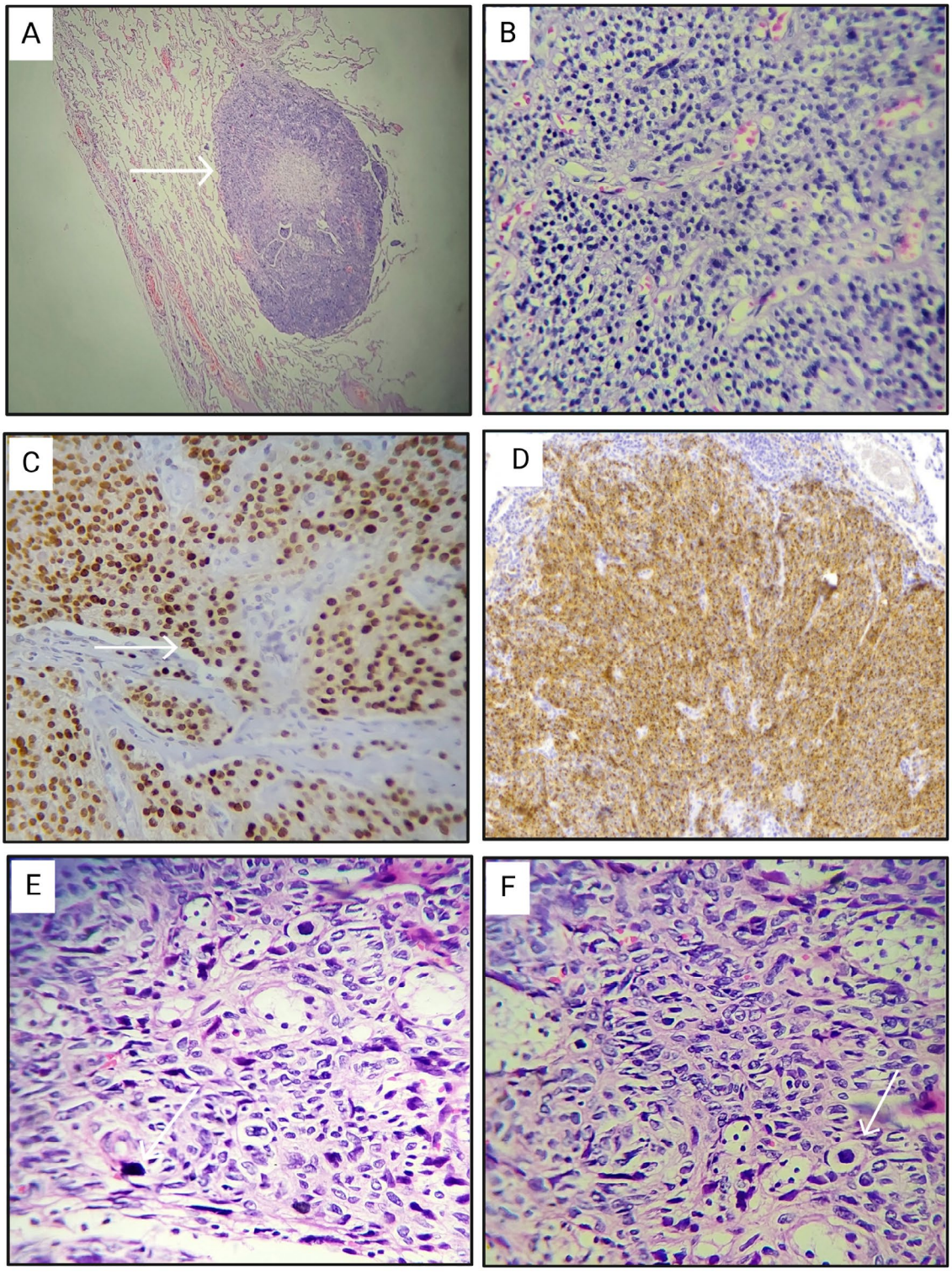

Fig. 1 Histopathological findings of the lung nodules (**A**-**D**) and retrospective histopathological review of the parathyroid gland specimen, diagnosed as parathyroid adenoma in the first surgery (**E**-**F**). **A**) Section of the lung parenchyma with a neoplastic nodule (hematoxylin-eosin ×40). **B**) Higher magnification of the previous image; the neoplastic cells are predominantly of chief cell origin (hematoxylin-eosin ×400). **C**) IHC stained section for GATA-3; diffuse nuclear immunoreactivity of tumoral cells is seen (×400). **D**) IHC stained section for PTH; the positive cytoplasmic reaction of the neoplastic cells is seen (×200). **E**) Spindling of the neoplastic cells, nuclear pleomorphism, and hyperchromasia (hematoxylin-eosin ×400). **F**) One atypical mitotic figure is shown (hematoxylin-eosin ×400)

Table 2 Patients with parathyroid cancer who were initially operated on with a different diagnosis, and after several years, parathyroid carcinoma diagnosis was established only through lung lesions biopsy (in current case and literature reviews)

No	Author, [reference]	Sex/Age[1]	The time interval[2]	Primary presentation	Primary diagnosis	Follow-up course	Secondary presentation which led to parathyroid carcinoma diagnosis	Imaging findings
1	Sarquis (2020) [4]	Female/18	7 years	N/A	Parathyroid adenoma (Left-inferior parathyroidectomy)	N/A	Nephrolithiasis, Osteopenia, Ca = 12.6 mg/dL, PTH = 582 pg/mL.	A 2.5 cm left apical multilobulated lung mass and a 7 mm right lung nodule
2	Rozhinsksaya (2017) [5]	Female/19	8 years	N/A	Thyroid nodule (Hemithyroidectomy)	Seven years later chest X-ray showed lung mass in check-up.	One-year history of Lung mass, Polyuria, Polydipsia, Anorexia, Nausea, MBD[3], Ca = 16.8 mg/dL, PTH = 249 pmol/L.	2.9 × 2.8 cm and 2.2 × 2.0 cm round tumors and 8 mm and 6 mm masses in the right lung
3	DasGupta (2014) [6]	Male/35	13 years	Hip pain[4], Biochemical evidence of primary hyperparathyroidism.	Parathyroid adenoma (Right-inferior parathyroidectomy)	Asymptomatic and had normal biochemical panel for more than 10 years.	Persistent hyperparathyroidism[5], Recent femoral fracture, Bone pain, Nephrocalcinosis and renal calculus, Osteoporosis, Ca = 12.8 mg/dL, PTH = 1500 pg/mL.	2.5 × 2.3 cm and 2.9 × 3.6 cm well-defined nodules in the right lung
4	Lim (2011) [7]	Female/32	10 years	Malaise, Nephrocalcinosis, MBD[3], Ca = 16.9 mg/dL, PTH > 1400 pmol/L.	Parathyroid adenoma (Right-inferior parathyroidectomy)	Post-op Ca = 11.4 mg/dL and PTH = 280 pmol/L; Lost to follow-up.	Low back pain, Weight loss, Ca = 16.0 mg/dL, PTH = 90 pmol/L.	A well-circumscribed right upper lobe mass
5	Kauffmann (2011) [8]	Female/62	4 years	Ca = 12.8 mg/dL, PTH = 150 pg/mL.	Parathyroid hyperplasia (Removing three parathyroid glands)	Post-op Ca = 9.4 mg/dL and PTH = 51 pg/mL; Lost to follow-up.	Enlargement of a remaining parathyroid gland in sonography[6], Ca = 18.6 mg/dL, PTH = 723 pg/mL.	Tiny pleural-based left lung nodules
6	Spielhagen (2009) [9]	Female/39	8 years	N/A	Thyroid nodule (Hemithyroidectomy)	Post-op Ca = 9.8 mg/dL and PTH = 123 pg/mL; Lost to follow-up.	Back pain, Anorexia, Weight loss, Nausea, Constipation, CKD[7], Ca = 18.4 mg/dL, PTH = 396 pg/mL.	Round foci in both hemithoraxes
7	Our case	Female/42	About 3.5 years	Chronic cough, Ca = 10.6 mg/dL, PTH = 249 pg/mL.	Parathyroid adenoma + PTC (Removing two parathyroid glands + total thyroidectomy)	Normal calcium levels in follow-up and asymptomatic for 32 months.	Epigastric pain, Lethargy, Constipation, Weakness, Osteoporosis, Ca = 13.2 mg/dL, PTH = 2131 pg/mL.	A few 3–5 mm nodules in the upper lobe of both lungs

[1]At primary presentation; [2]Between primary presentation and establish parathyroid carcinoma diagnosis; [3]MBD=Metabolic bone disease; [4]Giant-cell tumor; [5]One-year history of persistent hyperparathyroidism after right-superior parathyroidectomy due to adenoma; [6]So, partial left-superior parathyroidectomy was done but Ca and PTH did not drop; [7]CKD=Chronic kidney disease

Table 3 Clinical features in favor of parathyroid carcinoma

Symptomatic hypercalcemia such as fatigue, weakness, nausea, vomiting, polyuria, polydipsia
Serum calcium level > 14 mg/dL
Serum PTH concentration > 3 to 10 times higher than the normal upper limit
Palpable mass in the neck
Simultaneous renal or bone disease
Parathyroid crisis
Pancreatitis episodes
Recurrent laryngeal nerve palsy (without neck surgery history)

as angioinvasion, lymphatic, or perineural invasion. However, there were some histologic findings in favor of malignancy, including the presence of tumoral cell nodules enclosed by thick fibrotic bands with hemosiderin, areas of tumoral cells spindling with prominent nuclear atypia and bizarre nuclei, as well as easily identifiable mitotic figures (>5 per 2 mm^2) (Fig. 1E and F).

Preoperative localization studies can help plan surgery but cannot reliably distinguish between PC and PTA [14, 15]. The lung is the most common organ for distant metastasis in PC [16]. An important take-home message from this case is that there may not be any evidence of local recurrence or lymphatic invasion, as has been observed in other cases [4–9] (Table 2).

Most often, morbidity and mortality of PC are attributed to hypercalcemia and its complications rather than the tumor itself. Since PC does not respond well to chemotherapy and radiotherapy, the next plan for such a patient, in addition to medical management, could be surgical resection of metastases if feasible [14].

Abbreviations

FSE	Frozen section examination
PC	Parathyroid carcinoma
PTA	Parathyroid adenoma
PTC	Papillary thyroid carcinoma
PPE	Permanent pathological examination
PTH	Parathyroid hormone
RLN	Recurrent laryngeal nerve

Acknowledgements
The authors wish to thank Navid R. Ghaffari, MD, for the American English grammatical editing of this paper.

Author contributions
AAM and MP: data collection, writing original draft and prepared the figures, MHD: literature review, FH and SMT: revising the manuscript and editing, MBS: writing original draft and revising the manuscript. All authors read and approved the final manuscript.

Funding
None.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
The chief of the ethics committee of our institution waived IRB approval because of the retrospective and anonymous type of study (case report).

Consent for publication
Informed consent has been obtained from the patient included in this study.

Competing interests
The authors declare no competing interests.

Received: 20 June 2024 / Accepted: 26 November 2024
Published online: 04 December 2024

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