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Intrathyroid Parathyroid Carcinoma with Intrathyroidal Metastasis to the Contralateral Lobe: Source of Diagnostic and Treatment Pitfalls

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Intrathyroidal parathyroid carcinoma is extremely rare clinical entity with potentially multiple diagnostic pitfalls. We report a case of 40-year-old man presented with classical manifestations of primary hyperparathyroidism, severe hypercalcemia and profoundly increased serum parathyroid hormone level. Neck ultrasonography demonstrated multinodular goiter with predominant 34 mm nodule in left thyroid lobe. Additional 16 mm nodule was found beneath the left lobe. Routine percutaneous fine-needle aspiration of predominant nodule indicated follicular thyroid carcinoma, while left inferior nodule was confirmed to be of parathyroid origin. The patient underwent surgery, during which frozen sections identified medullary thyroid carcinoma with metastasis to upper mediastinal lymph node. Permanent sections of the predominant left lobe nodule revealed intrathyroidal parathyroid carcinoma surrounded with multiple microscopic metastases. Left inferior nodule was metastatic lymph node. Additional 10 mm intrathyroidal metastasis of primary parathyroid carcinoma was found within right thyroid lobe. This case indicates that fine-needle-aspiration and intraoperative biopsy are of limited value in diagnosing parathyroid carcinoma, especially if localized intrathyroidally. Oncological en-block resection is treatment of choice, implying ipsilateral lobectomy in case of thyroid invasion. This firstly described case of intrathyroidal parathyroid carcinoma causing intrathyroidal dissemination may influence future treatment strategies.

Key words: parathyroid carcinoma – thyroid nodule – diagnostic error – thyroidectomy

INTRODUCTION

Incidence of parathyroid carcinoma (PC) varies from 0.5 to 5% of patients with primary hyperparathyroidism (1). Preoperative and intraoperative diagnosis of PC is challenging, especially if localized within the thyroid gland. Hyperfunctioning intrathyroidal parathyroid glands occur in 3.4% of patients with primary hyperparathyroidism (2). Only five clinical cases of intrathyroidal PC have been published previously (3–7). We report a case of intrathyroid PC preoperatively and intraoperatively misdiagnosed as thyroid carcinoma, with additional PC within the contralateral thyroid lobe. This is the first reported case of PC causing intrathyroidal dissemination.

CASE REPORT

A 40-year-old man was admitted to gastroenterology department of a regional hospital due to anorexia, weight loss of

20 kg over a 2-months period and anemia. Family and past medical history were unremarkable. Investigations disclosed asymptomatic nephrolithiasis and mild gastritis. Three weeks later, he was admitted again due to intensive pain and multiple osteolytic lesions detected in both tibias. Peak serum calcium was 5.0 mmol/l (refernce range: 2.14–2.63 mmol/l) and ionized calcium 2.3 mmol/l (reference range: 1.15–1.40 mmol/l). Neck examination showed firm and enlarged left thyroid lobe. The endocrinologist had treated the patient with pamidronate, furosemide and fluid resuscitation and had referred him to our hospital.

On the day of admission his serum calcium level was 3.26 mmol/l (reference range: 2.14–2.53 mmol/l) and ionized calcium 1.7 mmol/l (reference range: 1.15–1.35 mmol/l) without the signs and symptoms of hypercalcemic crisis such as nausea, vomiting, renal insufficiency, severe dehydration, lethargy or confusion. His body mass index was 19.6 kg/m^2. Neck examination showed firm and enlarged left thyroid lobe.

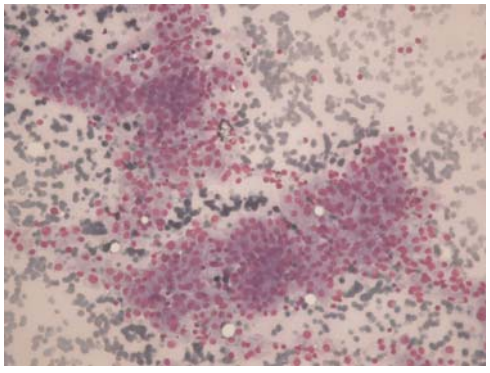

Figure 1. Fine-needle-aspiration (FNA) of intrathyroid parathyroid carcinoma (PC) showing highly cellular FNA smear in a colloid-free background showing syncytial clusters of moderately pleomorphic epithelial cells (May-Grünwald-Giemsa stain; magnification, ×100).

Profoundly increased parathyroid hormone (PTH) level of 989 pg/ml (reference range: 15–65 pg/ml) confirmed primary hyperthyroidism. Thyroid function tests were within normal ranges. Ultrasonography demonstrated multinodular goiter with predominant inhomogeneous 34 mm nodule within inferior part of left thyroid lobe and hypoechoic 11 mm nodule in right lobe. Another hypoechoic 16 mm nodule was found beneath the inferior pole of left lobe, interpreted as enlarged parathyroid gland. We performed routine percutaneous fine-needle-aspiration (FNA) of left thyroid nodule and the nodule beneath the left lobe. Aspirated material from left thyroid nodule was stained by May-Grünwald-Giemsa method and examined with light microscope. RT–PCR analysis of left thyroid nodule was performed as described by Samija et al. (8). The aspirate was highly cellular, and apart from some old and fresh blood, as well as some macrophages, consisted of numerous syncytial clusters of moderately pleomorphic epithelial cells with several, occasionally prominent, nucleoli (Fig. 1). RT–PCR analysis showed weak galectin-3 positivity, and negative CD44v6 and thyroglobulin expression. Final FNA diagnosis of poorly differentiated follicular thyroid carcinoma was established. FNA of the second nodule disclosed some peripheral blood cells, few bare nucleoli and high PTH level (>5000 pg/ml). Cytologist concluded that the second nodule was of parathyroid origin.

Multisection computed tomography was performed 6 days after FNA. It was used for more detailed visualization of the lesion and to assess the invasion of surrounding structures and enlarged lymph nodes. Inhomogeneous lesion measured 31 × 20 × 28 mm with invasion to surrounding fat tissue was found within the inferior part of the left thyroid lobe (Fig. 2). There were no signs of hemorrhage within tumor tissue, possibly caused by FNA. Multiple lymphatic nodes of regions 1, 2, 3 and 6 were also enlarged up to 12 mm. Additional lesion measured 12 × 8 mm was found within right thyroid lobe (Fig. 2).

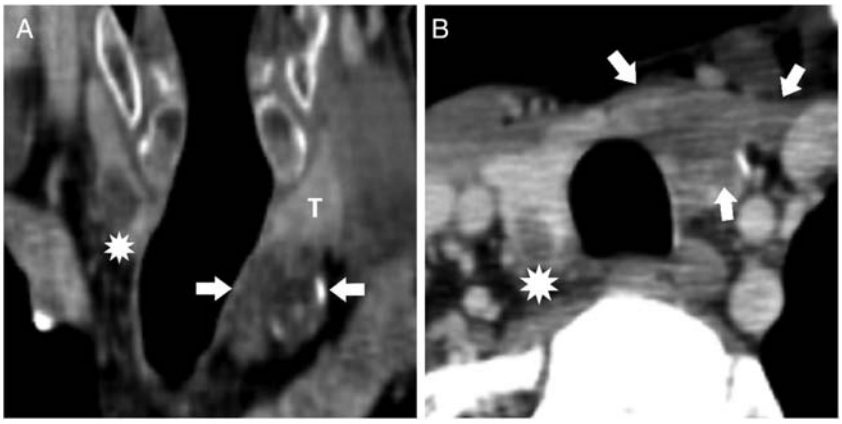

Figure 2. Multisection computed tomography in coronal oblique slices (A) and axial oblique slices (B) showed inhomogeneous, hypodense, partly calcified lesion (arrows) distinctly part of the left thyroid lobe (T) postoperatively confirmed as PC and well-bordered hypodense lesion in posterior part of right thyroid lobe (above asterisk) postoperatively confirmed as metastasis of primary tumor.

The patient remained hypercalcemic despite the pamidronate administration. Neck pain, redness or swelling were absent in the area where FNA was performed. The patient underwent surgery. During neck exploration, surgeon visualized firm mass that was distinctly part of the left thyroid thyroid with a plane between the tumor and the thyroid lobe. Three normal-sized parathyroid glands were identified. Left inferior parathyroid gland was missing, but replaced with enlarged lymph node. En-block resection of left thyroid lobe and adjacent lymph node was performed. Intraoperative biopsy of the left intrathyroid mass disclosed likely medullary thyroid carcinoma as well proved in adjacent upper mediastinal lymph node. Total thyroidectomy and bilateral modified radical neck dissection were then performed. Final pathohistological examination showed atypical epithelial cells with solid and trabecular arrangement (Fig. 3A), marked nuclear polymorphism, macronucleoli and mitotic figures (>5 mitoses/10 high-power fields) (Fig. 3C). Tumor cells were surrounded with dense, wide fibrous bands dividing tumor cells into lobules (Fig. 3A). Thyroid tissue was extensively infiltrated with tumor cells, but without clear evidence of vascular invasion. Multiple microscopic metastases were surrounding primary tumor (Fig. 3B and D). Only one, initially removed lymph node, was infiltrated with tumor tissue (Fig. 3E). Immunohistological staining of intrathyroid mass and upper mediastinal lymphatic node showed negative thyroglobulin, calcitonin and keratin expression while vimentin was weakly positive. PTH of the intrathyroid tumor showed strong expression (Fig. 3B and D) as well as lymphatic node (Fig. 3F). A diagnosis of lymph node metastatic PC was established. Additional analysis of right thyroid lobe revealed another well bordered and cystic tumor mass measured 10 mm, composed of tumor tissue consistent with primary tumor tissue (Fig. 3G). Immunohistological staining showed positive PTH expression (Fig. 3H), although weaker than the primary tumor probably due to excessive hemorrhage and necrosis within tumor tissue.

Postoperatively the patient became hypocalcemic, consistent with 'hungry bone' syndrome, and experienced major depressive episode. Supplementation with levothyroxine, oral calcium and calcitriol was started. Serum PTH level decreased to normal ranges (29 pg/ml) 7 days after surgery. Fluorine-8 fluorodeoxyglucose positron emission tomography–computed tomography showed no signs of residual tumor tissue or recurrence 2 months postoperatively. His calcium and PTH levels are within normal ranges 10 months postoperatively.

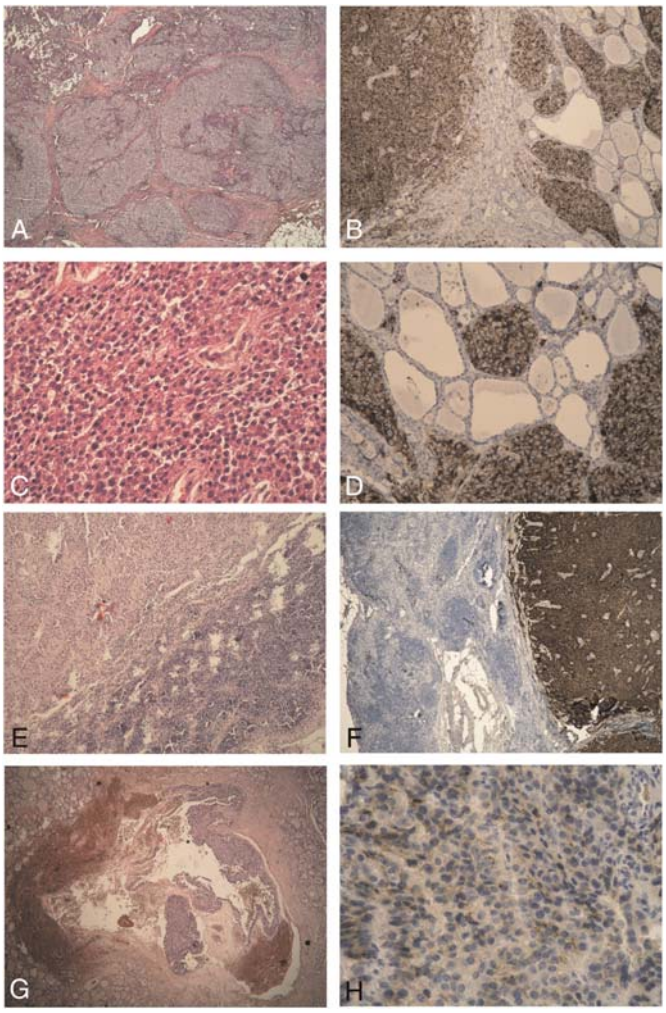

Figure 3. Intrathyroid PC within left thyroid lobe consisted of atypical epithelial cells in solid and trabecular arrangement, hematoxylin–eosin (HE) × 40 (A). Marked nuclear polymorphism, macronucleoli and mitotic figures, HE × 400 (C). Positive parathyroid hormone (PTH) expression of primary tumor tissue surrounded with multiple microscopic metastases, PTH × 40 (B) and PTH × 100 (D). Metastatic upper mediastinal lymph node, HE × 40 (E). PTH expression of metastatic lymph node, PTH × 40 (F). Necrotic and hemorrhagic tumor mass within right thyroid lobe consisted of identical tumor tissue as primary tumor (G), and showed positive PTH expression (H).

DISCUSSION

Only five patients with intrathyroidal localization of a PC have been reported previously (3–7). Preoperative diagnosis of PC was made in none of those patients (Table 1). There were initially two major diagnostic pitfalls in our case: ultrasonographic appearance of the tumor mass as predominant thyroid nodule in the setting of multinodular goiter and metastatic lymph node localized typically for enlarged parathyroid gland. Consequently, predominant thyroid nodule was assayed for galectin-3, CD44v6 and thyroglobulin without the determination of PTH level in punctate. Negative thyroglobulin expression indicated poorly differentiated thyroid carcinoma (9). Increased PTH level in inferior nodule determined the cause of hyperparathyroidism and indirectly suggested thyroid origin of predominant nodule. This is why technetium sestamibi scanning was not performed. FNA of the right lobe nodule, subsequently confirmed as intrathyroidal metastasis of primary PC, was not performed since it has not met the criteria of the Bethesda thyroid FNA classification system (10). To our knowledge,

Table 1. Clinical features of six patients with intrathyroid parathyroid carcinoma

Variable	Reference					
	Crescenzo et al. (3)	Kirstein et al. (4)	Schmidt et al. (5)	Foppiani et al. (6)	Temmim et al. (7)	Present case
Calcium (mg/dl)	12.7	11.1	>12	12.6	Increased	19.5
PTH (pg/ml)	205	625	580	721	Increased	989
Size (cm)	1.5	Unknown	3.2	3.0	6.0	3.2
Sestamibi scan	ND	Positive	Equivocal	Negative	Positive	ND
FNA	Follicular thyroid neoplasm	ND	ND	ND	Parathyroid neoplasm	Follicular thyroid carcinoma
Frozen sections	Parathyroid carcinoma	Unknown	Parathyroid carcinoma	Nodular goiter	Unknown	Medullary thyroid carcinoma
Surgical treatment	En-block resection	En-block resection	Total thyroidectomy	Total thyroidectomy	En-block resection	Total thyroidectomy
Metastases	None	None	None	None	None	Single lymph node and contralateral thyroid lobe
Outcome (follow-up)	Eucalcemic (1.5 years)	Eucalcemic (unknown)	Eucalcemic (1 year)	Eucalcemic (5 years)	Eucalcemic (2 years)	Eucalcemic (10 months)

PTH, parathyroid hormone; FNA, fine-needle aspiration; ND, not done.

FNA of PC metastatic lymph node has never been reported as source of pitfall in PC diagnostics.

The most recent meta-analysis by Talat et al. (11) showed poor correlation between serum calcium, PTH levels, tumor size and PC. Nevertheless, severe primary hyperparathyroidism and palpable neck mass are indicative for PC (1). FNA is not recommended in such cases due to inability of differentiating benign and malignant disease, but also due to potential dissemination of malignant cells in tract (1,12). However, if tumor mass presents as thyroid nodule, FNA is often performed. According to Tseleni-Balafouta et al. (13), FNA gives poor results in recognizing the parathyroid origin of a intrathyroid nodule. Most aspirates are misinterpreted as thyroid neoplasms because of the high cellularity and similar cytomorphological picture. In mentioned study, among 29 histologically confirmed intrathyroidal parathyroid lesions only two were diagnosed as parathyroid lesions. There were two PCs, both misinterpreted as thyroid carcinomas. According to Erbil et al. (14) and in reference to our case, PTH in aspirate should be determined whether FNA is performed in patient with primary hyperparathyroidism and concomitant thyroid nodule.

Intraoperative biopsy also gives poor results in diagnosing PC (1). In our case, intraoperative biopsy misdiagnosed PC as medullary thyroid carcinoma. Rapid intraoperative PTH test was not available in our hospital, which led to wrong intraoperative diagnosis. On macroscopic examination, tumor mass seemed distinctly part of the thyroid. Microscopic examination and the presence of tumor tissue in upper mediastinal lymph node were suggestive of medullary thyroid carcinoma. The use of rapid serum PTH test for intraoperative assessment of complete tumor removal has been reported in PC (1). Intraoperative FNA with determination of PTH in punctate was reported to be used for identifying parathyroid tissue (15). Both methods yield good results and should be used if possible. If such methods are not available, the surgeon should assume PC in patients with severe and symptomatic hypercalcemia and intraoperative presence of large, firm or scirrhous tumor, regardless of presurgical or intraoperative diagnosis (16). Differentiating between malignant and benign lesions based on tissue specimens can be quite difficult even in permanent sections. PC can be diagnosed only in the presence of capsular invasion or metastasis (1,16).

Treatment of choice for PC is oncological en bloc resection with central lymph node clearance and removal of all possibly affected soft tissues (11). In the case of thyroid tissue invasion, ipsilateral lobectomy is suggested. Our case is the first reported case of PC with multiple microscopic metastasis within the ipsilateral thyroid lobe and macroscopic metastasis within the contralateral lobe. Two cases of multifocal PCs have been reported previously (17,18), but in mentioned cases, tumors were found within parathyroid glands. In our case, second PC was found within the thyroid tissue, surrounded with thick ring of fibrous tissue. In addition, two normal-sized right parathyroid glands were found during neck

exploration, all of which suggest intrathyroidal metastasis of primary tumor. This finding suggests that in case of aggressive PC with infiltration of thyroid tissue, total thyroidectomy should be performed. Further studies on the presence of microscopic and macroscopic thyroid tissue metastases caused by thyroid invading PC are worthy.

In conclusion, PC should be suspected in patients with severe hypercalcemia, increased PTH and palpable neck mass. FNA and intraoperative biopsy must be used and interpreted in consideration of clinical picture and laboratory findings. This firstly described case of intrathyroidal PC causing intrathyroidal dissemination may influence future treatment strategies. Further studies are needed.

Conflict of interest statement

None declared.

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