CASE REPORT

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Parathyroid carcinoma detected within the thyroid

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ABSTRACT

Parathyroid carcinoma (PC) is a rare disease accounting for approximately 1% of primary hyperparathyroidism cases. The preoperative differentiation of PC is critical because PC can occasionally metastasise and invade the local tissue. However, this is challenging in asymptomatic cases and when the tumour is adjacent to the thyroid. Herein, we report a rare case of PC without clinical symptoms. Fine needle aspiration was performed, despite being contraindicated in PC, and an intrathyroidal tumour was preoperatively suggested.

Keywords: parathyroid carcinoma, primary hyperparathyroidism, fine needle aspiration

Abbreviations:
FNA : fine needle aspiration
PC : parathyroid carcinoma
PTH : parathyroid hormone

INTRODUCTION

Parathyroid carcinoma (PC) is a rare disease and accounts for approximately 1% of the cases of primary hyperparathyroidism.[1] Compared with parathyroid adenoma (PA), PC can occasionally metastasise and invade the local tissue; thus, preoperative diagnosis is critical, although it is difficult when patients are asymptomatic or when the tumour is located adjacent to the thyroid. In such cases, fine needle aspiration (FNA) is usually performed routinely but frequently leads to misdiagnosing the thyroid origin because both the parathyroid and thyroid glands are morphologically similar on cytological smears. Here, we report on a patient with PC that was preoperatively observed within the thyroid, and the FNA was performed, despite being contraindicated in PC.

CASE REPORT

A 71-year-old man was found to have a thyroid mass when examined at a local hospital.

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Computed tomography (CT) was performed after 1 year at a different hospital, and he was referred to our hospital for further examination of the thyroid mass. He was asymptomatic and had no significant past medical history and family history. Ultrasonography revealed multiple well-defined nodules and an impalpable ill-defined mass with microcalcifications (11.2 × 11.7 × 11.8 mm) in the upper pole of the right thyroid lobe (Fig. 1). Blood tests revealed normal thyroid function and mild hypercalcaemia (11.5 mg/dL), a high intact parathyroid hormone (iPTH) concentration (121.0 pg/mL), and hypophosphatemia (2.5 mg/dL). His renal function was normal (Table 1). A CT scan showed a low-density lesion within the right thyroid lobe and a nodule behind the right thyroid lobe (Fig. 2). After consulting radiologists, we concluded that the mass in the right thyroid was a thyroid tumour and that the nodule behind the right thyroid lobe was causing hyperparathyroidism. After obtaining informed consent, FNA of the right thyroid mass was performed, and pathological examination revealed atypical cells with fine granular chromatin, hyperchromatic nuclei, and a high nucleus-to-cytoplasm ratio, which indicated that the cells originated in the parathyroid gland and not the thyroid gland. Subsequent immunohistochemical examination revealed a parathyroid origin [GATA3(+), PTH(+), chromogranin A(+), synaptophysin(+), thyroid transcription factor-1(–), thyroglobulin(–), calcitonin(–)] (Fig. 3). A parathyroid scintigraphy examination using technetium-99m methoxy isobutyl isonitrile revealed an increase in early and delayed phase focal activity in the right upper pole of the right thyroid lobe with no such increase elsewhere (Fig. 4).

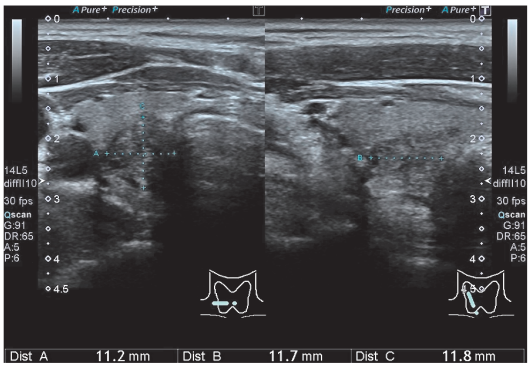


Fig. 1 Thyroid ultrasound

Ultrasonography showing an ill-defined mass (11.2 × 11.7 × 11.8 mm) in the upper pole of the right thyroid lobe. The depth/width ratio is ≥ 1.0.

Table 1 Blood examination

Blood Cell Count			
WBC	9.1×103 /μL	Ht	43.4 %
RBC	443×104 /μL	Plt	15.6×104 /μL
Hb	14.4 g/dL		
Blood Chemistry			
Alb	4.5 g/dL (4.1–5.1)	K	4.4 mmol/L (3.6–4.9)
AST	75 IU/L (13–33)	Cl	102 mmol/L (99–109)
ALT	133 IU/L (6–30)	Ca	11.5 mg/dL (8.7–10.3)
BUN	24 mg/dL (8–22)	P	2.3 mg/dL (2.5–4.7)
Cr	1.04 mg/dL (0.6–1.1)	Clucose	250 mg/dL (71–109)
UA	7.5 mg/dL (3.6–7.0)	HbA1c	14.5 % (4.3–5.8)
Na	139 mmol/L (138–146)		

Endocrine examination			
TSH	2.04 μIU/mL (0.5–5.0)	TgAb	<10 IU/L (<28)
Free-T3	3.37 pg/mL (2.3–4.3)	TPOAb	<9 IUmL (<16)
Free-T4	1.27 ng/dL(0.9–1.7)	Tg	44.9 ng/mL (<33.7)
TRAb	<0.8 IU/L (<2.0)	Intact-PTH	121.0 pg/mL (10–65)

TRAb: TSH receptor antibody
TgAb: Thyroglobulin antibody

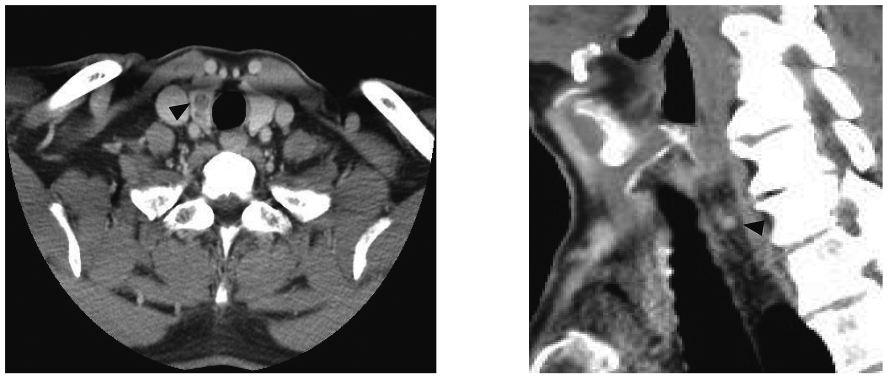


Fig. 2 Contrast-enhanced neck computed tomography
Contrast-enhanced neck computed tomography showing a low-density lesion within the right thyroid lobe on axial slices postoperatively confirmed as parathyroid carcinoma (arrow head) (A) and a nodule behind the right thyroid lobe on sagittal slices (arrow head) thought to be a parathyroid adenoma (B).

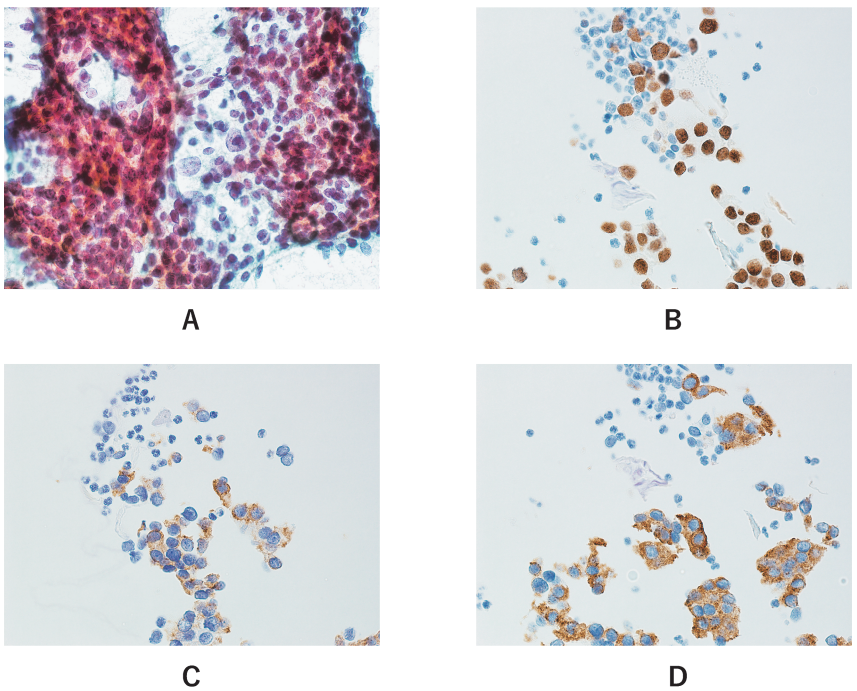
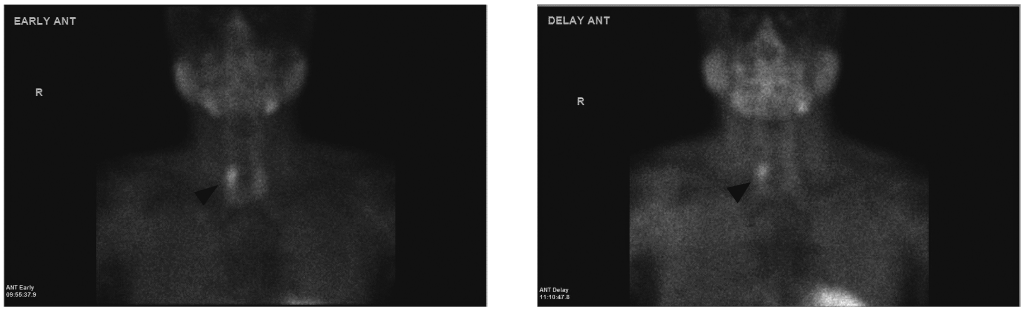


Fig. 3 Fine needle aspiration of the thyroid mass
Papanicolaou staining reveals cells with high nuclear-to-cytoplasm ratios with fine granular chromatin and hyperchromatic nuclei. Tubular structures can be observed, but no colloid substance is confirmed (A). The expressions of GATA3 (B), PTH (C), and chromogranin A (D) indicate that the cells originated in the parathyroid gland.



A B

Fig. 4 Tc-99m MIBI scintigraphy
Tc-99m MIBI scintigraphy showing an increase in focal activity in the early phase (arrow head) (A) and retention of the tracer in the delayed phase (B) in the right upper pole of the right thyroid lobe (arrow head).

The patient underwent surgery on account of primary hyperparathyroidism due to the mass in the right upper pole of the right thyroid lobe. Intraoperatively, a well-defined plurilocular mass with a diameter of approximately 1.5 cm was detected in the right upper lobe of the thyroid gland that was thought to have originated in the right upper parathyroid gland. Four-gland exploration was performed during which the right lower and upper glands were not detected. Neither adenopathy nor infiltration of the adjacent structures was observed. The right thyroid lobe was resected, followed by central neck lymph node dissection, as the possibility of malignancy could not be excluded using frozen sections. The preoperative and immediate postoperative iPTH concentrations were 131.0 pg/mL and 30.3 pg/mL, respectively, which indicated that the surgeon had correctly identified and resected the lesion. The surgical specimen was examined histologically. The mass was distributed inside and outside of the thyroid gland and had a maximum diameter of 12 mm. The tumour cells appeared as pseudopapillary solid nests with an irregularly shaped nucleus, nuclear enlargement, nucleolus enlargement, and visible chromatin.

The fibrous capsule was not visible. The thyroid gland was partially infiltrated without clear evidence of vascular invasion and lymph node metastases. Immunohistochemical examination revealed that the tumour had a parathyroid origin as was previously confirmed cytologically. Additional immunohistochemical examination yielded negative results for MDM2, and positive results for parafibromin. Ki-67 was apparently less than 4%. No abnormalities in the expression of BCL2 and p53 were confirmed. PC was diagnosed based on the presence of thyroid infiltration (Fig. 5). The initially high iPTH level returned to normal (26.9 pg/mL) 10 days after the surgery. No tumour recurrence or postoperative complications occurred during the five months of follow-up.

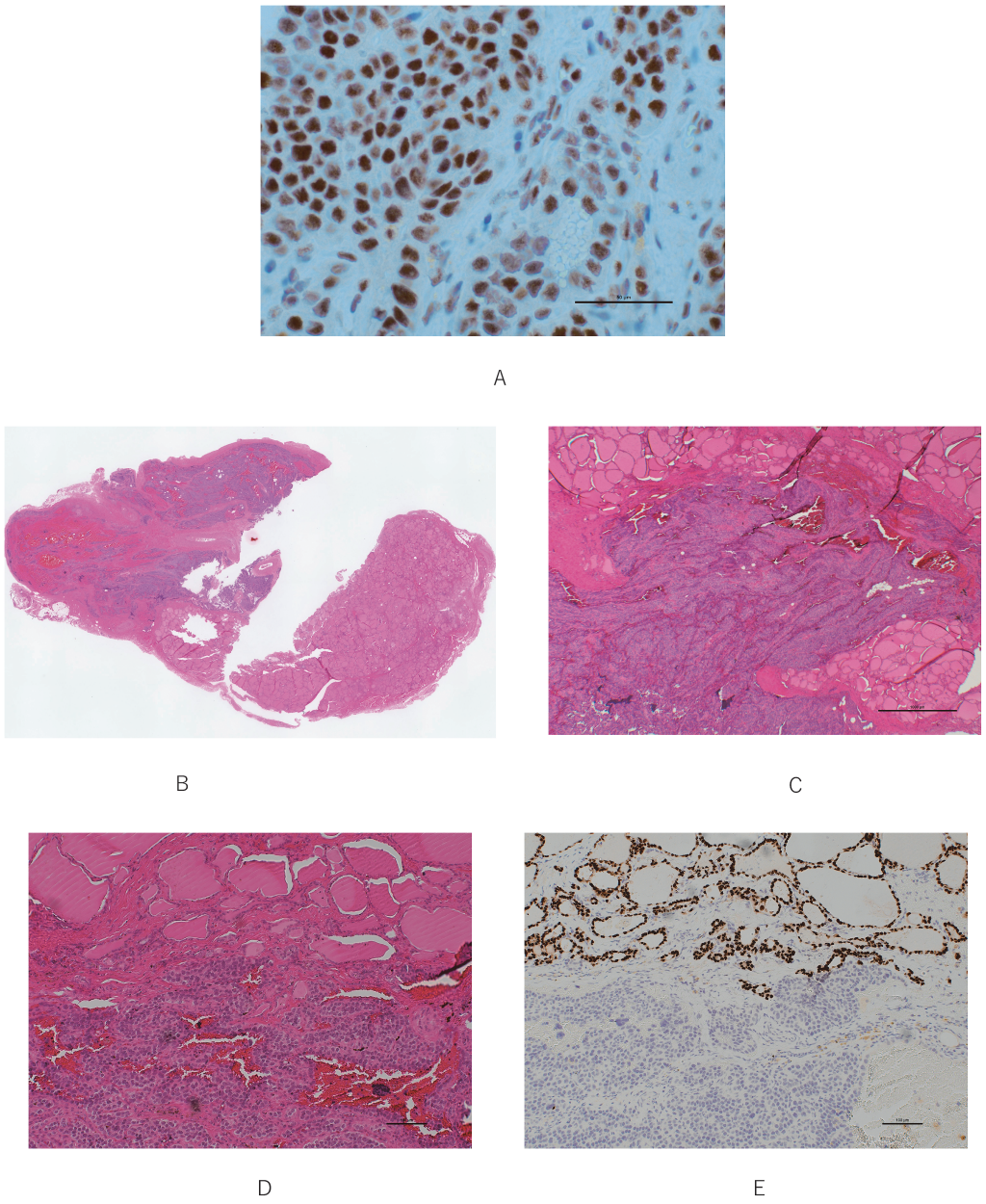


Fig. 5 Histological examination of the surgical specimen
Immunohistochemical examination yields positive results for parafibromin (A). Fibrous band, which is a typical feature of parathyroid carcinoma (PC), is not apparent. The tumour showing a solid growth pattern outside of the thyroid gland (B). PC is diagnosed based on tumour infiltration of the thyroid tissue (C, D). TTF-1 tested negative in the tumour cells (E).

DISCUSSION

PC is a rare malignancy that accounts for approximately 1% of the cases of hyperparathyroidism.[1] Patients with PC, compared with those with PA, are more likely to present with a palpable neck mass, high PTH levels (>300 pg/mL), high serum calcium level (>14 mg/dL), and clinical manifestations such as kidney stones, peptic ulcers, pancreatitis, and bone involvement.[2-7] PCs are rarely non-functional, although some cases of functional PCs have been reported.[8] PC sometimes metastasises, infiltrates the local tissue, and recurs[7,9]; thus, it is important to differentiate between PC and PA. PC appears histologically as broad fibrous bands, with a solid growth pattern, nuclear atypia, atypical mitoses, increased mitotic activity, and necrosis; however, these features are not highly specific to PC. Therefore, PC should be diagnosed based on 1) vascular invasion, 2) local invasion of adjacent structures, and 3) lymph node or distant metastasis.[10-13]

A rare case of intrathyroidal PC has been reported.[14] The parathyroid glands can be found in various locations and can be intrathyroidal. Intrathyroidal PC is thought to originate in such glands but is not clearly defined. In our case, the mass that was thought to be a thyroid tumour initially was not histologically intrathyroidal; however, the clinical course was similar to that of previously reported cases of intrathyroidal PC. Preoperative differentiation was difficult, and the origins of those tumours were likely to be considered as thyroid in many patients, although almost all patients underwent FNA.[14-16] This can be explained by the fact that parathyroid and thyroid lesions are morphologically similar on cytological smears.[16,17]

With the increasing use of FNA, an increasing number of parathyroid lesions are unintentionally aspirated for various reasons with a prevalence of up to 0.4%.[18-21] Parathyroid lesions should be suggested using cytological examination in those cases. Parathyroid lesions have architectural features such as scattered naked nuclei, loose clusters, a papillary pattern with a fibrovascular core, tight clusters, and a follicular pattern and cytological features such as anisokaryosis, stippled chromatin, well-defined cell borders, and oxyphilic cytoplasm.[22] The PTH assay using the washout fluid of the aspiration needle also has a high specificity, but this is limited to cases in which a parathyroid lesion is already suggested.[18] Immunocytochemical analysis of FNA specimens is useful in differentiating between parathyroid and thyroid tissues. The expressions of PTH, GATA3, chromogranin A, and synaptophysin are related to the parathyroid tissue, and GATA3 might be a useful marker with a higher sensitivity and specificity among them.[23]

Parafibromin is the transcription product of the tumour suppressor gene, *CDC73/HRPT2*, and its germline mutation is associated with the hyperparathyroidism-jaw tumour syndrome, which causes parathyroid neoplasia with an increased risk of parathyroid cancer. The *CDC73* mutation occurs in approximately 77% of the cases of PC and <1% of the cases of PA; moreover, approximately 20% of patients with apparently sporadic PC will have germline mutations in *CDC73*.[24] During an immunohistochemical examination, the loss of parafibromin expression indicates malignancy along with the loss of expression of the retinoblastoma protein, p27, BCL2, MDM2, and APC; positivity for galectin-3; overexpression of p53; and Ki-67 expression >5%.[13] In our case, PC was diagnosed only based on infiltration into the thyroid gland and the immunohistochemical findings were not typical for PC. This might explain our patient being asymptomatic.

Finally, FNA is contraindicated in PC and should be avoided if possible as the risk of tumour seeding along the needle track has been documented.[25,26] In one case, PC recurred subcutaneously 5 years after FNA, and subsequently, surgical resection was performed. The recurrent tumor was placed away from the surgical scar and histologically infiltrated the muscle and fibrous tissue.[25] If not malignant, secondary changes that occur during aspiration make histology-based diagnoses difficult.[20] Preceding technetium-99m methoxy isobutyl isonitrile scintigraphy would have helped in the diagnosis of our patient's condition, and FNA could have been avoided. Clinical data are

also required to improve the diagnostic sensitivity[22]; thus, cooperation between clinicians and pathologists is necessary.

CONCLUSION

We report a rare case of PC without clinical symptoms. Our patient underwent FNA, despite the contraindication for FNS, and a parathyroid lesion was suggested based on cytological findings. Thus, careful preoperative examinations are essential for correct diagnosis. Furthermore, histological criteria should be better established considering that the tumour did not have typical features of PC, except thyroid infiltration. More cases are necessary for understanding the clinical and pathological features of PC.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest associated with this manuscript. The authors have no conflicts of interest directly relevant to the content of this article.

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