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Case Report
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Recurrent Parathyroid Carcinoma in the Multiple Endocrine Neoplasia Type 2 (MEN2): A Case Report and a Review of Multiple Endocrine Neoplasia with Parathyroid Carcinoma Reported Cases in the World

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Abstract

Parathyroid Carcinoma (PC) is an infrequent endocrine malignancy with only a few thousand cases documented globally. Multiple Endocrine Neoplasia Type 2 (MEN2) is a hereditary syndrome characterized by the development of tumors in multiple endocrine glands. Although parathyroid hyperplasia or adenoma in multiple endocrine neoplasia 2A syndrome (MEN2A) is the most common type, parathyroid carcinoma is rare. Herein, we describe for a female patient of PC with MEN2A and review of all reported relevant cases retrieved through PubMed. A 60-year-old female patient who was diagnosed with PC in the context of medullary thyroid carcinoma (MTC) at the age of 48. [99mTc] MIBI image revealed hyperparathyroidism of the left inferior gland following elevated serum calcium levels, and postoperative pathology confirmed carcinoma of adenoepithelial origin with focal infiltration. Notably, her brother had experienced pathological rib fractures due to parathyroid adenoma, but genetic analysis did not reveal mutations in the RET gene associated with MEN2. Our review of the few published cases of parathyroid carcinoma within MEN syndromes (including MEN1, MEN2) reported in the literature indicates that, after surgery for MEN-PHPT, recurrent hypercalcemia and heterotopic lesions should be considered for the possibility of PC.

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Introduction

MEN2A is a hereditary syndrome characterized by the presence of MTC in approximately 95% of cases, pheochromocytoma (PHEO) in 50%, and hyperparathyroidism (PHPT) in about 20% of individuals. The MEN2A-PHPT is typically associated with parathyroid hyperplasia or multiple parathyroid adenomas [1]. The incomplete suppression of PTH in response to a calcium infusion test and the observation of parathyroid hyperplasia at the time of thyroidectomy in MEN2A patients without clear-cut hypercalcemia both suggest that parathyroid abnormalities are present in most cases [2]. The MEN2 gene is located on chromosome 10cen-10q11.2 and encompasses the Rearranged during Transfection (RET) protooncogene, which encodes a tyrosine kinase receptor characterized by cadherin-like, cysteine-rich extracellular domains, as well as a tyrosine kinase intracellular domain [3].

PC is one of the rarest cancers, accounting for 0.005% of all cancers and less than 1% of cases of primary hyperparathyroidism [4,5]. Only a few thousand cases have been reported in the literature since the first case was described by De Quervain in 1904 [6]. There have been reports of coexisting adenoma and carcinoma, of PC occurring in primary hyperparathyroidism, and rarely of long-standing secondary and tertiary hyperparathyroidism, but evidence of a causal relationship is lacking [7]. The American Joint Committee of Cancer Control (AJCC) acknowledges that a clear staging system for prognosticating the disease would be premature due to its rarity. Similarly, diagnostic criteria are not very clear and valuable for clinical application. There is currently no method available to definitively differentiate between difficult cases of parathyroid adenoma and carcinoma. It can only be determined by biological behavior based on invasion of adjacent structures and/or the presence of metastases. The pathological diagnosis needs to be further investigated in the diagnosis of PC due to the diagnostic criteria from the histopathological point of view, ICH is not definitive. Parathyroid

tumors have dense fibrosis that demarcates parathyroid tumor cells into lobulated aggregates. This can occasionally mimic "capsular" or "angiolymphatic" invasion. A significant proportion of PC cases are often misdiagnosed as benign diseases, leading to repeated recurrence and metastasis, which adversely impacts patient prognosis. Genetic testing is sometimes the only way to diagnose, but it often lags behind. The gain is seen involving 19p, Xc-q13, 9q33-qter, 1q31-q32, and 16p [8]. The majority of the PC are sporadic although an association with hyperparathyroidism-jaw tumor syndrome, multiple endocrine neoplasia (MEN) 1 and 2, and isolated familial hyperparathyroidism has been shown [9,10]. Up to now, only 22 cases of MEN1 associated with PC have been reported worldwide, while MEN2 is even rarer, with only 3 cases, and all of them are male patients (Table [11-28]). In clinical practice, surgeons treating patients with MEN-PHPT through parathyroidectomy should tailor the extent of gland resection and transplantation strategies to the individual patient's condition. The goal is to delay the need for reoperation as much as possible and prevent iatrogenic recurrence and metastasis of parathyroid tumors. Herein, we present a case in our center, which could be a notable example of diagnosis, perioperative management and prognosis for MEN2A-PC patients.

Case Presentation

A 60-year-old female with recurrent and metastatic PC was admitted to our center in December 2023, having undergone four surgeries intermittently, each followed by postoperative hypercalcemia. Her medical history includes a near-total thyroidectomy in May 2011 for MTC, which was initially misclassified as a benign thyroid adenoma. Post-surgery, the pathology revealed a 3.0 × 2.5 × 2.3 cm medullary carcinoma of the right thyroid lobe with no lymph node metastases.

In December 2017, persistent hypercalcemia and suspicion of MEN2A prompted a residual thyroidectomy, Total Parathyroidectomy (TPTX), and autotransplantation. Pathology identified a parathyroid adenoma with local infiltration in the left inferior gland (Figure 1A-1D).

By February 2021, the patient presented with parathyreosis. An excision of a hard, oval mass in the right sternothyroid muscle revealed a partially encapsulated, infiltrative round cell tumor, consistent with parathyroid carcinoma. The tumor measured 1.6 × 1.5 × 0.6 cm and exhibited uniform cancer cells arranged in nests, with fine granular chromatin and large amyloid deposits. Immunohistochemical staining was positive for PTH, CK19, GAL-3, CD56, and GATA-3 (Figure 1E-1H). Postoperative PTH and blood calcium were significantly reduced.

In December 2023, recurrent hypercalcemia led to a right Lateral Neck Dissection (LND). Pathological analysis of the group III lymph nodes and medical history supported the diagnosis of parathyroid carcinoma. Immunohistochemistry results included positive PTH, SDHB, and GATA-3, and negative results for calcitonin, CEA, CgA, CK19, Ki-67 (1%), and P53 (wild-type). Postoperatively, PTH and blood calcium levels initially decreased but later rebounded, complicated by a postoperative lymphatic fistula from extensive right cervical lymph node clearance.

Upon readmission, the patient had elevated blood calcium (3.3 mmol/L) and PTH (334 pg/ml). A second surgical exploration, guided by 11C-CHO-PET imaging, identified and excised two masses beneath the right sternocleidomastoid muscle and near the right clavicular head. Using the PTS, complete removal of these masses was achieved. Postoperative pathology confirmed parathyroid carcinoma (Figure 2). On the second postoperative day, the patient experienced hypocalcemia, and PTH levels normalized (Figure 3,4).

Discussion

Herein, we present a case of a 60-year-old female diagnosed with Medullary Thyroid Carcinoma (MTC) at onset, with subsequent diagnosis of Multiple Endocrine Neoplasia type 2A (MEN2A) based on Primary Hyperparathyroidism (PHPT) and family history. Despite no recurrence of MTC post-surgery, the patient experienced persistent issues with PHPT. After initial standard parathyroidectomy and transplantation. Pathological confirmation of normal parathyroid tissue transplanted into the right sternocleidomastoid muscle showed invasive bio-behavior after 3 years. Concurrently, Parathyroid tumor cells were found in the right cervical lymph nodes, indicating malignant character. Hence, LND of the right neck was deemed necessary. Postoperatively, the patient's blood calcium levels rose again, prompting [99mTc] MIBI imaging which revealed a small nodule (size of 0.9 cm × 0.5 cm) behind the right clavicular head, suggestive of residual hyperfunctioning parathyroid tissue (Figure 2A). Ultrasound also showed multiple hypoechoic lesions behind the right sternocleidomastoid muscle, indicating recurrent parathyroid lesions and suspicious lymph nodes (Figure 2B). The patient underwent a fourth lesion excision surgery, confirming atypical parathyroid tumors. However, the outcome of this surgery was less satisfactory compared to the previous two, with only marginal reduction in postoperative blood calcium levels, which subsequently rose again. Four months later, the patient underwent more precise

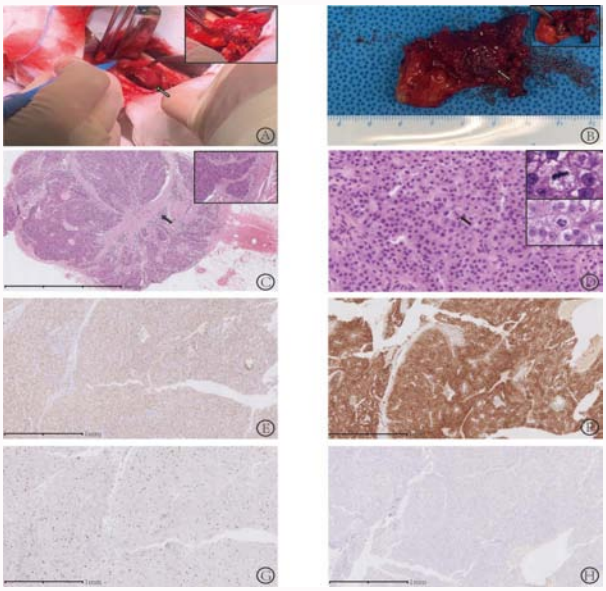

Figure 1: The removed left inferior parathyroid gland tissue in the second surgery shows lobular structures separated by fibrous connecive tissue under low magnification.Thick capsules are observed where some cell are arranged in a trabecular pattern.There are also atypical cells penetrating the capsules and infltrating surounding tissues(A). Immunohistochemical staining reveals predominantly chief cells,with some showing pleomorphism and frequent mitotic figures. Cyclin D1(+) ×10(B), GATA3(+) ×20(C), and Ki67(hotspot area>5%) ×20(D). The tumor resected from the right stemocleidomastoid muscle is identified as a small round tumor cells are aranged in a trabecular pattem, with nfilration beyond capsule into surounding muscle and blood vessels(E). Immunohistochemical staining shows PTH (+) ×10 with Ki-67 (hotspot area>5%) ×20 and CT (-) ×20(F), Cyclin DI (+) ×10(J), GATA-3(+) ×20(H).

Table 1: The message of multiple endocrine neoplasia with paratheroid carcinoma reported cases.

Year	Country	Age/ Sex	MEN-X	Symptomatology	Hormones	Ca (mmol/L)	PTH (pmol/L)	Surgery	Mass Size	Pathology	Y/ Recurrence	Metastasis	MEN mutation	Germline mutations	Ref
MEN1															
1992	China	48/M	PIT	-	-	4.05	14.7	Hemithyroidectomy and resection of the LI parathyroid gland	-	Nests of uniform cells separated by dense collagenous septa and mitotic figures	3	Chest wall Neck and sternum metastasis	-	-	[11]
2000	Japan	51/F	-	Moderate hypercalcemia	-	2.67	-	Total parathyroidectomy (RS parathyroid carcinoma and multiple adenoma of the other three glands)	-	1PC (with capsular invasion) + 3PA	-	-	842delC in exon 4	Three sisters and one daughter	[12]
2002	Italy	35/M	NET (Gastrinoma)	Severe symptomatic hypercalcemia:	Gastrin 720 pg/mL	3.35	75	First surgery: single gland parathyroidectomy	2.5cm	1PC(vascular invasion)+3PA	3	Anterior media-stinum	-	-	[13]
				clinical suspicion of acute pancreatitis	(reference range 10-100 pg/mL)			Second surgery:SPTX		Nuclear pleomorphism together with moderate nuclear changes					
2007	UK	69/F	PIT (Macro-prolactinoma)	Severe symptomatic hypercalcemia	PRL 21200mU/L	3.9	37.7	First surgery: three parathyroid glands Second surgery: mediastinal ectopic parathyroid carcinoma	4.5 cm (ectopic)	1PC(LS)+3PH	-	Mediastinum	-	-	[14]
			NET0 (Non-functioning pancreatic tumor)	Tracheal compression by a large mediastinal mass						dense fibrous capsule and features of infiltrative cell mitoses densmoplasia fat necrosism and fibrous banding					
		32/M	NET (gastrinoma and insulinoma)	Severe symptomatic hypercalcemia	Gastrin 82 pg/mL	3.7	28	Two parathyroid glands	-	1PC(LI)+1PN	-	-	-	Mother	
				a long term of intractable dyspepsia and severe upper abdominal pain	(reference range 40 pg/ mL)					Fibrous banding, atypical mitoses, extra-capsular extension and moderate					
					Cortisol 72nmol/l					Ki 67 staining					
					(reference range 50)										
2009		53/F	PIT (Non-functioning pituitary adenoma)	Nausea and severe primary hyperparathyroidism	-	3.35	143.66	Surgical resection of 5 benign parathyroid glands plus a combined thyroid/ parathyroid mass, followed by radiation therapy	-	1PC(RI)	-	-	c.1406_13dup8	-	[15]
			NET (Gastrinoma)							Fibrous bands with vascular and perineural invasionand tumour fat					
			AA												
2010		44/F	PIT (Pituitary Macro-adenoma)	two years history of right sided neck pain and	-	2.71	8.7	First surgery:single parathyroidectomy	RI	4PA	Short time	Lung	-	-	[16]
			NET (non-functioning pancreatic endocrine tumor)	generalised aches and pains				Second surgery: SPTX	2.× 1 ×0.5 cm	Distant metastasis.					
								+autotransplantation	PA or PH						
2011	Spain	50/M	NET (gastrinoma)	Moderate hypercalcemia two years' duration consisting of abdominal pain and diarrhea	Gastrin 135 ng/L	3.1	21.6	First surgery:	RI 1.7cm PC	Trabecular pattern with areas of necrosisin filtrated the capsule and the peripheral fibroadipose tissue	-	Infiltration of the thyroid gland	W183C in exon 3 of the MEN1 gene	One of his two children (a daughter), parents die	[17]
			AA(non-functioning adrenal adenomas)					duodenopancreatectomy together with asplenectomy and colecistectomy							
								Second surgery:							
								three parathyroids + Hemithyroidectomy							

2011	Lithuania	39/F	PIT (pituitary micro-prolactinoma) NET (pancreatic endocrine tumor) AA SL	General weakness Fatigue Weight loss Bilateral galactorrhea	Prolactin >3600 mIU/L	2.7	34.3	Resection of two parathyroids +Hemithyroidectomy + Neck lymphadenectomy	RI 2.5cm LS 2.0cm 	2PC Infiltration of thyroid. Both the tumors grew penetrating the capsule of the parathyroid glands, invaded into the thyroid gland	-	Infiltration of the thyroid gland	c.129insA in exon2	Father	[18]
2013	Korea	59/F	PIT AA (adrenal adenoma and two pituitary micro-adenomas)	-	-	3.18	26.31	Single gland parathyroidectomy (inner thyroid nodule) + Hemi-thyroidectomy	RI 2.1 cm PC	within the mid pole of the right thyroid gland Abnormal morphology within fibrous connective tissue plus thyroid invasion	-	Infiltration of the thyroid gland	-	-	[19]
2016	USA	62/M	NET (nonfunctioning pancreatic endocrine tumor) AA (nonfunctional adrenal tumor) CT (bronchial carcinoid tumour 		Gastrin level hight	3.1	14	First surgery: single gland parathyroidectomy (LS) Second surgery: single gland parathyroidectomy (RS)	LS: PC RS:PH 	Histological evidence of local invasion (nerve)	-	Esophagus	-	Daughter and mother	[20]
		54/M	NET (nonfunctioning pancreatic endocrine tumor) CT (Bronchial-carcinoid) 	Mild hypercalcemia	-	2.63	4.5	First surgery: SPTX Second surgery□RI+LS(benign HPT) 	RS: 1.8 cm PC 	Lobular feature Capsular invasion extending into the adipose tissue Abutting the adjacent thyroid	3	Recurrence	c.703G>A (p.E235K) in exon 4 	Family history	
		55/M	PIT NET (nonfunctioning pancreatic endocrine tumor) AA 	Hypercalcemia Weight loss Fatigue Lethargy and fullness in the left cervical region	-	3.45	71.4	SPTX + 1/2 auto-plantation	LS:3.0 cm PC 	Dense fibrotic bands and angulated parathyroid nests admixed Consistent with an infiltrating tumor	6 months	Recurrence	c.1378C>T (p.R460X) in exon 10 	Family history	
		32/F	NET (nonfunctioning pancreatic endocrine tumor) CT	Migraines and malaise	-	3	-	First surgery: resection of 2+1/2 parathyroids Second surgery: single gland parathyroidectomy	0.7 cm PC	Thick bands Lobular feature	2	Recurrence	-	-	

	Japan	40/M	PIT (prolactinoma)	Pain from the recurrent urinary stone attack	PRL 11.7 ng/mL	2.7	21.5	First surgery: resection of 3 parathyroids + Hemithyroidectomy + LI auto- plantation		RI PC	-	Infiltration of the thyroid gland	-	mother	[21]
			NET (nonfunctioning pancreatic endocrine tumor)		Gastrin 270 pg/mL			Second surgery: Completion thyroidectomy + resection of 1 intrathyroidal mass	RS 1 cm	Capsular and vascular invasion					
			CT (lung carcinoid tumor)		(high-calcium cause)				LI 2.5 cm						
									PH						
									Inner left thyroid lobe 2.5 cm						
									PC						
	Italy	61/M	NET (pancreatic endocrine tumor)	Nephrolithiasis	-	-	-	Resection of 2 parathyroids	-	Capsular invasion	-	Infiltration of esophageal	c.1252G>A (p.D418N)	0	
			AA	Renal stones						Oesophageal infiltration					
2017		55/M	AA	Renal stones	-	1.48 (iCa)	3.2	Single gland parathyroidectomy	-	Characteristic neoplastic invasion of parathyroid carcinoma cells into adjacent vessels and gross invasion of the surrounding thyroid tissue.	-	Infiltration of surrounding adipose tissue	c.1252G>A (p.D418N)	0	[22]
		48/F	NET (pancreatic endocrine tumor)	Recurrent abdominal pain	Gastrin 86 pg/ml	3.2	22.3	First surgery: behind sternum manubria on the right side+level of the left thyroid Second surgery: En-bloc excision of the parathyroid glands Third surgery: RI	-	2PH+PC+PA	-	-	IVS2-3G>C, c.497A>T and c.499G>T	0	[23]
2018	Italy	62/M	NET PIT AA (non-functioning adrenal nodule)	A large asymptomatic, left-sided palpable neck mass	-	2.92	41.5	Resection of 2 parathyroids + Hemithyroidectomy + Neck lymphadenectomy	retrosternal adjacent to thyroid left lobe 9 cm PC	Macroscopically normal. Pathology confirmed PC without thyroid invasion or lymphatic metastases	-	-	No CDC73 gene mutation or deletion	Brother	[24]

2020	China	51/F	NET (pancreatic endocrine tumor) AA	Bone pain-induced restricted movement	-	2.56	232.2	First surgery: single gland parathyroidectomy (LS) Second surgery: TPTX + autoplantation	LS PA RI+RS PN	Multiple nodules with fibrous bands tumor cells arranged in sheets or glands.	-	-	c.917T>G (p.L306R)	2daughters and 1 grandson, 1 elder sister and her son, and 2 younger sisters and one of their sons	[25]
		52/F	PIT (macro-prolactinomas)	A 10-year history of recurrent nephrolithiasis	-	3.35	75.2	Resection of 2 parathyroids	LS+RI APN	-		-	c.431T>C (p.F144S)	-	
		51/M	PIT NET (pancreatic endocrine tumor) AA Atypical carcinoid (mediastinum) Lipoma (abdominal wall)	A 12-year history of recurrent nephrolithiasis	-	2.83	40.3	Resection of 2 parathyroids	LI+RS PA	-	1	Recurrence (LS)	c.549G>C (p.W183C)	suspect	
PC: parathyroid carcinoma; PH: parathyroid hyperplasia; PA: parathyroid adenoma; PN: normal parathyroid; PIT, pituitary adenoma; NET: Neuroendocrine Tumour; AA: Adrenal Adenoma; CT: Carcinoid Tumor; SL: Subcutaneous Lipoma; TPTX: Total Parathyroidectomy; SPTX: Subtotal Parathyroidectomy; LI: Left Inferior; LS: Left Surperior; RI: Right Inferior; RS: Right Surperior															
MEN2															
2002	Spain	49/M	MTC Phaeochromocytoma	Acute myocardial infarction	Calcitonin 75.8 ng/l	3.6	39.2	First surgery: LS parathyroid gland Second surgery: right hemithyroidectomy	LS: PA LI fat tissure RI: PN RS not identified	-	6	pulmonary metastasis	-	Son	[26]
1997	UK	47/M	MTC	Thirst and polyuria for 8 weeks	Calcitonin 5110ng/l	3.3	102	First surgery: three parathyroid glands Second surgery: total thyroidectomy	RS+LS:not identify LI+RI:PN	-	-	T1+ right frontal bone	(Cys634Tyr) ofexon 1l	-	[27]
2014	Spain	54/M	Pheochromocytoma	-	Calcitonin 2.1ng/l	2.3	6.1	First surgery: adrenalectomy Second surgery: total thyroidectomy with central lymphadenectomy	LI:1.4 cm PC	parathyroid chief cells in trabecular, infiltrative pattern with fibrotic septae and vascular invasion.	-	-	(Cys6l8Arg) ofexon 10	Family history	[28]
2023	China	60/F	MTC	Fracture history	-	3.3	55.9	First surgery thyroidectomy (MTC) Second surgeryTPTX + Transplantation Third surgery intrasternocleidomastoid mass + right cervical lymph node dissection Forth surgery Posterior to right clavicle head + right neck lymph node dissection Fifth surgery stern- ocleidomastoid mass and partial muscle bundle+posterior to right clavicle head	LS:1.5 × 1.4×1 cm PC	Trabecular pattern with areas of necrosisin filtrated the capsule and the peripheral fibroadipose tissue	3/3/3 month	Recurrence	-	Brother	-

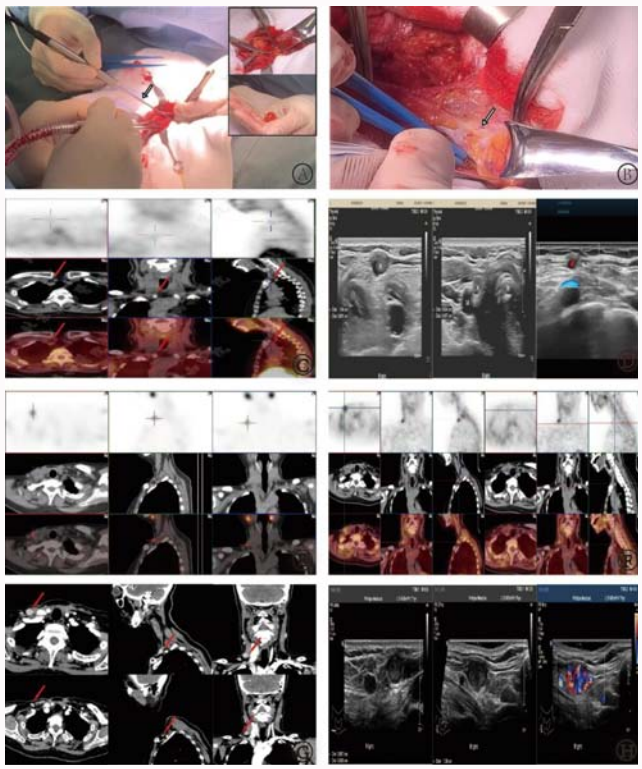

Figure 2: Parathyroid auto-fluorescence identification technology was utilized. Suspicious lesion was examined, followed by pathological examination(A). The parathyroid tissue transplanted during the second surgery opted into a muscle margin location and marked the site with non-absorbable sutures(B). MIBI imaging prior to the forth surgery failed to detect the lesion within the stermocleidomastoid muscle, raising the suspicion that mutual suppression between multiple lesions may have caused this limitation(C). The characteristics of the parathyroid mass on contrast-enhanced CT scans of the neck at difference sectional planes the mass is located posterior to the inferior segment of the clavicular head of the right sternocleidomastoid muscle. During the arterial phase, heterogeneous enhancement is observed(G). Additionally, a notable advantage is ability to detect another smaller mass (red marker), consistent with findings in CHO-PET(F), which was not identified by MIBI before the patient's final surgery(E).

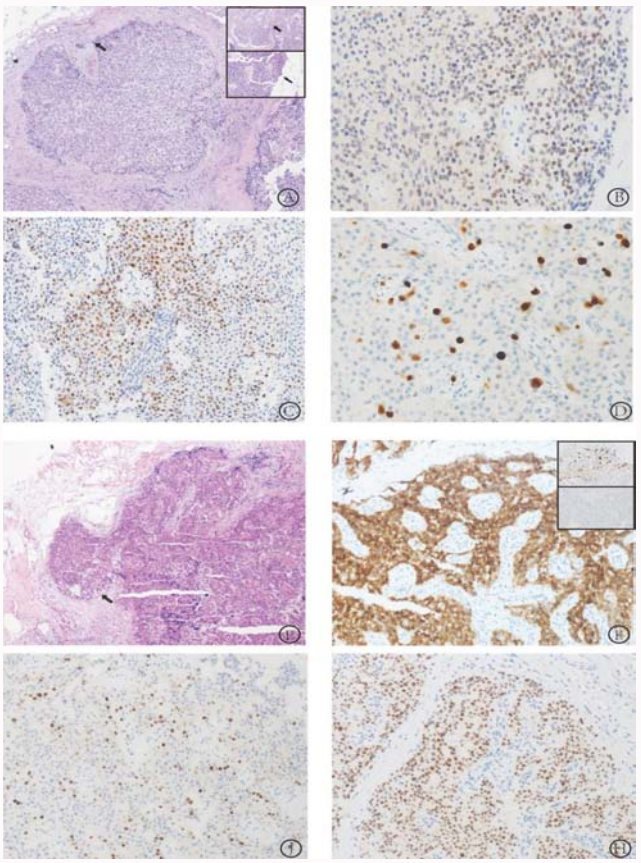

Figure 3: Broad fibrous bands, solid growth and infiltrative growth are common morphological features of parathyroid carcinomas(A). The diagnosis of parathyroid carcinoma is rendered histologically when a parathyroid tumor shows unequivocal invasion evidence of vascular and around tissue invasion (B, C, D). Iriad of high-risk histopathological features: Foci of oagulative necrosis, prominent macronucleoli, and mitotic activity>5/50 high-power fields (E, F). CD34 staining reveals endothelial cells within the tumor tissue that are undergoing angiogenesis(G). Ki67 hotspot areas are greater than 10%(K), higher than those in the previously removed tumor tissue; GATA3(+), PTH (+), TTF (-), MGMT (-) indicate that the tumor originates from the parathyroid gland, and that the medullary thyroid carcinoma has not recurred (H, I, J, L).

localization and evaluation, leading to another surgery resulting in a significant reduction in postoperative blood calcium levels. Although the fifth surgery proceeded successfully and removed recurrent lesions, resulting in decreased biochemical markers postoperatively, the overall prognosis for the patient's disease remains poor. The high risk of recurrence and the challenges of subsequent surgeries necessitate careful consideration.

MTC, as a relatively rare malignant tumor in the thyroid carcinoma, typically presents as sporadic. However, it is crucial to screen for rare diseases such as MEN2 at the initial diagnosis. About 10% of these cases develop Primary Hyperparathyroidism (PHPT), often with multiple lesions, and a probability of PC, as seen in this instance. Therefore, preemptive parathyroid examination and methods of transplantation should be considered during surgery.

For patients with familial or genetic hyperparathyroidism, even morphologically normal parathyroid tissues during surgery or confirmed normal by pathology have a high probability of future malignant transformation, necessitating consideration of the feasibility of surgery for recurrent PHPT. Transplantation into the deltoid muscle is a viable option. Additionally, using non-absorbable suture as marks during parathyroid transplantation, as done in this case (Figure 2C), and limiting the transplantation site to a single muscle bundle in the sternocleidomastoid muscle (clavicular head) can aid in locating recurrent tumors and preserving muscle function post-resection.

For primary hyperparathyroidism patients, surgical removal of hyperfunctioning parathyroid glands remains key treatment modality. Nonetheless, challenges persist in preoperative diagnosis and intraoperative localization. In cases of multifocal neuroendocrine tumors, there is an inhibitory relationship between the lesions, where more functionally active mass can reduce the detectability of others. Upon reviewing the two surgeries performed on this patient at our center, we observed that after resecting the lesions identified by the initial functional radionuclide imaging, other less detectable lesions became visible on the more sensitive 11C-CHO-PET scan (Figure 2D-F). For patients with recurrent and multi-lesion parathyroid diseases, we recommend preoperative parathyroid enhanced CT scan to supplement the subjectivity and irreversibility of ultrasound examination (Figure 2G), as well as to comprehensively evaluate possible lesions that may be present, and to compensate for the

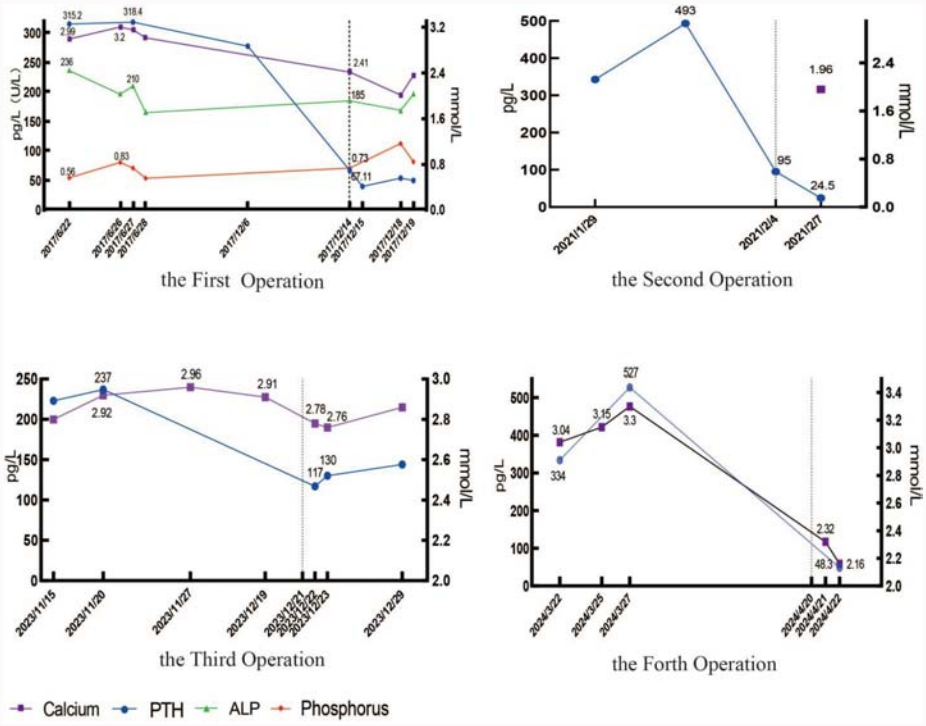

Figure 4: Illustrates the changes in laboratory parameters before and after the four parathyroid surgeries undergone for patient. Postoperatively, there was a consistent decrease in calcium ion levels and Parathyroid Hormone (PTH) concentrations. However, the first three surgeries failed to prevent the recurrence of hypercalcemia and hyperparathyroidism. Similarly, although the biochemical markers returned to normal after the final surgery, there is a high likelihood of recurrence in the future.

deficiency of [99mTc]MIBI in functional imaging of multiple lesions (Figure 2E). To some extent, it can delay the need for a second surgery. Intraoperative frozen pathology remains the primary method for identifying responsible lesions. The excised and sent tissues are deemed suspicious lesions largely depends on the surgeon's experience. This process is subjective and has a high incidence of mistakenly identifying adipose tissue and lymph nodes as lesions. Intraoperative PTH test facilitates the assessment of the surgical outcome but does not directly contribute to the localization of responsible lesions. Utilizing autofluorescence detection (PTS) during the second surgery, as a tool for identifying parathyroid tissue, can significantly reduce surgical time and improve the clearance rate of residual lesions, including metastatic lymph nodes (Figure 2A). Nonetheless, its accuracy in distinguishing atypical parathyroid hyperplasia and parathyroid carcinoma requires further clinical validation and exploration.

This patient's condition is unique, highlighting areas for improvement in early diagnosis and standardized parathyroid transplantation. With multiple recurrences of PHPT and neck metastases, the likelihood of further recurrence post-surgery is high, necessitating consideration of alternative treatment modalities. In addition, the patient has nodules in the lung and abnormal lymph nodes in the mediastinum, which should be vigilant against metastatic cancer. To our knowledge, this is the fourth reported case of MEN2A combined with PC worldwide and the first female patient, marking the first reported case in Asia.

Our analysis of the limited published cases of PC within the MEN syndrome, as documented in the literature (Table [11-28]), reveals that individuals in the MEN1-PC subgroup had an average serum calcium level of 3.11 ± 0.09 mmol/L (with a range from 2.56 to 4.05 mmol/L) and an average Parathyroid Hormone (PTH) level of 48.21 ± 12.81 pmol/L (with a range from 3.2 to 232.2 pmol/L), with an average onset age of 50.14 ± 9.9 years. Conversely, those in the MEN2-PC subgroup exhibited a mean serum calcium level of 3.13 ± 0.28 mmol/L (with a range from 2.3 to 3.6 mmol/L) and an average PTH level of 50.80 ± 19.96 pmol/L (ranging from 6.1 to 102 pmol/L), with an average onset age of 52.5 ± 5.8 years. Notably, there was no significant difference in the mean age at disease onset, the average level of calcium and PTH between the two groups (P=0.652, 0.572, 0.662). After a detailed analysis of each patient, excluding ectopic PC, the location of the lesion was predominantly in the inferior parathyroid glands, with a higher incidence on the right side.

Conclusion

For patients with MEN2-PC, we can exhibit a phenotype distinct from MEN2A-PC and MEN2B-PC. Comparative analysis of reported cases of MEN2A-PC indicates that, in contrast to MEN2A where the initial symptom is typically MTC and occurs in almost all patients at an average age of diagnosis between 19-33 years [9], the onset of MTC in MEN2A-PC tends to be delayed. The age in this patient was 48 years, one case not yet presenting with symptoms at the time of reporting, another diagnosed at 47 years old, and the other discovered at 50 years old. The mortality rate in MEN2A-PC is not driven by MTC as in MEN2A, but rather by PC, such as distant metastasis and hypercalcemic crisis. Analysis of the first three cases revealed one case with suspected hypercalcemia leading to myocardial infarction, another with lung metastasis, the last one with non-functional PC without MTC, indicating a generally better prognosis for this group of patients compared to MEN2 [10]. The patient's MTC did not recur after surgery, without any signs of PHEO. By combining existing cases with future reports and conducting a rational analysis of genotypic

and phenotypic data, these patients could potentially represent a new subtype of MEN.

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