# Parathyroid Carcinoma, an Uncommon Diagnosis

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ABSTRACT

Parathyroid carcinoma should be considered in patients with clinical manifestations of severe hyperparathyroidism and hypercalcemia and corresponding abnormal laboratory values. Findings on several imaging modalities are highly suggestive of the diagnosis and often reveal malignant features, including local invasion or disseminated disease. Ultrasonography further aids in localizing the lesion and preoperative planning. 99mTc-sestamibi scintigraphy is also valuable in lesion localization, especially with delayed-phase image acquisition, although false negative results can occur. Surgical resection, along with prospective histopathological examination, is the primary treatment. The role of chemotherapy and radiation therapy remains controversial. Here, we present a case of a 67-year-old woman with histopathology-confirmed parathyroid carcinoma despite a negative 99mTc-sestamibi scintigraphy.





# CASE REPORT

## CASE REPORT

A 67-year-old female with a past medical history of poorly controlled hypertension presented to the emergency department with a two-week history of generalized malaise, altered mental status, behavioral disturbances, weakness, and weight loss. At presentation, physical examination was significant for rightward gaze deviation and a palpable left level IV neck mass. The patient underwent brain imaging, which was negative for intracranial pathology. Laboratory tests on admission were significant for severe hypercalcemia (calcium level of >18 mg/dL [Normal range: 8.5-10.5 mg/dL]), hyperparathyroidism (parathyroid hormone [PTH] level greater than 2500 pg/mL), acute kidney injury (creatinine level of 1.5 mg/L) and leukocytosis (white blood cell count of 18 K/uL). Her altered mental status was suspected to be due to hypercalcemia, and the initial differential diagnosis included parathyroid adenoma and parathyroid carcinoma (PC).

### Imaging Findings

A contrast-enhanced computed tomography (CT) of the neck showed a 3 x 3.1 x 3.2 centimeter (cm) irregular, heterogeneous, necrotic mass abutting the inferior pole of the left thyroid lobe, ipsilateral common carotid artery (CCA), and internal jugular vein (IJV) (Figure 1). Thyroid sonography demonstrated a necrotic left cervical mass deep to the strap muscles adjacent to the inferior pole of the left thyroid lobe with similar dimensions (Figure 2). These findings in conjunction with the clinical presentation and laboratory values, increased the suspicion of PC as a potential diagnosis.

The patient subsequently underwent parathyroid scintigraphy with 99mTc-sestamibi, which did not demonstrate abnormal radiopharmaceutical uptake in the lesion (Figure 3). However, given the constellation of findings, specifically, the PTH >2500 pg/mL and calcium >18mg/dL, PC was the primary diagnosis, and the patient was tentatively staged with a Tumor, Nodal, Metastatic (TNM) stage of T2N0M0 (AJCC) [1].

### Management

After medical stabilization, the patient underwent surgical en-bloc resection of the mass, left thyroid lobe and isthmus, superior and inferior parathyroid glands, and the left neck nodes levels III and IV with the adjacent strap muscles. Intraoperatively, the tumor infiltrated the left thyroid lobe and surrounding strap muscles and adhered to the left IJV. Ligation of the vein was avoided by carefully dissecting the tumor from the connective tissue. Intraoperatively, the PTH decreased from 706 pg/mL to 130 pg/mL, confirming the successful removal of the tumor.

### Gross Pathology Appearance:

The neck mass was ovoid, red-tan, and hemorrhagic, measuring 6.0 x 5.0 x 3.0 cm. The cut surface showed a yellow-tan tumor with small areas of necrosis. The tumor was grossly adherent to the thyroid gland and adjacent structures (Figure 4). The entire specimen was submitted for microscopic examination.

### Histopathology

The tumor consisted of sheets of predominantly oncocytic cells with perinuclear clearing, nuclear enlargement with coarse chromatin, and prominent macronucleoli. The tumor infiltrated the skeletal muscle, adjacent fat, and thyroid tissue. No angioinvasion was identified (Figure 4).

The histopathological diagnosis of PC is restricted to tumors that show at least one of the following findings: (i) angioinvasion (vascular invasion), (ii) lymphatic invasion, (iii) perineural invasion, (iv) local malignant invasion into the adjacent structures/organs, or (v) regional or distant metastasis [2]. Hence, the presence of invasion into adjacent structures was consistent with the diagnosis of PC.

The tumor cells showed focal expression of PTH and Chromogranin; Thyroid transcription factor 1 (TTF-1) was negative (positive in the adjacent thyroid tissue). PCs can have variable PTH immunohistochemistry staining [3,4].

After a multidisciplinary discussion, the TNM staging was determined to be pT3N0M0. Subsequently, the decision was made to irradiate the tumor bed and ipsilateral neck due to adherence to the internal jugular vein, which was preserved during the surgery with concern for residual microscopic disease.

### Follow up

Unfortunately, the patient was lost to follow-up due to health insurance issues.

## DISCUSSION

### Etiology and Demographics

Primary hyperparathyroidism (PHPTH) is one of the most common endocrine disorders. Most cases are secondary to parathyroid adenomas, with parathyroid hyperplasia accounting for a minority of cases. PC is a rare cause of PHPTH, typically accounting for less than 1% of cases and approximately 0.005% of all malignancies [5]. Although exceedingly rare, the reported incidence of PC has increased over the past few decades [6]. Males and females are equally affected and often present between the fifth and sixth decades of life [6], unlike benign PHTPH, which demonstrates a three-fold female predominance and presents a decade later than PC [6].

The exact etiology of PC remains unknown, with most cases thought to be sporadic [7]. However, there are familial cases, such as those associated with hyperparathyroidism-jaw tumor (HPT-JT) syndrome, isolated familial hyperparathyroidism, and multiple endocrine neoplasias (MEN) type 1 and MEN2A syndromes [7]. A germ-line mutation in the CDC73 tumor suppressor gene is identified in approximately one-third of patients diagnosed with sporadic PC [8].

### Clinical Presentation and Diagnosis

Parathyroid hormone increases serum calcium levels by several mechanisms, i.e., by directly enhancing osteoclast activity and differentiation, leading to calcium release from bone, enhancing renal tubular calcium reabsorption, and augmenting intestinal calcium absorption [9]. Hypercalcemia can also occur through indirect means, such as limiting the binding of calcium to phosphate and elevating the amount of free calcium by lowering serum phosphate levels [9]. Parathyroid hormone can enhance vitamin D activation, leading to augmented renal and intestinal calcium absorption [9]. These direct and indirect processes give rise to the characteristic clinical manifestations of hyperparathyroidism and hypercalcemia [6].

Clinical suspicion of functioning parathyroid carcinoma should arise based on physical examination and laboratory values indicative of extreme hyperparathyroidism, such as severe hypercalcemia, hypophosphatemia, and hypervitaminosis D, along with average to elevated parathyroid hormone [6]. Imaging findings of a parathyroid lesion may help support the diagnosis, while histopathologic evaluation remains the gold standard for diagnosis [6]. Most PCs are hyper-functional, with less than 2% being non-functional [10,11]. Non-functional PCs are more challenging to diagnose and often present with local or disseminated disease [10].

Histopathologic evaluation and confirmation of PC is generally made following en-bloc surgical tumor resection [5,12]. Fine needle aspiration biopsy (FNAB) is discouraged because specimens are usually insufficient for diagnosis and can result in tumor seeding along the biopsy tract with a risk of capsular rupture and dissemination of tumor cells [11,13,14].

### Imaging Findings

Several imaging modalities can be utilized to evaluate patients with suspected PC. Ultrasonography (US) largely contributes to presurgical planning by localizing and characterizing the parathyroid lesion [15], followed by 99mTc-sestamibi scintigraphy (MIBI) [16]. Ultrasound findings suggestive of a parathyroid malignancy include lesion size greater than 3 cm, heterogenous echotexture, irregular margins, local tissue invasion, and intralesional calcifications. These findings aid in differentiating a PC from an adenoma [17,18]. The MIBI dual-phase scintigraphy, when positive, can accurately localize abnormal parathyroid tissue, especially with delayed phase images, since the radiopharmaceutical is often retained longer by the tumor than surrounding normal thyroid and parathyroid glands [16]. Despite MIBI scintigraphy demonstrating a sensitivity of 91% for detecting PCs, false negative results can occur [19].

On computed tomography (CT), PCs exhibit malignant features, such as an increased length-to-width ratio, irregular shape, local infiltration, and calcifications [20]. Additionally,

PCs often demonstrate poor contrast enhancement due to the high rate of necrosis [20]. On magnetic resonance imaging (MRI), PCs may present as ill-defined, heterogeneous, T2-hyperintense lesions on fat-suppressed sequences [21]. Nuclear imaging with 18F-FDG PET/CT can also aid in lesion localization, assessing the extent of the disease, evaluating recurrence, and identifying metastatic disease [22].

### Treatment and Prognosis

After initial medical management of malignant hypercalcemia, surgery is the definitive treatment for PC [23]. Due to the rarity of the disease, standardized guidelines for the extent of resection are not established [24]. A radical surgical approach with en-bloc resection and excision of the adjacent thyroid lobe, involved lymph nodes, and surrounding tissue by an experienced surgeon is often performed [23,25]. The American Association of Endocrine Surgeons does not recommend prophylactic central or lateral neck dissection because there is no observed increase in overall survival [24]. Unfortunately, despite appropriate surgical efforts, PCs recur in more than 50% of patients after 2-3 years [7].

The role of radiotherapy remains controversial. PC is generally considered radioresistant, with only a few studies favoring its role in adjuvant therapy [11,26,27]. Currently, radiotherapy is recommended for palliative treatment, although based on small, less impactful studies. Therefore, the utility of radiation therapy remains to be determined [24]. Similarly, chemotherapy has a limited role in treating PC, with minimal to no response observed in a few case reports available in the literature [5,6,23]. Currently, attempts are being made to identify small-molecule chemotherapy drugs that can target specific genetic mutations, such as sorafenib therapy for patients with CDC73 germ-line gene mutations [28,29]. The prognosis of PC is relatively favorable due to its indolent course [6]; the long-term survival rate is 78-91% at five years and 60-72% at ten years [6]. Many studies have examined prognostic factors for long-term outcomes, with surgical management being the only consistent variable predictive of overall survival [6]. Gender, age, extent of local invasion, regional nodal, and distant metastases have produced variable results regarding long-term survival and prognosis [6].

### Differential Diagnosis

The differential diagnosis of PC is broad and depends on the lesion's functional status. Functional lesions with clinical manifestations of hypercalcemia are commonly due to parathyroid adenomas or glandular hyperplasia [6]. Nonfunctioning lesions may present with compressive or invasive symptoms suggesting a malignant entity such as invasive thyroid carcinoma [6]. Based on the imaging findings in this case, the diagnostic considerations include necrotic lymphadenopathy and, although rare, metastatic disease to the parathyroid gland [30]. Other etiologies of hypercalcemia, such as medications, multiple myeloma, granulomatous disease, and paraneoplastic syndromes, should also be excluded.

## TEACHING POINT

Parathyroid carcinoma is exceedingly rare and should be suspected in patients with physical and laboratory manifestations of severe hyperparathyroidism and hypercalcemia. Various imaging modalities often demonstrate a malignant lesion near the thyroid, with evidence of local invasion or disseminated disease. Ultrasonography aids in localizing the primary lesion and preoperative planning. Although 99mTc-sestamibi scintigraphy is also highly valuable for lesion localization, especially with delayed-phase image acquisition, it may yield false negative results.

## REFERENCES


1. Amin MB, Edge SB, Greene FL, et al. The Eith Edition American Joint Committee on Cancer (AJCC) Staging Manual. *CA Cancer J Clin.* 2017; 67(2): 93-99. PMID: 28094848.
2. Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO Classification of Parathyroid Tumors. *Endocr Pathol.* 2022; 33(1):64–89. PMID: 35175514.
3. Suganuma N, Iwasaki H, Shimizu S, et al. Non-functioning parathyroid carcinoma: a case report. *Surg Case Reports*. 2017; 3(1): 1–6. PMID: 28726134.
4. Tomita T. Immunocytochemical staining patterns for parathyroid hormone and chromogranin in parathyroid hyperplasia, adenoma, and carcinoma. *Endocr Pathol.* 1999; 10(2): 145–156. PMID: 27519218.
5. Cetani F, Pardi E, Marcocci C. Update on parathyroid carcinoma. *J Endocrinol Invest.* 2016; 39(6): 595–606. PMID: 27001435.
6. Rodrigo JP, Hernandez-Prera JC, Randolph GW, et al. Parathyroid cancer: An update. *Cancer Treat Rev.* 2020; 86: 102012. PMID: 32247225.
7. Cetani F, Pardi E, Marcocci C. Parathyroid carcinoma: a clinical and genetic perspective. *Minerva Endocrinol.* 2018; 43(2): 144–55. PMID: 28949121.
8. Hyde SM, Rich TA, Waguespack SG, Perrier ND, Hu MI. CDC73-Related Disorders. GeneReviews®. 2018; PMID: 20301744.
9. Khan M, Jose A, Sharma S. Physiology, Parathyroid Hormone. StatPearls. 2022; PMID: 29763115.
10. Cetani F, Frustaci G, Torregrossa L,et al. A nonfunctioning parathyroid carcinoma misdiagnosed as a follicular thyroid nodule. *World J Surg Oncol.* 2015; 13(1): 270. PMID: 26350418.
11. Harari A, Waring A, Fernandez-Ranvier G, et al. Parathyroid carcinoma: a 43-year outcome and survival analysis. *J Clin Endocrinol Metab.* 2011; 96(12): 3679–3686. PMID: 21937626.
12. Salcuni AS, Cetani F, Guarnieri V, et al. Parathyroid carcinoma. *Best Pract Res Clin Endocrinol Metab.* 2018; 32(6): 877–889. PMID: 30551989.

13. Agarwal G, Dhingra S, Mishra SK, Krishnani N. Implantation of parathyroid carcinoma along fine needle aspiration track. *Langenbeck's Arch Surg.* 2006; 391(6): 623–626. PMID: 17021789.
14. Kim J, Horowitz G, Hong M, Orsini M, Asa SL, Higgins K. The dangers of parathyroid biopsy. *J Otolaryngol Head Neck Surg.* 2017; 46(1): 4. PMID: 28061891.
15. Smith RB, Evasovich M, Girod DA, et al. Ultrasound for localization in primary hyperparathyroidism. *Otolaryngol Head Neck Surg.* 2013; 149(3): 366–371. PMID: 23748916.
16. Schulte KM, Talat N. Diagnosis and management of parathyroid cancer. *Nat Rev Endocrinol.* 2012; 8(10): 612–622. PMID: 22751344.
17. Sidhu PS, Talat N, Patel P, Mulholland NJ, Schulte KM. Ultrasound features of malignancy in the preoperative diagnosis of parathyroid cancer: a retrospective analysis of parathyroid tumours larger than 15 mm. *Eur Radiol.* 2011; 21(9): 1865–1873. PMID: 21556910.
18. Nam M, Jeong HS, Shin JH. Differentiation of parathyroid carcinoma and adenoma by preoperative ultrasonography. *Acta Radiol.* 2017; 58(6): 670–675. PMID: 27609904.
19. Digonnet A, Carlier A, Willemse E, et al. Parathyroid Carcinoma: A Review with Three Illustrative Cases. *J Cancer.* 2011; 2(1): 532. PMID: 22043238.
20. Takumi K, Fukukura Y, Hakamada H, et al. CT features of parathyroid carcinomas: comparison with benign parathyroid lesions. *Jpn J Radiol.* 2019; 37(5): 380-389. PMID: 30863971.
21. Yildiz S, Aralasmak A, Yetis H, et al. MRI findings and utility of DWI in the evaluation of solid parathyroid lesions. *Radiol Med.* 2019; 124(5): 360–367. PMID: 30607865.
22. Zafereo M, Yu J, Angelos P, et al. American Head and Neck Society Endocrine Surgery Section update on parathyroid imaging for surgical candidates with primary hyperparathyroidism. *Head Neck.* 2019; 41(7): 2398–2409. PMID: 31002214.
23. Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. *Curr Treat Options Oncol.* 2012; 13(1): 11–23. PMID: 22327883.
24. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg.* 2016; 151(10): 959–968. PMID: 27532368.
25. Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. *Ann Surg Oncol.* 2010; 17(8):2156–2174. PMID: 20221704.
26. Munson ND, Foote RL, Northcutt RC, et al. Parathyroid carcinoma: is there a role for adjuvant radiation therapy? *Cancer.* 2003; 98(11): 2378–2384. PMID: 14635072.
27. Busaidy NL, Jimenez C, Habra MA, et al. Parathyroid carcinoma: a 22-year experience. *Head Neck.* 2004; 26(8): 716–726. PMID: 15287039.
28. Rozhinskaya L, Pigarova E, Sabanova E, et al. Diagnosis and treatment challenges of parathyroid carcinoma in a 27-year-old woman with multiple lung metastases. *Endocrinol Diabetes Metab Case Rep.* 2017; 2017: 16-0113. PMID: 28458892.
29. Kutahyalioglu M, Nguyen HT, Kwatampora L, et al. Genetic profiling as a clinical tool in advanced parathyroid carcinoma. *J Cancer Res Clin Oncol.* 2019; 145(8): 1977–1986. PMID: 31309300.
30. Bauer JL, Toluie S, Thompson LDR. Metastases to the Parathyroid Glands: A Comprehensive Literature Review of 127 Reported Cases. *Head Neck Pathol.* 2018; 12(4): 534–541. PMID: 28875280.

## FIGURES

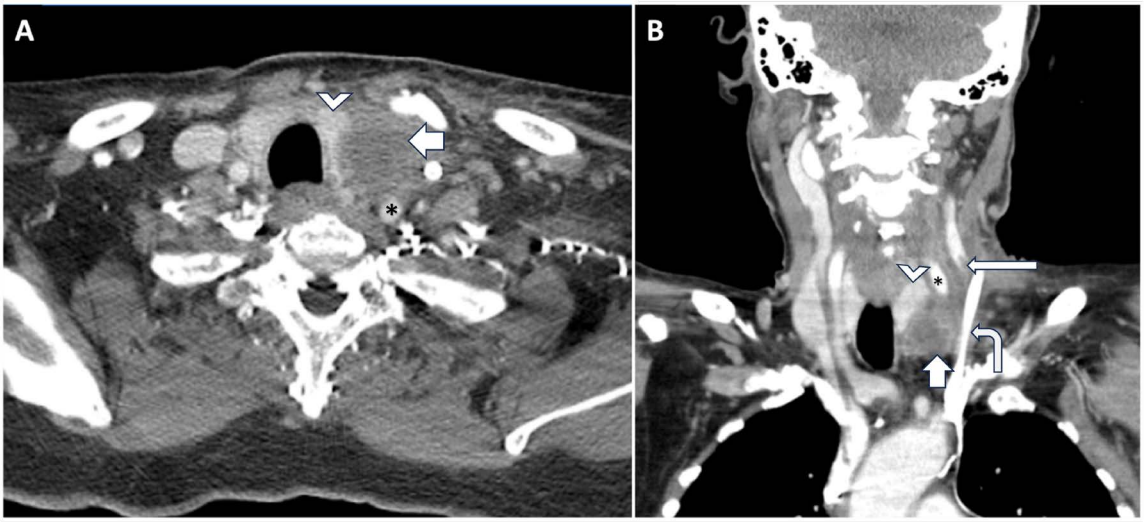


**Figure 1:** Axial (A) and coronal (B) contrast-enhanced computed tomography (CT) demonstrate a 3 x 3.1 x 3.2 cm irregular, necrotic mass (short arrow) abutting the inferior pole of the left thyroid lobe (arrowhead) and ipsilateral carotid sheath structures causing posterior displacement of the left common carotid artery (asterisk). Note the central venous catheter within the left internal jugular vein (bent arrow). A filling defect is seen consistent with a jugular vein thrombus (thin arrow).

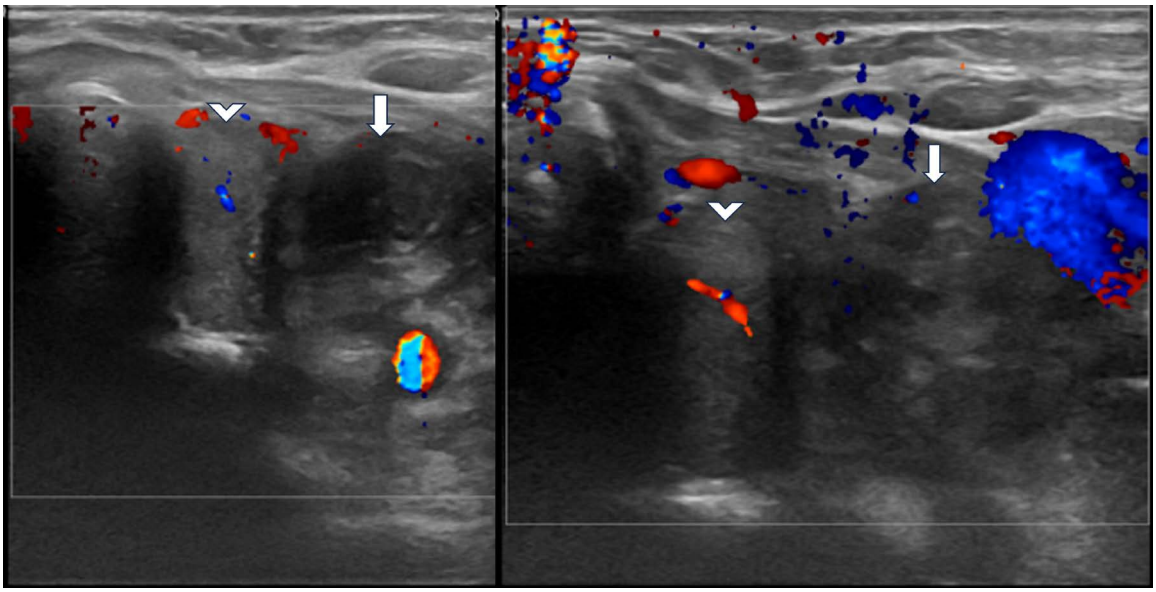

**Figure 2:** Transverse Color Doppler images at the level of the thyroid gland demonstrate a heterogenous, relatively avascular/necrotic mass (arrow) adjacent to the inferior pole of the left lobe of the thyroid gland (arrowhead).

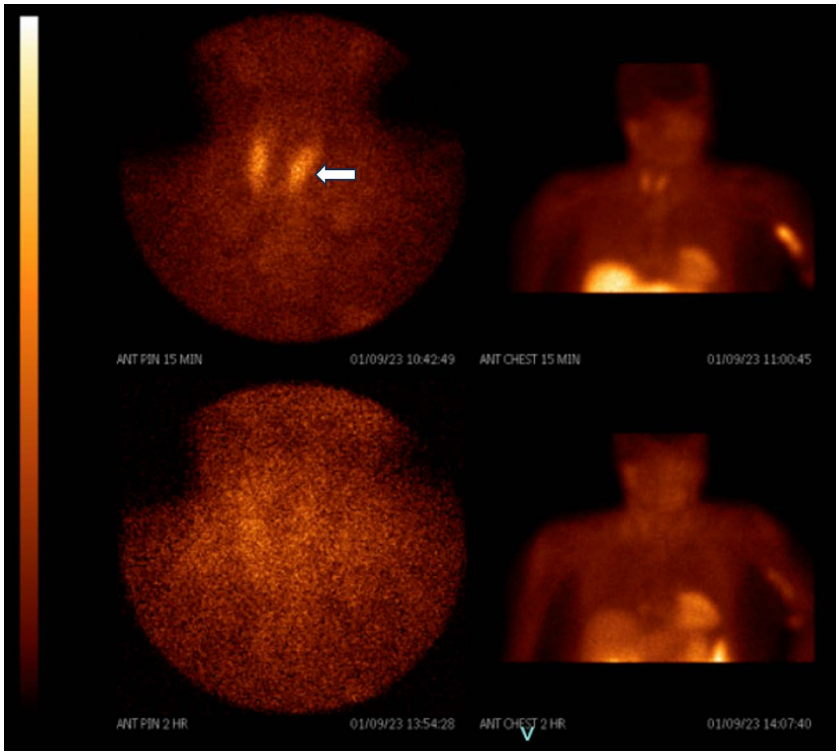


**Figure 3:** Coronal Planar SPECT, images of a 99mTc-sestamibi (MIBI) scan, demonstrate physiologic symmetric thyroid glandular radiopharmaceutical uptake and wash-out without abnormal parathyroid activity. This a false-negative MIBI study in a pathologically confirmed case of parathyroid carcinoma. Note the medial displacement of the left thyroid lobe (arrow).

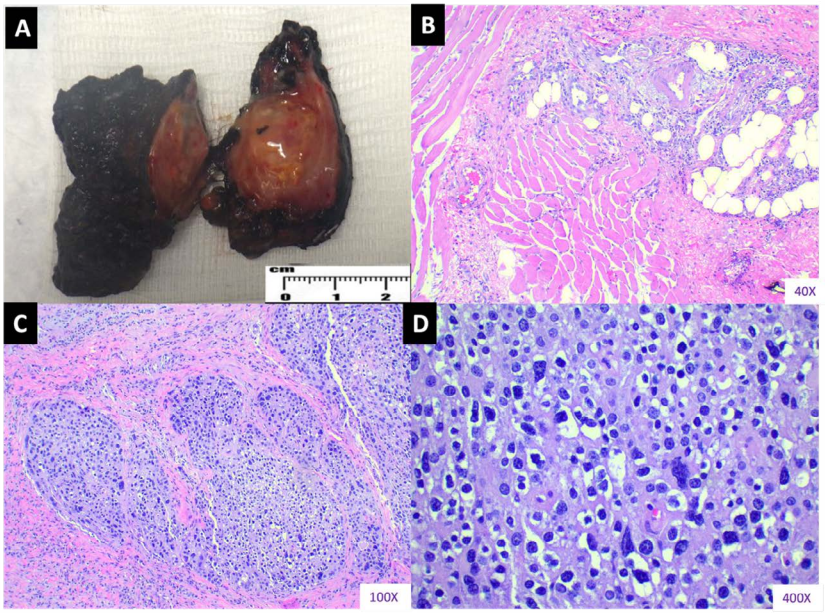


**Figure 4**: Parathyroid Carcinoma. (A) (Gross Picture) The cut surface reveals a yellow-tan tumor adherent to the thyroid gland and adjacent structures. (B) (H&E, 40x) Shows tumor infiltrating the skeletal muscle and adjacent fat tissue. (C) (H&E, 100x) Neck mass excision showing sheets of tumor cells in an infiltrative pattern. (D) (H&E, 400x) Demonstrates carcinoma cells, predominantly oncocytic with marked pleomorphism, perinuclear clearing, coarse chromatin, and prominent macronucleoli.

KEYWORDS

Parathyroid carcinoma; Head and Neck; Neuroradiology; Nuclear medicine; Hyperparathyroidism; Sestamibi