Case Report ISSN 2833-0307

Endocrinology, Metabolism and Nutrition

# Parathyroid Carcinoma Revealed by Normocalcemic Primary Hyperparathyroidism: An Unusual Presentation

**Malak Riznat*, Mohamed Malad, Hajar Srifi, Jade Issouani and Ahmed Anas guerboub**

*Department of Endocrinology of Mohamed V Military Hospital of Rabat, Morocco.*

***Correspondence:**
Malak riznat, Department of Endocrinology of Mohamed V Military Hospital of Rabat, Morocco, Phone number : +212 0676119039.

**Received:** 01 Apr 2025; **Accepted:** 30 Apr 2026; **Published:** 10 May 2026

**Citation:** Malak Riznat, Mohamed Malad, Hajar Srifi, et al. Parathyroid Carcinoma Revealed by Normocalcemic Primary Hyperparathyroidism: An Unusual Presentation. Endocrinol Metab Nutr. 2026; 5(1): 1-5.

## ABSTRACT

***Introduction:*** *Parathyroid carcinoma is a rare malignant tumor, accounting for less than 1% of primary hyperparathyroidism cases. It typically presents with severe hypercalcemia, very high PTH levels, and a large cervical mass. However, some atypical forms can complicate preoperative diagnosis.*

***Clinical Case:*** *We report the case of a 44-year-old woman with no significant medical history, in whom a parathyroid incidentaloma was discovered during the investigation of neck pain. Phosphocalcic testing revealed a persistent elevation of PTH with normal serum calcium, confirming normocalcemic primary hyperparathyroidism after correction of a vitamin D deficiency. Localization imaging demonstrated a left parathyroid lesion. A parathyroidectomy was performed. Histopathological examination confirmed parathyroid carcinoma by immunohistochemistry. Due to persistent postoperative abnormalities, further surgery and staging were performed.*

***Conclusion:*** *This case highlights that parathyroid carcinoma can present with subtle biological features without overt hypercalcemia. It underscores the importance of rigorous evaluation of normocalcemic hyperparathyroidism and the difficulty of preoperative diagnosis.*

## Keywords

Parathyroid carcinoma, Normocalcemic hyperparathyroidism, Incidentaloma, PTH, Difficult diagnosis.

## Introduction

Parathyroid carcinoma is a rare endocrine tumor, accounting for less than 1% of cases of primary hyperparathyroidism [1].

It is characterized by a potentially aggressive course with a risk of local recurrence and metastasis. Preoperative diagnosis remains difficult, as specific clinical criteria are lacking in some cases [2].

Classically, parathyroid carcinoma presents with severe hypercalcemia associated with very high parathyroid hormone levels, as well as a palpable cervical mass. Renal and bone complications are frequently observed. However, these features are not always present, sometimes making it difficult to distinguish from parathyroid adenoma [3].

The definitive diagnosis relies primarily on the anatomopathological analysis of the surgical specimen, performed by an experienced pathologist [2].

The identification of criteria for capsular, vascular, or perineural invasion is a major element in confirming the diagnosis.

Primary normocalcemic hyperparathyroidism is a recently better-defined entity characterized by a persistent elevation of PTH in the presence of normal serum calcium, after exclusion of secondary causes. This form is most often associated with parathyroid

adenomas and rarely with malignant lesions.

We report an unusual case of parathyroid carcinoma discovered in the context of normocalcemic primary hyperparathyroidism, highlighting the diagnostic difficulties and the importance of appropriate management.

## Case Reported

This is a 44-year-old female patient with no significant past medical history. Specifically, she reported no history of renal colic, kidney stones, spontaneous fractures, or chronic bone pain. There was also no family history of hyperparathyroidism or endocrine disorders. Her general condition was good, with no evidence of asthenia, weight loss, or digestive problems suggestive of hypercalcemia.

The patient initially consulted for chronic mechanical neck pain, which prompted a cervical MRI. This examination incidentally revealed a thyroid nodule, leading to a cervical ultrasound for further characterization.

Cervical ultrasound confirmed the presence of the thyroid nodule and revealed, in the left retrothyroidal region, a well-defined, heterogeneous, hypoechoic formation with cystic changes and internal vascularization on color Doppler. This lesion measured 21 × 14 × 13 mm and was suggestive of a parathyroid adenoma. Furthermore, the examination revealed bilateral, subcentimeter, benign-appearing jugulocarotid lymphadenopathy.

Following the discovery of this parathyroid incidentaloma, a complete calcium and phosphate assessment was performed. This revealed an elevated parathyroid hormone (PTH) level of 399 pg/ml, a normal total serum calcium level but at the upper limit of normal at 101 mg/l, and hypophosphatemia at 21 mg/l. Vitamin D levels were also measured, revealing a deficiency of 14 µg/l.

A 24-hour urinary calcium excretion was performed, revealing a calcium excretion of 283 mg/24 h. The quality of the urine collection was deemed satisfactory given a creatinine excretion of 1314 mg/24 h. The urinary calcium/creatinine ratio (UCCR) was inconclusive at 0.015.

Vitamin D supplementation was initiated. After correcting the vitamin status for approximately six months, laboratory tests were performed. These showed a persistent elevation of PTH at 330 pg/ml, with a stable serum calcium level of 101 mg/l. The serum albumin level was 43 g/l. The 24-hour urinary calcium excretion was 313 mg/24 h. The vitamin D level was corrected to 36 µg/l.

After excluding various causes of secondary hyperparathyroidism, including vitamin deficiency, renal failure and drug-induced causes, the diagnosis of primary normocalcemic hyperparathyroidism was made.

The assessment of the patient's condition, including renal and bone evaluations, was normal. Imaging showed no renal stones, and bone density scans revealed no abnormalities. Surgery was indicated due to the patient's age being under 50, in accordance with current guidelines.

The localization workup included a cervical ultrasound confirming the left retrothyroid lesion. A cervicothoracic CT scan was also performed and revealed a formation consistent with a left inferior parathyroid adenoma without obvious signs of locoregional invasion.

The patient underwent a targeted parathyroidectomy. Surgical exploration allowed for the excision of the left parathyroid lesion. Histopathological examination of the surgical specimen confirmed a parathyroid carcinoma. Immunohistochemical analysis showed p53 expression associated with an elevated Ki-67 proliferation index, supporting the malignant nature of the lesion.

In the postoperative period, PTH levels remained elevated, suggesting the persistence of pathological tissue. Given these results, further surgical intervention was decided upon, including a jugulocarotid lymph node dissection combined with a left thyroid lobectomy.

A postoperative staging assessment was undertaken, including a bone scan and a PET scan to look for any secondary lesions or tumor persistence.

## Discussion

Parathyroid carcinoma is one of the rarest malignant tumors, with a prevalence of less than 0.005 of all cancers and less than 1% of subjects with primary hyperparathyroidism [1].

Its incidence is extremely low. Its annual incidence is approximately 3.5 to 5.7 cases per 10 million inhabitants.
With a peak incidence around age 50 and no sex predominance [4].

Parathyroid carcinoma was first described in 1904 by Fritz de Quervain, a Swiss surgeon [5].

From an etiopathogenetic point of view,The majority of parathyroid carcinomas (PC) are sporadic, and more rarely, they can occur in a hereditary or syndromic context [6,7].

The etiology of these tumors remains largely obscure, even a century after their first description. The literature reports cases of coexistence of adenoma and carcinoma, of CP occurring in the context of primary hyperparathyroidism, and more rarely of long-term secondary or tertiary hyperparathyroidism, but evidence of a causal association is lacking [8].

The risk of CP is increased in the case of a personal or family history of HPT-JT syndrome (Hyperparathyroidism –Jaw Tumor or HPT 1-jaw tumor).

This syndrome, with autosomal dominant transmission, linked to a mutation in the CDC73/HRPT2 gene, is associated with a prevalence of CP of approximately 15%. Conversely, 20 to 40%

of patients with apparently sporadic CP may carry a germline mutation in the CDC73 gene [9,10].

And, more rarely, this carcinoma may be part of the spectrum of multiple endocrine neoplasia type 1 or type 2 [11]. The largest reported cohort comes from the SEER database in the United States, including 609 cases of parathyroid carcinoma recorded between 1975 and 2016 [12].

Multivariate analysis of this series identified tumor size greater than 4 cm, age over 40 years, male sex, Caucasian origin, the presence of distant metastases, and poor histological differentiation as independent predictors of mortality ($p < 0.001$). Parathyroid carcinoma primarily affects individuals around the age of 50. Advanced age, poor histological differentiation, and the presence of distant metastases are associated with a poorer prognosis. Initial complete surgical resection remains the main factor improving survival [12].

The preoperative diagnosis of parathyroid carcinoma remains complex and is based primarily on the combination of clinical, biological and radiological findings [13].

It should be suspected in the presence of particularly severe or unusual primary hyperparathyroidism, especially when occurring in a young or male patient, as well as in the presence of a large parathyroid mass, generally greater than or equal to 3 cm, although smaller malignant lesions may be observed [13].

Clinically, the manifestations are primarily related to the consequences of marked hyperparathyroidism. Bone involvement, including diffuse pain, pathological fractures, and bone demineralization, as well as renal complications such as urolithiasis or renal failure, are the most frequently described. These signs may be accompanied by a deterioration in general condition, cervical compression secondary to a local mass, including dysphonia, dysphagia, or dyspnea, as well as complications of severe hypercalcemia, including polyuria, polydipsia, gastrointestinal disturbances, neuropsychiatric manifestations, gastroduodenal ulcer, or pancreatitis. Biologically, parathyroid carcinoma is most often accompanied by significant hypercalcemia, generally greater than 140 mg/L (3.5 mmol/L), associated with an elevation of alkaline phosphatases and a marked increase in parathyroid hormone, which can reach several times the upper limit of normal [14,15].

However, these features are not always present, and some paucisymptomatic or normocalcemic forms can delay diagnostic suspicion. Our observation illustrates this unusual presentation.

From a biological standpoint, certain hormonal peculiarities can be observed in parathyroid carcinoma. Indeed, some malignant tumors are capable of preferentially secreting abnormal forms of parathyroid hormone, particularly the N-terminal fragment of PTH [16].

This atypical secretion can lead to discrepancies between different PTH assays depending on the generation of immunoassay used. Furthermore, ectopic production of other hormonal peptides, such as human chorionic gonadotropin (hCG), has also been described in some cases of parathyroid carcinoma [17].

Rubin et al. reported that, among eight cases of parathyroid carcinoma studied, four presented with abnormally high N-PTH production. This biological abnormality was demonstrated by a ratio greater than 1 between the third-generation PTH assay, which is capable of specifically detecting the N-terminal fragment, and the second-generation assay, which does not detect it [16].

The elevation of the N-terminal fragment of PTH in some parathyroid carcinomas is explained by abnormal hormonal secretion linked to incomplete differentiation of tumor cells, leading to increased production of biologically active N-terminal forms.

These results suggest that the combined use of these assays could help to strengthen the diagnostic suspicion of malignancy in certain atypical situations.

Parathyroid carcinoma can, in rare cases estimated at less than 5%, be non-functional, without any biological abnormalities suggestive of the diagnosis. In these situations, the absence of hypercalcemia and a significant elevation of PTH makes preoperative suspicion particularly difficult. The diagnosis then relies essentially on the histopathological examination of the surgical specimen. This situation has been reported in several cases in the literature and appears comparable to that observed in our patient, in whom the diagnosis of malignancy was only established after postoperative histological analysis [18].

As for the morphological aspect, it is a generally large mass exceeding 3 cm and easily detectable by ultrasound.
The "3+3" rule, meaning that the combination of serum calcium > 3 mmol/L and height > 3 cm should raise suspicion of CP, has been proposed by some authors [19].

However, all the elements described above do not allow for a definitive diagnosis of parathyroid carcinoma; the final, definitive diagnosis is histological and unfortunately remains difficult to recognize given the rarity of this pathology.

Histologically, it is necessary to look for signs of microscopic invasion (vascular invasion and/or perineural invasion and/or complete capsular invasion) or unequivocal signs of invasion of tissues or organs surrounding the tumor or documented metastases [20].

Each report must include the tumor weight and size, histological grade, number of mitoses, mention of the presence or absence of necrosis, perineural invasion, lymphovascular invasion, and local extension into adjacent organs [20]. The presence of these histological characteristics such as nuclear pleomorphism,

trabecular architecture, necrosis, high proliferation index, loss of tissue expression of parafibromin does not, on its own, allow for a diagnosis, as they can also be present in cases of simple parathyroid tumors and are therefore not specific to parathyroid carcinomas.

Based on these histological criteria, a TNM classification should be initiated to better characterize the tumor. Regarding the tumor genetics of CP, the most frequent somatic molecular alterations affect the CDC73 gene (40 to 50% of cases) and the regulation of the PI3K/AKT/mTOR pathway (40-80% of cases) [21].

After a diagnosis of carcinoma has been made, usually post-operatively, an assessment of the extent of the disease must be carried out, including both a conventional morphological component and a functional component.

On cervical ultrasound, the carcinomatous lesion typically presents with signs of suspicion of malignancy: irregular borders, invasion of peritumoral tissues, hypoechogenicity or heterogeneous echostructure, as well as a shape that is thicker than it is wide [22].

Cervicothoracic CT, ideally in dynamic acquisition (4D) with contrast injection, as well as cervical MRI, are recommended to assess the local extent of the disease, look for locoregional invasion and detect possible distant locations [23].

Functionally, tumor cells exhibit avidity for 18F-FDG, allowing the use of FDG PET-CT after diagnostic confirmation to assess tumor extent. However, caution is advised in interpreting the images, as some benign lesions, particularly osteolytic brown tumors associated with hyperparathyroidism, can also show increased FDG uptake and mimic metastatic lesions [24].

The PET scanner with choline can also be used as a staging assessment [25].

Fine needle cytology is formally contraindicated [26].

The recommended surgery consists of en bloc removal of the parathyroid tumor, avoiding rupture of the capsule and local seeding, combined with ipsilateral thyroid lobo-isthmectomy in case of adhesions and central lymph node dissection according to intraoperative findings [27].

In most cases, the recurrent laryngeal nerve can and should be preserved. However, if it is invaded, it must be resected along with the tumor, ensuring that the contralateral nerve remains functional.

There is no formally validated adjuvant treatment for parathyroid carcinoma, even in cases of incomplete resection. The role of adjuvant radiotherapy remains poorly defined. Indeed, a multivariate analysis showed that the use of radiotherapy was not associated with a significant improvement in survival [28]. However, it may be used to limit the risk of relapse [29].

Therefore, it is always necessary to assess the benefit-risk of this therapy and not to overlook the risk of post-radiation fibrosis which could compromise a possible surgical intervention.

Parathyroid carcinoma is characterized by a significant metastatic potential. Metastases can be synchronous, present at the time of diagnosis in 5–10% of cases, or metachronous, appearing during follow-up in nearly half of cases [30].

The preferred sites are lung (40–72%), bone (20–30%), liver (10–14%), and distant lymph nodes (10%). More unusual involvement, particularly in the brain (9%), pleura, or pericardial regions, remains possible [30].

In advanced or metastatic disease, systemic treatments are based primarily on chemotherapy, particularly with dacarbazine and anthracyclines, as well as on targeted anti-angiogenic therapies. Tyrosine kinase inhibitors such as sorafenib, cabozantinib, and lenvatinib have shown some efficacy, allowing for prolonged disease stabilization and, more rarely, objective tumor responses [30]. It should also be noted that CP is not sensitive to chemotherapy [31].

## Conclusion

Parathyroid carcinoma is a rare tumor, and its diagnosis remains challenging, particularly in atypical forms. This case demonstrates that it can present in the context of normocalcemic primary hyperparathyroidism, without the classic signs of severe hypercalcemia. This unusual presentation highlights the limitations of clinical and biological criteria in preoperative suspicion. A definitive diagnosis relies on histopathological examination, supported by immunohistochemistry. Management primarily involves initial complete surgical resection, an essential condition for improving the prognosis. Prolonged follow-up remains crucial due to the risk of recurrence or metastasis.

## References


1. Basceken SI, Genc V, Ersoz S, et al. Is local resection sufficient for parathyroid carcinoma?. Clinics. 2015; 70: 247-249.
2. Mucci-Hennekinne S, Desolneux G, Luyckx F, et al. Carcinome parathyroïdien: Étude multicentrique de 17 patients. J Chir. 2008; 145: 133-137.
3. Jakoubkova S, Vokurka J, Cap J, et al. Parathyroid carcinoma: clinical presentation and treatment. International Congress Series. 2003; 1240: 991-995.
4. Fernandes JMP, Paiva C, Correia R, et al. Moreira da Costa A. Carcinome parathyroïdien:d'un rapport de cas à une revue de la littérature. Int J Surg Rapport de cas. 2018; 42: 214-217.
5. Fritz de Quervain. Parastruma maligna aberrata. Deutsche Zeitschrift für Chirurgie. 1904; 100: 334-352.
6. Kebebew E. Carcinome parathyroïdien. Curr Treat Options in Oncol. 2001; 2: 347-354.
7. Sharretts JM, Simonds WF. Génétique clinique et moléculaire des néoplasmes parathyroïdiens. Best Pract Res Clin Endocrinol Metab. 2010; 24: 491-502.

8. Shane E. Revue clinique 122: carcinome parathyroïdien. J Clin Endocrinol Metab. 2001; 86: 485-493.
9. Cardoso L, Stevenson M, Thakker RV. Molecular genetics of syndromic and non-syndromic forms of parathyroid carcinoma. Hum Mutat. 2017; 38: 1621-1648.
10. Shattuck TM, Välimäki S, Obara T, et al. Somatic and germline mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N Engl J Med. 2003; 349: 1722-1729.
11. Song A, Yang Y, Liu S, et al. Prevalence of Parathyroid Carcinoma and Atypical Parathyroid Neoplasms in 153 Patients with Multiple Endocrine Neoplasia Type 1: Case Series and Literature Review. Front Endocrinol. 2020; 11: 557050.
12. Ullah A, Khan J, Waheed A, et al. Parathyroid Carcinoma: Incidence, Survival Analysis, and Management: A Study from the SEER Database and Insights into Future Therapeutic Perspectives. Cancers (Basel). 2022; 14: 1426.
13. Roser P, Leca BM, Coelho C, et al. Diagnosis and management of parathyroid carcinoma: a state-of-the-art review. Endocr Relat Cancer. 2023; 30: 220287.
14. Bae JH, Choi H J, Lee Y, et al. Preoperative predictive factors for parathyroid carcinoma in patients with primary hyperparathyroidism. J Korean Med Sci. 2012; 27: 890-895.
15. Schaapveld M, Jorna FH, Aben KKH, et al. Incidence and prognosis of parathyroid gland carcinoma: a population-based study in The Netherlands estimating the preoperative diagnosis. Am J Surg. 2011; 202: 590-597.
16. Rubin MR, Silverberg SJ, D'Amour P, et al. An N-terminal molecular form of parathyroid hormone (PTH) distinct from hPTH(1 84) is overproduced in parathyroid carcinoma. Clin Chem. 2007; 53: 1470-1476.
17. Rubin MR, Bilezikian JP, Birken S, et al. Human chorionic gonadotropin measurements in parathyroid carcinoma. Eur J Endocrinol. 2008; 159: 469-474.
18. Giessler GA, Beech DJ. Nonfunctional parathyroid carcinoma. J Natl Med Assoc. 2001 ;93: 251-255.
19. Cetani F, Pardi E, Marcocci C. Update on parathyroid carcinoma. J Endocrinol Invest. 2016; 39: 595-606.
20. Williams MD, DeLellis RA, Erickson LA, et al. Pathology data set for reporting parathyroid carcinoma and atypical parathyroid neoplasm: recommendations from the International Collaboration on Cancer Reporting. Hum Pathol. 2021; 110: 73-82.
21. Pandya C, Uzilov AV, Bellizzi J, et al. Genomic profiling reveals mutational landscape in parathyroid carcinomas. JCI Insight. 2017; 2: 92061.
22. Machado NN, Wilhelm SM. Parathyroid Cancer: A Review. Cancers. 2019; 11: 1676.
23. Christakis I, Vu T, Chuang HH, et al. The diagnostic accuracy of neck ultrasound, 4D-Computed tomographyand sestamibi imaging in parathyroid carcinoma. Eur J Radiol. 2017; 95: 82-88.
24. Hatzl M, Röper-Kelmayr JC, Fellner FA, et al. 18F-Fluorocholine, 18F-FDG, and 18F-Fluoroethyl Tyrosine PET/CT in Parathyroid Cancer. Clin Nucl Med. 2017; 42: 448-450.
25. Morand GB, Rupp NJ, Huellner MW, et al. Transnasal-Transpterygoid Endoscopic Removal of an 18F-Choline-Avid Parathyroid Carcinoma Metastasis in the Skull Base. JAMA Otolaryngol Head Neck Surg. 2019; 145: 978-980.
26. Rodrigo JP, Hernandez-Prera JC, Randolph GW, et al. Parathyroid cancer: An update. Cancer Treat Rev. 2020; 86: 102012.
27. Schulte KM, Talat N, Miell J, et al. Lymph node involvement and surgical approach in parathyroid cancer. World J Surg. 2010; 34 :2611-2620.
28. Limberg J, Stefanova D, Ullmann TM, et al. The Use and Benefit of Adjuvant Radiotherapy in Parathyroid Carcinoma: A National Cancer Database Analysis. Ann Surg Oncol. 2021; 28: 502-511.
29. Munson ND, Foote RL, Northcutt RC, et al. Parathyroid carcinoma: is there a role for adjuvant radiation therapy?. Cancer. 2003; 98 :23782384.
30. Alberti A, Smussi D, Zamparini M, et al. Treatment and outcome of metastatic parathyroid carcinoma: A systematic review and pooled analysis of published cases. Front Oncol. 2022; 12: 997009.
31. Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. Curr Treat Options Oncol. 2012; 13: 11-23.