

Recurrent Sporadic Parathyroid Carcinoma in a 29-Year-Old Filipino Female Presenting with Primary Hyperparathyroidism: A Case Report and Literature Review

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ABSTRACT

Parathyroid carcinoma is a rare endocrine malignancy with an indolent course but a high risk of recurrence. Diagnosis remains challenging, requiring integration of clinical, biochemical, radiologic, and histopathologic findings. We report a young patient presenting with primary hyperparathyroidism complicated by multiple pathologic fractures and chronic renal failure. Despite initial surgical and medical management, late aggressive recurrence occurred, resulting in significant systemic complications. This case highlights the need for vigilant long-term surveillance and improved diagnostic and therapeutic strategies.

Key words: parathyroid carcinoma, tumor recurrence, hyperparathyroidism, bone pains, pathologic fractures, case report, Philippines

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INTRODUCTION

Parathyroid carcinoma is an exceptionally rare endocrine malignancy, typically characterized by indolent growth and a slow, progressive clinical course. The mean age at diagnosis reported in published studies is approximately 56 years, making occurrence in young adults distinctly uncommon. In this report, we present a recurrent sporadic parathyroid carcinoma in a 29-year-old Filipino female, who represents the second youngest patient documented in the literature to date.

While many published cases describe relatively favorable outcomes and prolonged survival following surgical management, parathyroid carcinoma is also recognized for its high propensity for recurrence, posing significant challenges in long-term treatment. Unlike typical cases, the index patient demonstrated an unusually long eight-year symptom-free interval prior to recurrence, followed by a more aggressive clinical course complicated by severe skeletal manifestations, multiple electrolyte imbalances and chronic renal failure. This case underscores the critical importance of early recognition, vigilant surveillance, and multidisciplinary management in patients with parathyroid carcinoma, even after apparent remission.

Due to the rarity of this malignancy, this case warrants thorough documentation, as it provides valuable insights into **diagnostic techniques**, treatment approaches, and the complexities associated with managing recurrent disease. Moreover, it underscores the necessity for further research to **standardize staging** systems and refine clinical protocols, ultimately aiming to improve diagnostic accuracy and long-term survival for similar future cases.

CASE

This is the case of a 29-year-old female who initially presented in 2014 with recurrent bone pain and multiple fractures and was diagnosed with primary hyperparathyroidism secondary to parathyroid carcinoma. She



underwent a 3 ½ parathyroidectomy with en bloc left thyroid lobectomy and isthmusectomy, with histopathology confirming the diagnosis. Postoperatively, the patient reported significant relief of symptoms following surgical and medical treatment. However, due to poor archiving in previous years, the original histopathology slides and previous biopsy reports were unavailable for retrospective review.

The patient experienced an eight-year period of symptomatic relief before bone pain recurred, accompanied by onset of chronic renal failure, prompting hospitalization. Physical examination revealed a palpable, firm, movable

mass measuring 1.5 x 1.5 cm in the right paratracheal area. Neck ultrasonography revealed two well-defined hypoechoic solid lesions in the superior and inferior segments of the right thyroid lobe, measuring 2.1 x 1.7 cm and 3.4 x 1.7 cm, respectively (Figure 1). The left thyroid lobe was surgically absent.

The patient has no other significant comorbidities, and her family history is unremarkable. She presents with kyphoscoliotic chest deformity, exhibiting severe lower thoracolumbar dextroscoliosis (Figure 2A), along with multiple deformities in the right humerus and bilateral femurs. Radiologic examination of the humerus revealed

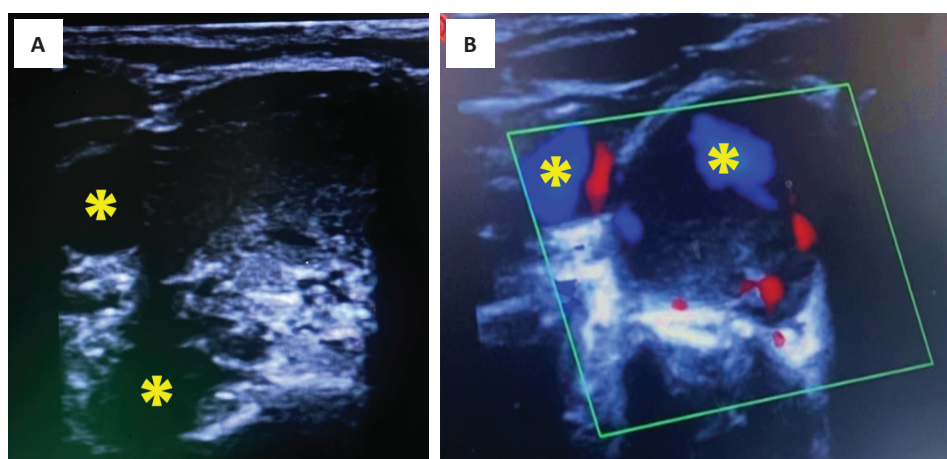


Figure 1. Ultrasound of the neck revealed hypoechoic solid lesions (*) in the superior and inferior segments of the right thyroid lobe with ill-defined margins (A & B), and minimal perivascularity noted (B).

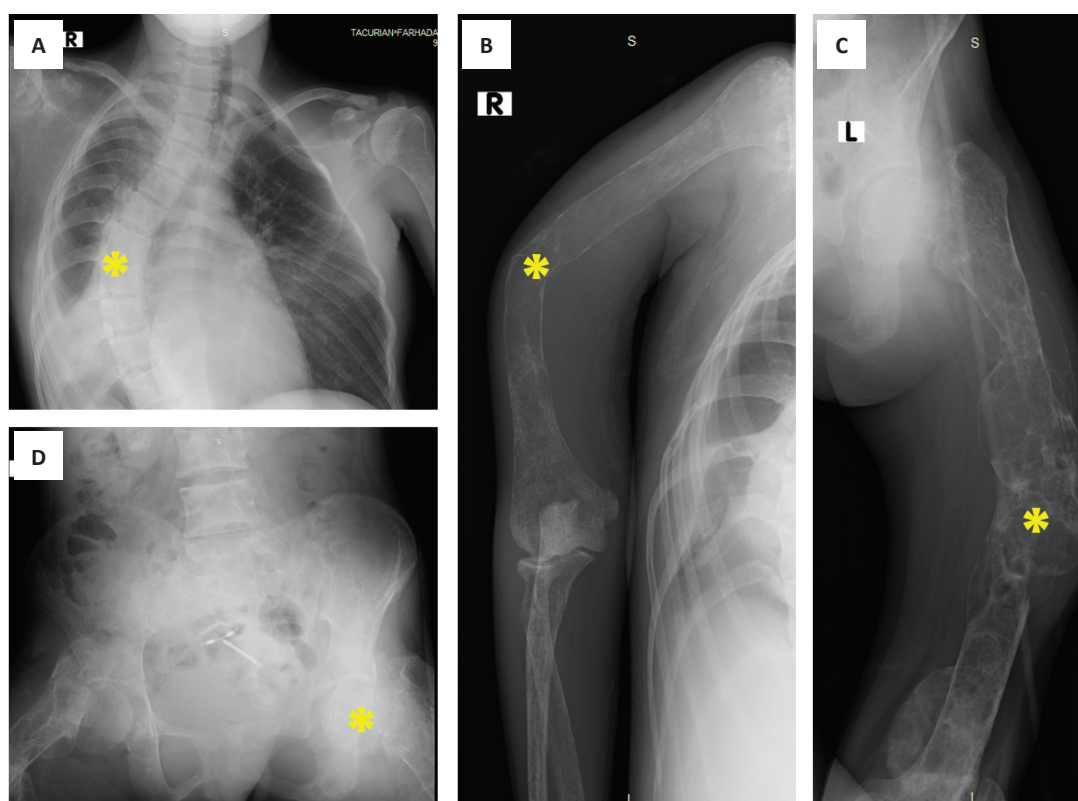


Figure 2. Multiple abnormal radiologic findings: (A) Chest radiography, postero-anterior view revealed severe lower thoraco-lumbar dextroscoliosis; (B) Humerus, antero-posterior view revealed pathologic fracture with angulation and impaction in the right humerus (*) with diffuse osteopenia; (C) Thigh, antero-posterior view showed pathologic fracture of the left femur with expansile osteolytic changes along the midshaft and distal posterior aspect; and (D) Pelvis radiography, anterior-posterior view revealed right femoral neck pathologic fracture (*) and mixed osteolytic-blastic changes.

a pathologic fracture with angulation and impaction in the right humerus, along with diffuse osteopenia and blastic changes in the proximal ulna. A pathologic fracture was also noted in the left femur, with expansile osteolytic changes along the midshaft and distal posterior aspect, accompanied by diffuse osteopenia. Additionally, mixed osteolytic-blastic changes were observed in the pelvis, which may suggest a metastatic process. A pathologic fracture was also noted in the right femoral neck. KUB ultrasound revealed bilateral nephrolithiasis. Additional diagnostic tests revealed multiple electrolyte imbalances (serum calcium: 14.03 mg/dL; serum potassium: 2.5 mmol/L; serum sodium: 135 mmol/L), anemia, elevated intact parathyroid hormone (546.96 pg/ml) level, hypothyroidism, and chronic renal failure (233 μ mol/L).

In the subsequent year, patient had undergone right inferior parathyroidectomy with en bloc total lobectomy, right frozen section biopsy and intraoperative iPTH for margin assessment and diagnosis. The specimen submitted for pathology consists of a single, intact, fresh, tan red to bright red, smooth and glistening parathyroid gland (3.1 x 2.3 x 1.6 cm) and left thyroid lobe (4.0 x 2.5 x 1.3 cm). Serial sections of the parathyroid gland show an encapsulated, tan gray to tan brown, slightly fleshy, homogenous, solid mass with lobulated appearance (Figure 3).

Histopathologic examination of the parathyroid gland revealed an encapsulated, well-delineated mass composed of tumor cells arranged in a solid growth pattern (Figures 4 and 6). The tumor cells exhibited distinct cytoplasmic membranes, moderately enlarged, irregularly round to ovoid vesicular nuclei, and inconspicuous to prominent nucleoli, with abundant eosinophilic cytoplasm. Broad fibrous bands were observed between tumor cells, and frequent mitotic figures were noted (Figures 5 and 9). Lymphovascular and capsular invasion were also present (Figures 7 and 8).

Along with the clinical and other diagnostic findings, the histomorphologic features are consistent with a diagnosis of parathyroid carcinoma. Immunohistochemical studies were performed to support the diagnosis, including GATA3, TTF-1, AE1/AE3, synaptophysin, chromogranin A, CEA, Ki-67, and PTH. The tumor cells showed strong nuclear reactivity with GATA3, a parathyroid-specific marker. Negative staining with TTF-1 further confirmed that the tumor is of parathyroid origin and excluded the differential diagnoses of well-differentiated or poorly differentiated thyroid carcinoma. Additionally, the negative staining with CEA ruled out medullary thyroid carcinoma.

Although strong cytoplasmic (granular) and nuclear expression of chromogranin A and GATA3, respectively, may suggest paraganglioma, the strong membranous expression of AE1/AE3 in this case ruled out this diagnosis. The immunoprofile, showing positive staining for GATA3, PTH, AE1/AE3, and chromogranin A, alongside negative staining for TTF-1, CEA, and synaptophysin, narrowed the differential diagnoses to parathyroid adenoma, atypical parathyroid adenoma, and parathyroid carcinoma.

However, the histomorphologic features, including moderate nuclear atypia, presence of macronucleoli,



Figure 3. Gross appearance of the parathyroid gland (*) and left thyroid lobe (▲).

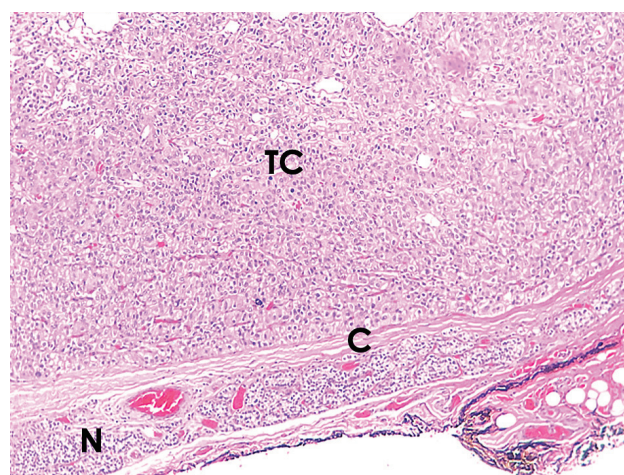


Figure 4. Encapsulated (C) mass showing uniform tumor cells (TC) in solid sheet growth pattern (H&E, 40x).

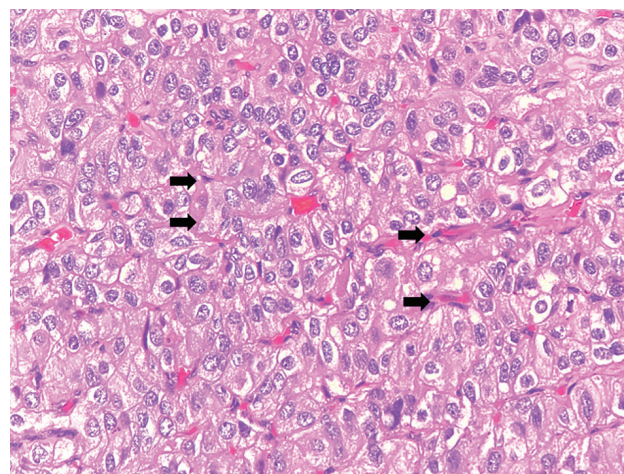


Figure 5. Uniform tumor cells with mild to moderate atypia. Seen also are dense fibrous bands (➡) between tumor cells (H&E, 100x).

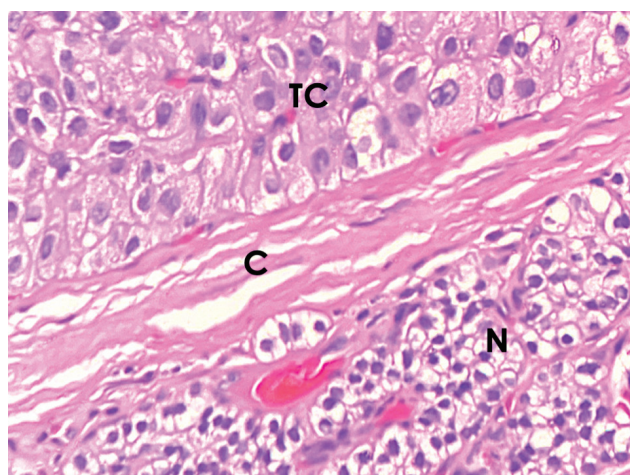


Figure 6. Transition between parathyroid tumor cells (TC) and remnant normal parathyroid tissue (N) (H&E, 40x).

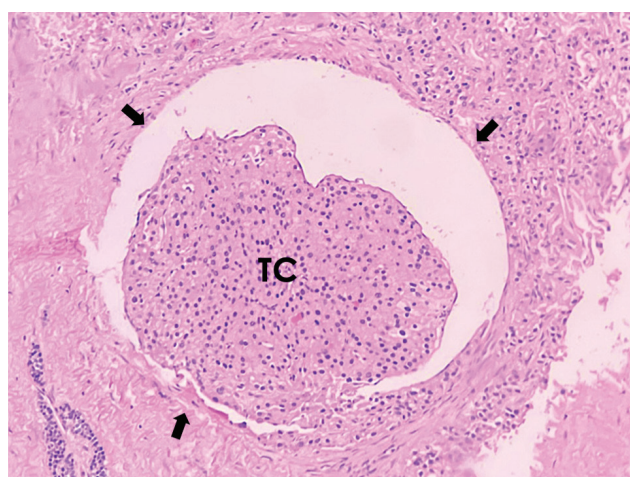


Figure 7. Lymphovascular invasion of tumor cells (H&E, 100x).

increased mitotic activity ($>9/10 \text{ mm}^2$), lymphovascular invasion (Figure 8F), and a high proliferative index (Ki-67: 10%), strongly support the diagnosis of parathyroid carcinoma.

Despite successful surgical intervention and multidisciplinary supportive management, the patient's clinical condition did not improve. Further treatment with radiation or systemic therapy was not pursued, as her condition became unstable several days after admission. She subsequently developed an acute myocardial infarction, which led to her demise.

DISCUSSION

Parathyroid carcinoma is an exceedingly rare endocrine malignancy, representing approximately 0.005% of all cancers and accounting for less than 1% of primary hyperparathyroidism cases.^{1,2} While it can occasionally occur as part of genetic syndromes, it is more commonly sporadic.³ Hereditary conditions linked to parathyroid carcinoma include hyperparathyroidism-jaw tumor (HPT-JT) syndrome, multiple endocrine neoplasia (MEN) syndromes, and non-syndromic familial isolated primary

hyperparathyroidism (FIHP).⁴ The mean age at diagnosis is 56 years (ranging from 15 to 89 years), with no significant sex predilection.^{5,6} The youngest reported patient with parathyroid carcinoma was 13 years old. In the presented case, the patient was initially diagnosed with parathyroid carcinoma at the age of 19. Cases of parathyroid carcinoma are rarely documented, both in the Philippines and globally. Due to its rarity, there is no universally accepted standardized approach for diagnosis, prognosis, or treatment, and the TNM staging system is not consistently applied.^{7,8}

Genomic alterations associated with parathyroid carcinoma (PC) are predominantly characterized by mutations in the **CDC73** germline gene, which encodes a loss-of-function protein known as parafibromin. Recent whole-exome sequencing studies of PC have revealed additional mutations in several other genes, including **mTOR**, **KMT2D**, **CDKN2C**, **THRAP3**, **PIK3CA**, and **EZH2**, as well as amplification of the **CCND1** gene. Notably, alterations in the **PI3K/AKT/mTOR** signaling pathway are frequently observed in the sporadic forms of parathyroid carcinoma.⁹ In this case, the patient had no family history of hyperparathyroidism or parathyroid tumors.

It typically presents with severe symptomatic hypercalcemia, which is often associated with significant skeletal and renal complications. These may include multiple pathologic fractures, nephrolithiasis, and various electrolyte imbalances.¹⁰ The extent of these complications can lead to substantial morbidity, highlighting the critical need for early recognition and intervention.

The diagnosis of parathyroid carcinoma remains challenging. Currently, histopathologic diagnosis is derived in parathyroid tumors that exhibit at least one of the following features: (1) angioinvasion (vascular invasion), (2) lymphatic invasion, (3) perineural invasion, (4) local malignant invasion into adjacent structures or organs, or (5) regional or distant metastasis.¹¹ In the present case, along with moderate nuclear atypia, the tumor exhibits macronucleoli, increased mitotic activity, a high Ki-67 index, and lymphovascular invasion. Clinical findings that may raise suspicion for malignancy include the presence of a palpable neck mass, a parathyroid gland larger than 3 cm, severe hypercalcemia ($>12 \text{ mg/dL}$), markedly elevated parathyroid hormone (PTH) levels (more than three times the upper limit), and intraoperative adhesions.¹² If only some of these criteria are met, the tumor may be classified as an atypical parathyroid tumor.

Immunohistochemistry studies have been employed in the literature with variable diagnostic results, adding complexity to the diagnosis. Parathyroid carcinoma is typically characterized by the immunohistochemical loss of expression of markers such as parafibromin, APC, E-cadherin, p27, BCL2, MDM2, and 5-hydroxymethylcytosine. In contrast, positive expression of PGP9.5, galectin-3, and TERT is often observed. Parafibromin, encoded by the **CDC73/HRPT2** gene, is implicated in both hereditary hyperparathyroidism-jaw tumor syndrome and sporadic parathyroid carcinomas. Loss of parafibromin expression, typically resulting from **CDC73** mutations, has been associated with dysregulated cell proliferation, transcriptional control, and histone

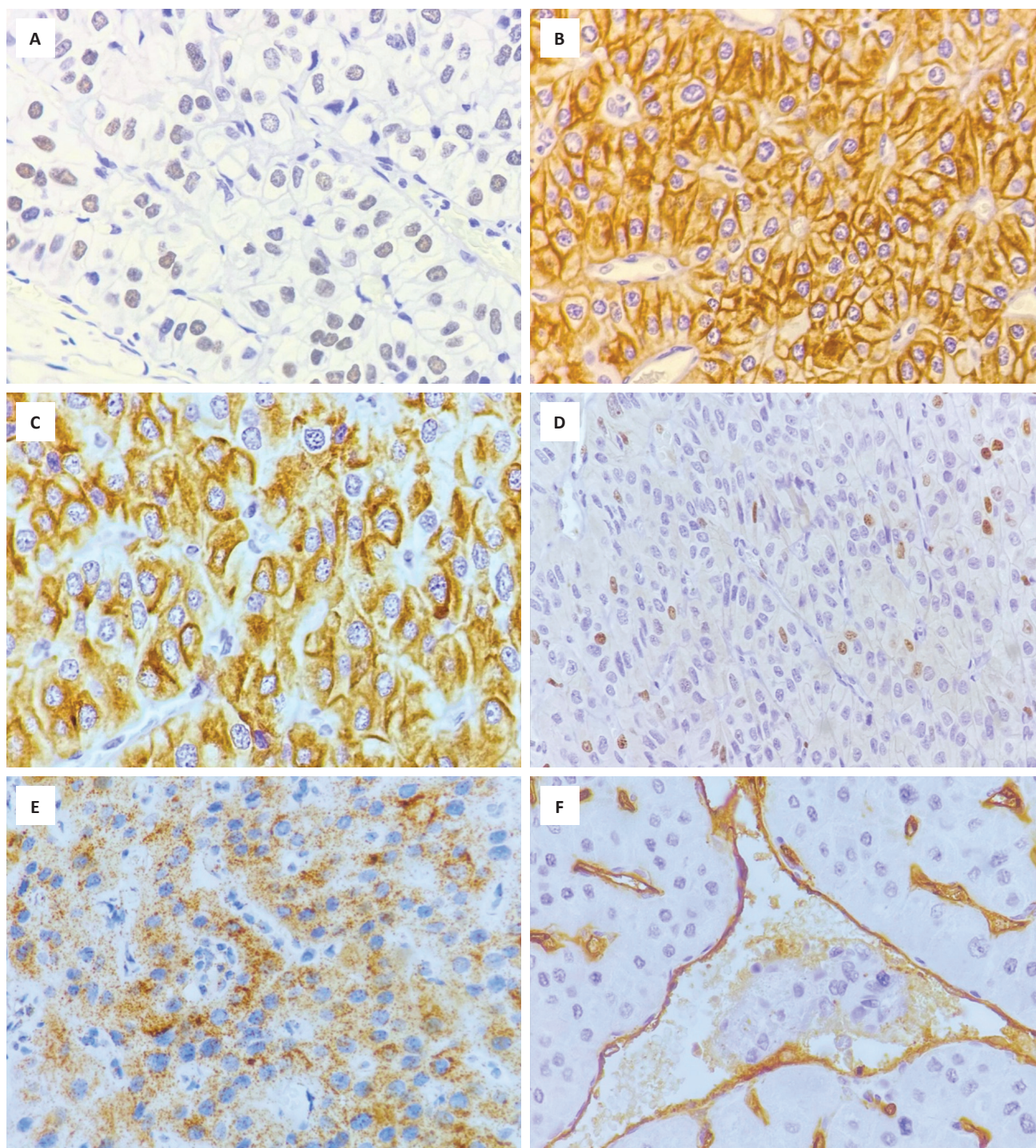


Figure 8. Immunohistochemical stains demonstrating weak and focal nuclear staining for GATA3 (**A**); strong, diffuse membranous staining for pancytokeratin (**B**); strong and diffuse cytoplasmic (granular) staining for chromogranin A (**C**); nuclear staining for Ki-67 (**D**); moderate, focal cytoplasmic granular staining for PTH (**E**); and strong membranous staining for CD34, highlighting lymphovascular invasion (**F**) (all images at 400x magnification).

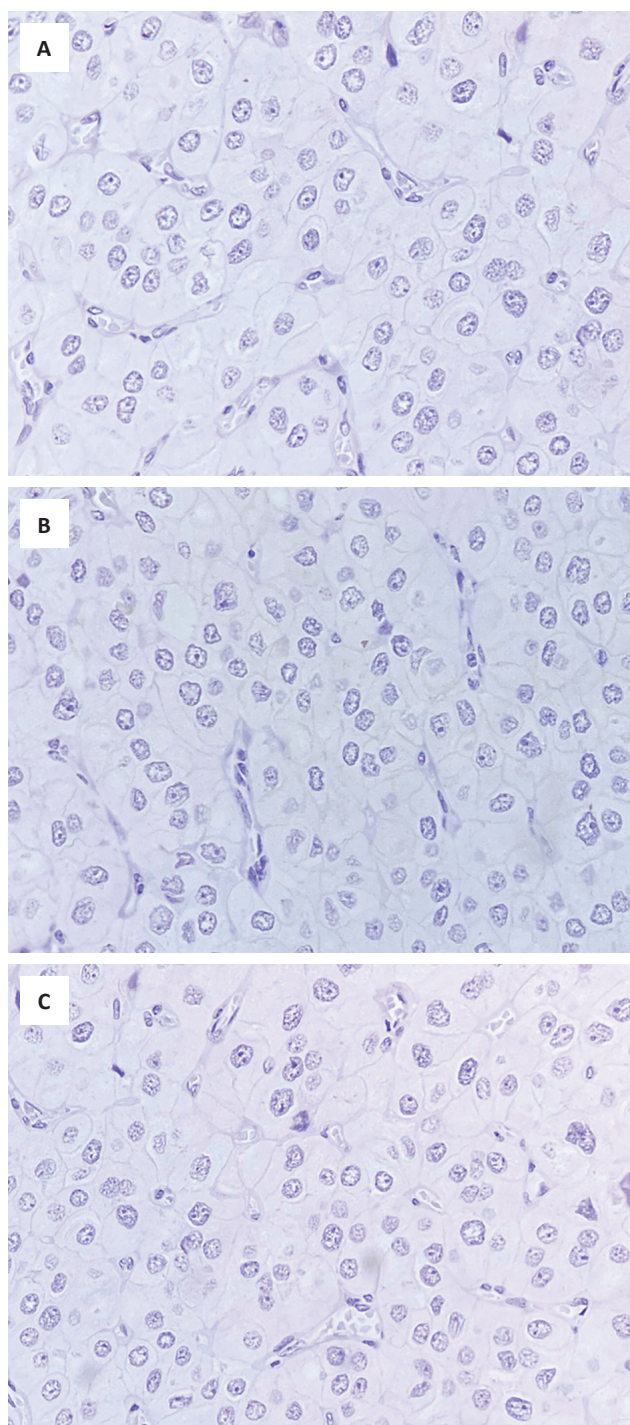


Figure 9. Immunohistochemical stains showing negative staining for TTF-1 (A), synaptophysin (B), and CEA (C) (all images at 400x magnification).

modification. However, the diagnostic utility of parafibromin immunohistochemistry (IHC) in parathyroid carcinoma remains variable.¹³ Some studies reported loss of parafibromin expression in 29.1% of atypical parathyroid adenomas, a frequency intermediate between parathyroid carcinoma and parathyroid adenoma.¹⁴ Thus, while parafibromin IHC is not definitive, it may serve as a supportive diagnostic adjunct in suspected parathyroid carcinoma. Additionally, there is frequently overexpression of p53 and an elevated Ki-67 labeling

index, often exceeding 5%. While parathyroid hormone (PTH) is typically expressed in parathyroid carcinoma, its presence alone is not specific, as other neuroendocrine neoplasms can also demonstrate aberrant PTH staining. The co-expression of PTH and GATA3, however, can help confirm the parathyroid origin of the tumor. Similar to other epithelial neuroendocrine tumors, parathyroid carcinoma usually shows positive staining for cytokeratins and chromogranins.¹¹

Parathyroid carcinoma typically exhibits an indolent and slowly progressive course, characterized by low rates of lymph node and systemic metastasis, but a higher incidence of local recurrence. Mortality is primarily attributed to complications arising from hypercalcemia, rather than the tumor burden itself.^{2,15} According to the literature, the reported 5-year survival rate ranges from 76% to 85%, while the 10-year survival rate ranges from 49% to 77%.⁶

The primary treatment for parathyroid carcinoma is surgical excision of the tumor.¹⁶ If there is a strong pre-operative suspicion of parathyroid carcinoma, it is essential for the surgeon to consider more aggressive approaches, such as en bloc resection, to improve disease outcomes, as the prognosis is heavily influenced by the extent of surgical resection.^{17,18} The surgical approach for parathyroid carcinoma consists of the en bloc resection of the primary tumor with negative margins, usually associated with the excision of ipsilateral thyroid lobes and adjacent involved structures.¹⁹ For tumors that are not amenable to surgical removal, adjuvant treatments, including radiotherapy, chemotherapy, immunotherapy, and ablation, may be considered. Management of hypercalcemia often involves a combination of bisphosphonates, calcimimetic agents, and the osteoclast inhibitor denosumab.¹⁵ Mortality from parathyroid carcinoma is typically linked to complications of hypercalcemia rather than the direct impact of tumor burden itself.

CONCLUSION

The diagnosis of parathyroid carcinoma continues to present significant challenges. Accurate diagnosis requires the integration of clinical, biochemical, radiologic, histomorphologic, and immunohistochemical findings. Parathyroid carcinoma is notably characterized by its tendency for recurrence and resistance to conventional treatment modalities. Despite its typically slow clinical progression, long-term surveillance and aggressive management strategies are often recommended to optimize patient outcomes. Given the rarity of parathyroid carcinoma, each case provides valuable insights that can help refine diagnostic approaches and treatment protocols. Documenting such cases is essential, as it contributes to the development of more effective strategies for managing future cases, ultimately improving patient care and survival outcomes.

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ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

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AUTHOR DISCLOSURE

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DATA AVAILABILITY STATEMENT

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