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Case Report

Exploring intrathyroid parathyroid carcinoma: A literature review on diagnostic approach and clinical correlation

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ABSTRACT

Intrathyroidal parathyroid carcinoma is an exceptionally rare and often underrecognized malignancy arising from the parathyroid glands located ectopically within the thyroid gland, usually posing a diagnostic and therapeutic challenge due to its overlapping clinical and pathological features with benign parathyroid adenomas, hyperplasia, and other thyroid neoplasms. Despite advancements in diagnostic imaging and histopathological techniques, the incidence of intrathyroidal parathyroid carcinoma remains low, and much of the current knowledge is based on case reports and small series, highlighting the need for a consolidated review of its clinical course, diagnostic criteria, and management strategies. We report a case of a 60-year-old female presenting with midline neck swelling, which was diagnosed as intrathyroidal parathyroid carcinoma based on histopathology and immunohistochemistry, along with a detailed review emphasizing its clinical features, diagnostic approaches, and management strategies, while identifying areas for future research to elucidate this enigmatic malignancy better.

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INTRODUCTION

Parathyroid carcinoma is a rare malignancy accounting for <1% of all cases of primary hyperparathyroidism, which must be differentiated from other parathyroid pathologies.[1] The differentiation becomes even more difficult when it is not at its usual anatomical site. It can also occur at sites where the parathyroid gland is found ectopically, like the retroperitoneal space, mediastinum, thymus, and thyroid gland. Of these, the intrathyroidal localization of the parathyroid gland has a reported prevalence of 0.2% only.[2] Even more rare is the carcinoma of the intrathyroidal

parathyroid gland, with less than 20 reported cases in the literature. The patient usually presents with severe fatigue, kidney stones, pathological fractures, brown tumors, and hypercalcemia. However, patients with non-functioning non-secreting cancers can remain asymptomatic for a long period.[3] Imaging modalities like sestamibi scanning, ultrasound, magnetic resonance imaging, and high-resolution 4-dimensional Computed Tomography (CT) can aid in preoperative localization of the affected parathyroid gland, but cannot help in diagnosing and differentiating between adenoma and carcinoma.[4] Unusual location, nonspecific clinical symptoms, and overlapping features on imaging and fine needle aspiration cytology make the preoperative and intraoperative diagnosis of intrathyroid parathyroid carcinoma very challenging.[5] Final diagnosis is almost always made postoperatively on histopathology and immunohistochemistry.[6] Parathyroid carcinoma has a high probability of local recurrence, regional node involvement, and distant metastasis, making complete surgical resection with microscopic negative margins the primary treatment. Post-operative serum calcium and PTH level assay is used to evaluate the efficacy of treatment and to predict its recurrence.[7]

In this article, we report a case of intrathyroidal parathyroid carcinoma and review existing literature on intrathyroidal parathyroid carcinoma, focusing on diagnostic challenges, histopathological features, and treatment outcomes.

CASE REPORT

A 60-year-old female presented to the medicine outpatient department (OPD) with complaints of generalized weakness and weight loss for 1 month, which was gradual in onset, progressive in nature, and associated with constipation. The patient was a known case of hypothyroidism for 15 years and type II Diabetes mellitus for 5 years, for which he was under regular medication. On physical examination, a palpable midline neck swelling was found moving with deglutition, for which USG neck was done along with routine investigations involving thyroid profile, renal function tests, serum calcium, and vitamin D. USG revealed an enlarged left lobe of thyroid with TIRADS IV, likely malignant. Serum calcium and PTH levels were raised (14.6mg/dL and 300.1 pg/ml, respectively). The rest of the investigations were within normal limits. Because of hypercalcemia and raised PTH level, parathyroid scintigraphy using Sestamibi and whole-body PET CT study was done. Scintigraphy scan revealed an abnormal focus of tracer (Sestamibi) uptake in the left neck region, suggestive of malignant disease. PET-CT also revealed an enlarged left lobe of thyroid with metabolically active, relative hypodense nodule at the lower pole -likely malignant disease along with a sub-centimetric size solitary cervical lymph node likely metastatic. No definite scan evidence of any abnormal hypermetabolic disease focus was found elsewhere in the body. FNAC done on the thyroid lesion was suggestive of malignancy, possibly medullary thyroid carcinoma. Considering the malignant possibility, total thyroidectomy with left parathyroid excision and level VI excision was performed, and the specimen was sent to the histopathology department for definitive diagnosis. Left lobe of thyroid, measuring 5x3.5x3 cm, and the atrophic right lobe, measuring 2x1.5x0.8cm, were sent separately along with the left superior parathyroid and level VI lymph node. Cut section of the left lobe of the thyroid appeared variegated with multiple grey white lobules extending and covering the full thickness, along with a cystic area. Microscopic examination of the left lobe of the thyroid showed multiple nodules of tumor cells composed of clear cells with a low N: C ratio and focal areas of pleomorphism. Hyperchromasia, atypical mitosis, and foci of capsular and vascular invasion were noted. (fig. 1A,1B,1C). Adjacent thyroid tissue showed features suggestive of lymphocytic thyroiditis. However, resected margins were free from tumor cells, with the closest resected margin being 2mm away from the tumor. The right lobe of the thyroid was atrophic and free of tumor cells, but sections examined from the level VI cervical lymph node revealed metastatic tumor deposits. Immunohistochemistry was applied to identify the origin of these tumor cells in the thyroid and lymph node. On IHC, these tumor cells were found to be positive for Cytokeratin (CK), Synaptophysin, CyclinD1, Galectin, GATA 3, and negative for TTF-1, Calcitonin, vimentin, CD10, and PAX8. Ki67 index was elevated ~10% (>5%). (fig.2,3). Clinical, biochemical, histological features, and immunohistochemistry findings lead to the diagnosis of intrathyroidal parathyroid carcinoma with metastasis to cervical lymph node level VI. Follow-up biochemistry analysis of serum PTH levels and serum calcium levels showed a significant drop to 3.5 pg/ml and 9.4mg/dl, respectively, and were within a normal range.

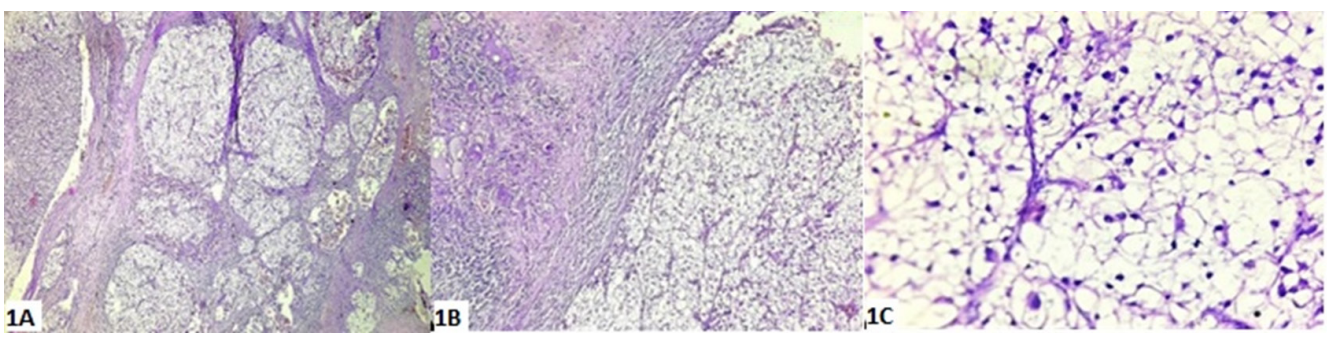

Figure 1: *1A) Low power view (10X) showing multiple nodules of clear cells separated by fibrous bands and capsular invasion; 1B) Higher power (40X) showing nodule of malignant clear cells (right side) and foci of normal thyroid tissue revealing thyroiditis (left side); 1C) Higher power view (100X) showing malignant cells with clear cytoplasm and distinct membrane with central to eccentric hyperchromatic nucleus. [H&E]*

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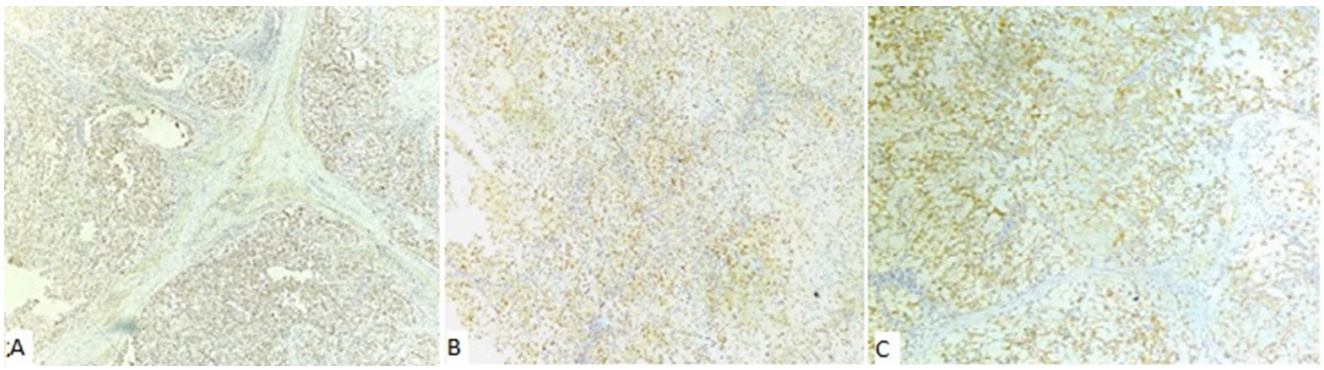

Figure 2: *A)Galectin3: Positive nuclear and cytoplasmic staining in tumor cells; B)Cyclin D1: Positive nuclear staining in tumor cells; C) Synaptophysin: Positive cytoplasmic staining in tumor cells. [Immunohistochemistry]*

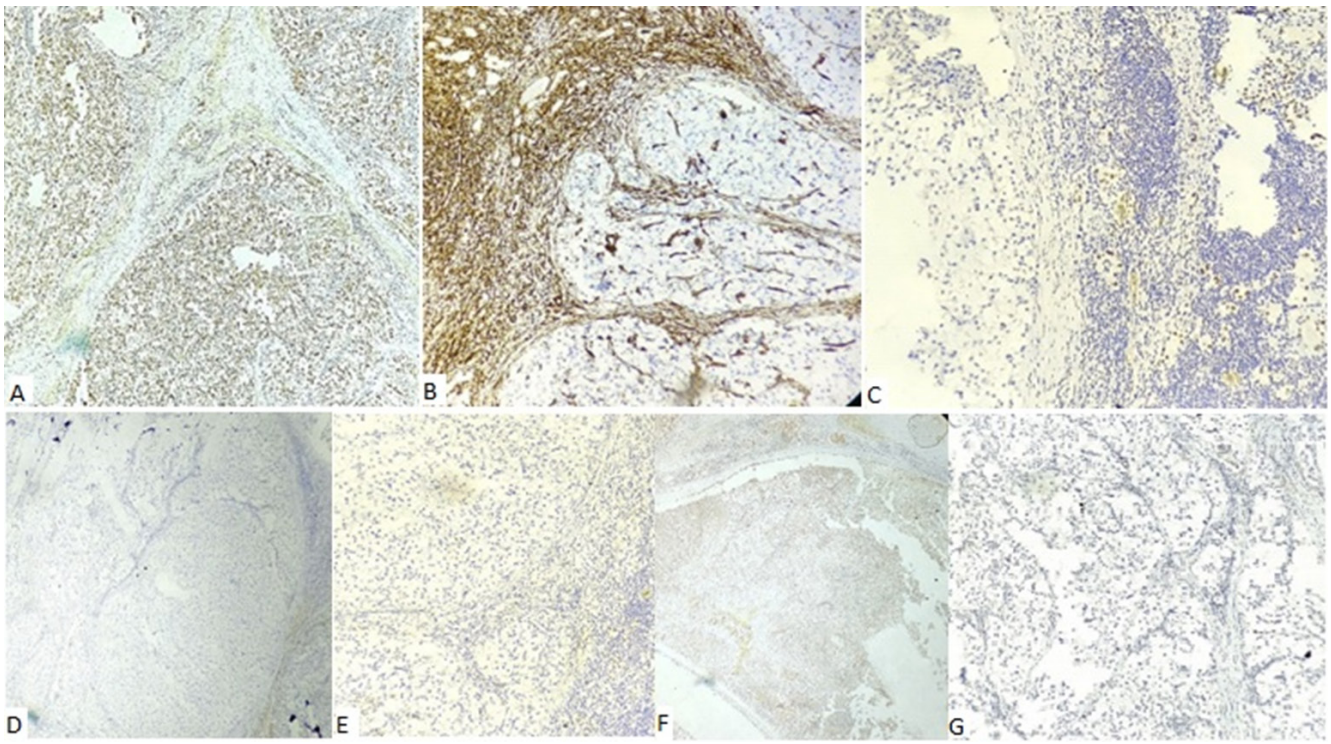

Figure 3: *A)GATA3: Positive nuclear staining in tumor cells; B) Vimentin: Negative in tumor cells; C)TTF-1 – Negative in tumor cells (left side),positive in normal thyroid tissue(right side), D&E) CD10, PAX8 respectively- negative in tumor cells; F) Ki67: Low power view showing nuclear expression in 10% of tumor cells; G) Calcitonin: Negative expression in tumor cells. [Immunohistochemistry]*

DISCUSSION

The parathyroid gland originates from the third and fourth branchial arches and is behind the thyroid. It can be found ectopically within the thymus, along the anterior surface of the carotid sheath, mediastinum, and rarely within the thyroid gland due to aberrant migration during embryogenesis. Out of these, intrathyroidal location is the most unusual site.[4,8,9] Parathyroid carcinoma is a rare malignancy accounting for less than 1% of all primary hyperparathyroidism, equally affecting both genders with a median age of 45 years.[10] Long-standing secondary hyperparathyroidism, previous history of head and neck irradiation, are some of the risk factors. It usually occurs sporadically or is related to other diseases without a familial history and presents with symptoms of hyperparathyroidism and hypercalcemia.[11] In the literature, around 700 cases of parathyroid carcinoma have been reported to date, but only 2-3% of these were intrathyroidal parathyroid carcinoma. Ectopic location, overlapping clinical and pathological features with benign thyroid adenomas, hyperplasia, and thyroid neoplasm make its diagnosis challenging.[10]

Literature on intrathyroid parathyroid carcinoma is sparse, and most authors agree that a combination of histopathological features, along with specific immunohistochemistry and biochemistry, is required to differentiate parathyroid carcinoma from other lesions of the thyroid and parathyroid. Clinical suspicion of severe hyperparathyroidism is helpful, and serum calcium, PTH levels, and ultrasound of the

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neck are the primary investigations done. A scintigraphy scan using sestamibi and MRI of the cervical area aids in locating the parathyroid gland, but these can not differentiate between adenoma and carcinoma.[4] As per the literature, a malignant diagnosis should be suspected if there is a fast onset of acute symptoms, serum calcium levels >14mg/dl, serum PTH level>10 times the normal value, and metastasis detection on imaging techniques.[9,12,13]

According to our review of literature, as summarized in Table 1, the youngest patient diagnosed with intrathyroid parathyroid carcinoma is 14 years of age in a study conducted by Herrera-Hernandez et al[14], and the eldest is 76 years of age in the study conducted by Schmidt et al.[15] Out of 20 studies including the present study, 16 patients were hypercalcemic, whereas the serum calcium levels were within normal limits in 4 studies done by Kirsten et al,[16] Quartey et al,[17] Cao and wang[18] and Kenza Benali et al[10]. Serum PTH levels were raised preoperatively in 19 cases, and in 1 case reported by Cao and Wang[18,] preoperative serum PTH levels were not available. However, in all the cases, post-operative serum calcium and PTH levels were normal. The definite diagnosis in all the cases was made postoperatively on biopsy. On histopathology, a nodular and solid growth pattern was commonly seen with distinct broad fibrous bands. The tumors were mostly composed of chief cells; however, oxyphil cells and transitional cells were also seen exhibiting focal nuclear atypia and prominent macronucleoli. Increased mitotic activity (>5/10mm^2) and necrosis, if present, were usually associated with an aggressive growth pattern. One of the following features is necessary for definitive diagnosis of parathyroid lesion malignancy: Angioinvasion (vascular invasion), lymphatic invasion, perineural (intraneural) invasion, invasion of adjacent structures/organs, metastasis. The cells themselves, rather cytologically bland, tend to be larger than normal parathyroid or adenomatous tissue. In our case, the tumor cells were pleomorphic with clear cytoplasm, with low mitosis and presence of capsular and vascular invasion.[6] Normal thyroid tissue and parathyroid tissue were also identified. Along with parathyroid carcinoma, the possibility of thyroid carcinoma, clear cell renal cell adenoma, and parathyroid adenoma was also considered. To identify the origin of cells, TTF-1, Calcitonin, galectin, PAX8, CD10, synaptophysin, Cyclin D1, and GATA 3 were applied. Negative expression of TTF-1 and calcitonin on IHC ruled out thyroid malignancy. PAX8 and CD10 were applied to differentiate the tumor cells from metastasis of clear cell renal cell carcinoma, which came out to be negative. Overexpression of immunostain for galectin 3 ruled out parathyroid adenoma. Positive granular cytoplasmic expression of synaptophysin confirms its neuroendocrine origin. Further positive cyclin D1 and GATA 3 expression leads to the diagnosis of parathyroid carcinoma. Parathyroid-specific markers PTH and Parafibromin were not available, hence could not be applied.

On the management front, complete surgical resection with microscopically negative margins is considered ideal for cure and is considered the gold standard. Since parathyroid carcinoma has a very high risk of recurrence and metastasis, a close follow-up over time with serum calcium and PTH levels is advised.[7] There is no definite protocol for the use of radiotherapy and chemotherapy in improving survival and recurrence. Though the dataset for the evidence base of radiotherapy is limited to small case series only and points towards the beneficial effect of adjuvant radiotherapy in preventing tumor recurrence, its role remains unclear.[19-25] Since patient survival depends on a specific single surgical process, pre-operative clinical suspicion is crucial, and an interdisciplinary team approach, including surgeon, radiation oncologist, and pathologist, provides the best chances of diagnosis and cure of this malignancy.

Table 1: Summary of literature review

S.NO	YEAR	STUDY	AGE	SEX	S. CALCIUM	S. PTH LEVELS
1	1993	Ernst et al.[26]	52	F	Increased	Increased
2	1998	Crescenzo et al.[27]	60	F	Increased	Increased
3	2001	Kirsten and Ghosh[16]	74	M	Normal	Increased
4	2002	Schmidt et al.[15]	76	F	Increased	Increased
5	2006	Hussein et al.[28]	63	F	Increased	Increased
6	2007	Foppiani et al.[29]	67	F	Increased	Increased
7	2011	Herrera-Hernendez et al.[14]	14	F	Increased	Increased
8	2011	Quartey et al.[17]	55	M	Normal	Increased
9	2011	Kruljac et al.[31]	40	M	Increased	Increased
10	2013	Vila Duckworth et al.[9]	51	F	Increased	Increased
11	2014	Lee et al.[30]	59	F	Increased	Increased
12	2015	You WN et al.[32]	33	F	Increased	Increased
13	2016	Tejera Hernandez et al.[8]	25	M	Increased	Increased
14	2016	Merazka et al.[33]	36	F	Increased	Increased
15	2018	Balakrishnan et al.[4]	60	F	Increased	Increased
16	2018	Alharbi et al.[34]	63	M	Increased	Increased
17	2019	Cao and Wang[18]	56	F	Normal	Not available
18	2020	Poortmans et al.[7]	26	F	Increased	Increased
19	2020	Kenza Benali et al.[10]	56	F	Normal	Not available
20	2025	Present study	60	F	Increased	Increased

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CONCLUSIONS

Intrathyroidal parathyroid carcinoma poses significant diagnostic challenges due to its atypical presentation within the thyroid gland. Accurate diagnosis relies heavily on histopathological examination and immunohistochemical profiling. Surgical resection remains the cornerstone of treatment, although ongoing monitoring for potential recurrence or metastasis is essential given the aggressive nature of this malignancy.

Conflict of Interest: None

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