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Diagnostic Pitfall: Parathyroid Carcinoma Expands the Spectrum of Calcitonin and Calcitonin Gene-Related Peptide Expressing Neuroendocrine Neoplasms

Anjelica Hodgson[1] · Sara Pakbaz[1,2] · Farnoosh Tayyari[3] · James Edward Massey Young[4,5] · Ozgur Mete[1,2,6]

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Case History

A 59-year-old man with primary hyperparathyroidism (PTH 76 pmol/L, normal range 2–9 pmol/L) and associated hypercalcemia (3.4 mmol/L, normal range 2.15–2.55 mmol/L) was found to have a CT and Sestamibi scan-localized left thyroid component neck mass. Intraoperatively, the mass was noted to be adherent to the left side of the thyroid and required en bloc resection of the mass with the left lobe. In addition, the patient underwent right hemithyroidectomy for nodular goiter. Postoperatively, the serum PTH level was noted to have significantly dropped (5.6 pmol/L, within normal range), supporting the uniglandular source of hyperparathyroidism.

What Is Your Diagnosis? (Figs. 1–4)

Clinicopathological Diagnosis: Calcitonin- and CGRP-expressing parathyroid carcinoma and C-cell hyperplasia in the thyroidectomy specimen.

✉ Ozgur Mete
ozgur.mete2@uhn.ca

[1] Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

[2] Department of Pathology, University Health Network, 200 Elizabeth Street, 11th floor, Toronto, ON M5G 2C4, Canada

[3] Department of Pathology, St. Joseph's Hospital, Hamilton, ON, Canada

[4] Department of Surgery, St. Joseph's Hospital, Hamilton, ON, Canada

[5] Department of Surgery, McMaster University, Hamilton, ON, Canada

[6] Endocrine Oncology Site, The Princess Margaret Cancer Centre, Toronto, ON, Canada

Grossly, the mass measured 2 cm and was attached to the inferior aspect of the left thyroid lobe. It displayed a locally invasive nodular growth and was received fragmented (Fig. 1a). The tumor consisted of epithelial cells exhibiting nuclear enlargement, variable perinuclear clearing, and prominent macronucleoli (Fig. 1b). Band-forming fibrosis was noted within the lesion (Fig. 1c). Angioinvasion characterized by intravascular tumor cells admixed with thrombus was also identified. There was no necrosis (Fig. 1d). The mitotic activity was 6 per 50 high power fields. Surrounding the mass, a rim of non-tumorous parathyroid parenchyma was identified. The contralateral perithyroidal parathyroid gland which was removed did not show any significant abnormality. In addition, the thyroidectomy specimen showed bilateral C-cell hyperplasia which was also confirmed with calcitonin immunohistochemical staining (Fig. 2).

The tumor cells were positive for chromogranin-A, low molecular weight keratin (CAM5.2), PTH (Fig. 3a), GATA-3 (Fig. 3b), monoclonal calcitonin (Fig. 3c), and calcitonin gene-related peptide (CGRP) (Fig. 3d); and were negative for thyroglobulin, TTF-1 (clone SPT24), monoclonal CEA (Fig. 3e), serotonin, bombesin, and alpha-subunit. Reduced expression for bcl-2 (Fig. 3f), Rb (Fig. 3g), and p27 was seen along with variable reactivity for PGP9.5 (Fig. 3h). Parafibromin (protein encoded by *CDC73/HRPT2*) showed nucleolar loss while the nucleoplasm of the tumor nuclei remained positive (Fig. 4). The Ki67 labeling index was 6.17% in 2123 tumor cells from hot spots using a Leica Biosystems automated image analysis nuclear algorithm.

Overall, the combined clinical, morphological, and immunohistochemical features were diagnostic of a parathyroid carcinoma with aberrant calcitonin and CGRP expression. Given the presence of a parathyroid neoplasm with associated bilateral C-cell hyperplasia,

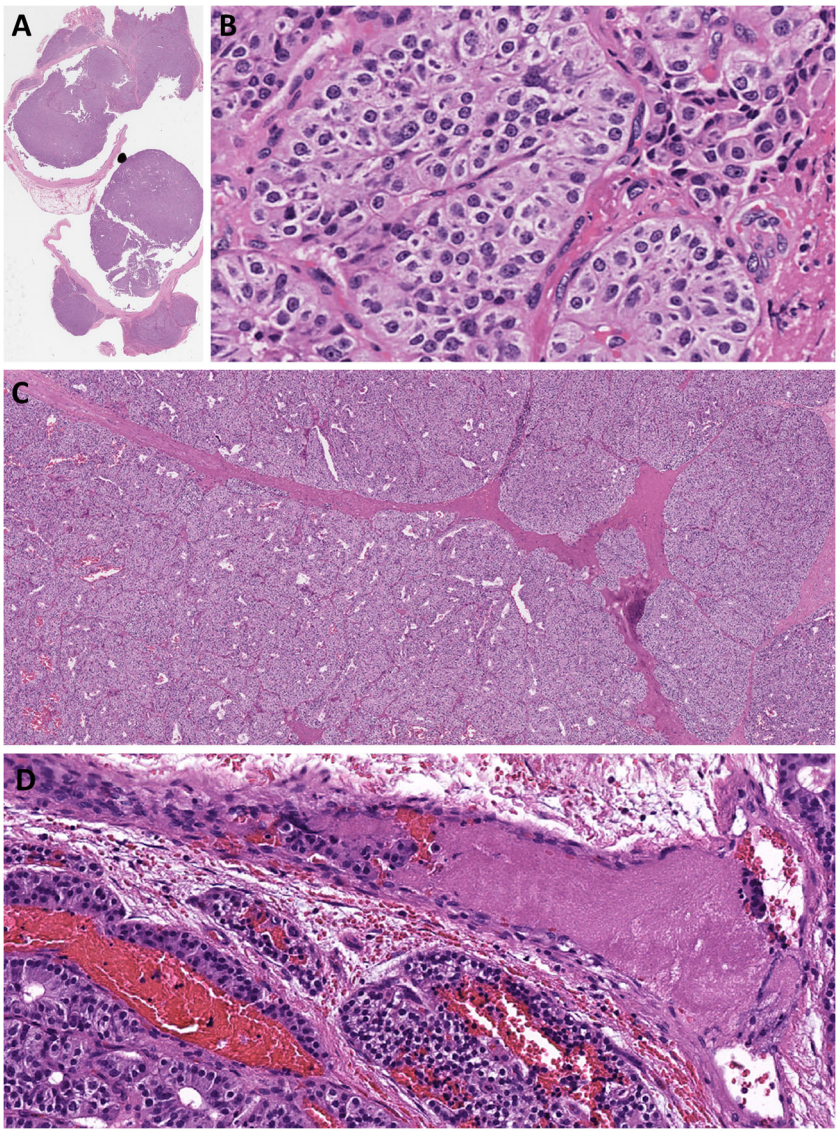

Fig. 1 Characteristics of the tumor. The mass displayed a locally invasive nodular growth (**a**) and was composed of epithelial cells exhibiting nuclear enlargement, variable perinuclear clearing, and prominent macronucleoli (**b**). Band-forming fibrosis was seen (**c**) along with angioinvasion (**d**) characterized by intravascular tumor cells admixed with thrombus and attached to the endothelium

the patient underwent further *RET* germline testing; no pathogenetic *RET* variants were identified. Somatic and/or germline *CDC73/HRPT2* alterations were not investigated. Given the absence of *RET* germline mutations, bilateral C-cell hyperplasia is considered to represent a secondary phenomenon to primary hyperparathyroidism-related hypercalcemia.

Comment

Parathyroid carcinoma is a rare epithelial malignant neuroendocrine neoplasm derived from the hormone-secreting parenchymal cells of the parathyroid gland. In the absence of metastatic spread, the diagnosis of parathyroid carcinoma requires the identification of malignant invasive growth including vascular invasion, lymphatic invasion, perineural invasion, or invasion into surrounding structures [1]. As would be expected, proliferations arising from the parathyroid glands often stain with PTH, the prototypical hormone secreted by native parathyroid cells. While most diagnosticians consider PTH immunoreactivity sufficient to confirm parathyroid origin in the appropriate morphological and clinical setting, it should be recognized that PTH or PTHrp (PTH-related peptide) can be expressed by other

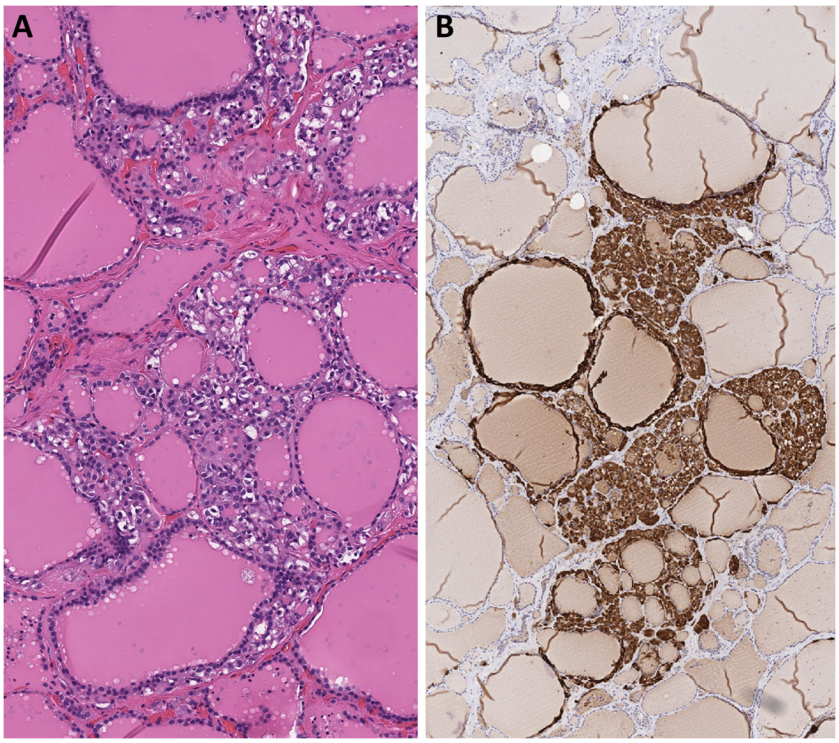

Fig. 2 C-cell hyperplasia in the thyroidectomy specimen. Both thyroid lobes showed increased numbers of C-cells (**a**). Calcitonin immunohistochemistry confirmed the presence of C-cell hyperplasia (**b**). Patients with hyperparathyroidism can manifest with C-cell hyperplasia; however, the bilateral nature of C-cell hyperplasia in association with a parathyroid neoplasm warranted exclusion of *RET* germline-driven pathogenesis in this case

neuroendocrine neoplasms [2]. The same is true for other hormones that can be aberrantly expressed by other neuroendocrine neoplasms [3]. Furthermore, metastases to the parathyroid glands, although rare, do not only cause diagnostic challenges but have also been shown to cause deranged calcium homeostasis [4]. Unlike hormones, developmental transcription factors are rarely aberrantly expressed in well-differentiated neuroendocrine neoplasms. Therefore, the use of transcription factors in association with hormones and other specific site-specific biomarkers has a better diagnostic accuracy in the confirmation of the cellular origin of a neuroendocrine neoplasm. For instance, positivity for PTH along with transcription factors GCM2 (a master regulatory gene for parathyroid development) and/or GATA-3 (a transcription factor involved in the embryological development of the parathyroid gland and adult proliferation of mature parathyroid tissue) confirms parathyroid origin [2].

The presented case underscores indeed a potential diagnostic challenge related to aberrant immunoreactivity of calcitonin and CGRP in a parathyroid carcinoma. Most diagnosticians would consider calcitonin positivity to be a diagnostic biomarker of medullary thyroid carcinoma (MTC); however, calcitonin along with CGRP expression is not specific to MTC. These tumors are often distinguished from other tumors by their co-expression of monoclonal CEA with calcitonin and/or CGRP. In fact, several neuroendocrine neoplasms (including but not limited to those of primary head and neck regions, pulmonary, thymic and pancreatic origins) can be immunoreactive for calcitonin and/or CGRP [5, 6]. A frequent challenge occurs when dealing with a TTF-1 and calcitonin/CGRP-expressing well-differentiated neuroendocrine neoplasm as the possibility of a well-differentiated pulmonary neuroendocrine tumor (carcinoid tumor) must be considered. In such scenarios, positivity for additional pulmonary neuroendocrine cell biomarkers (serotonin, bombesin, and alpha-subunit) and negativity for monoclonal CEA would confirm pulmonary origin [6].

In the presented case, the identification of underlying C-cell hyperplasia resulted in the order of C-cell related immunohistochemical biomarkers in the tumor. While

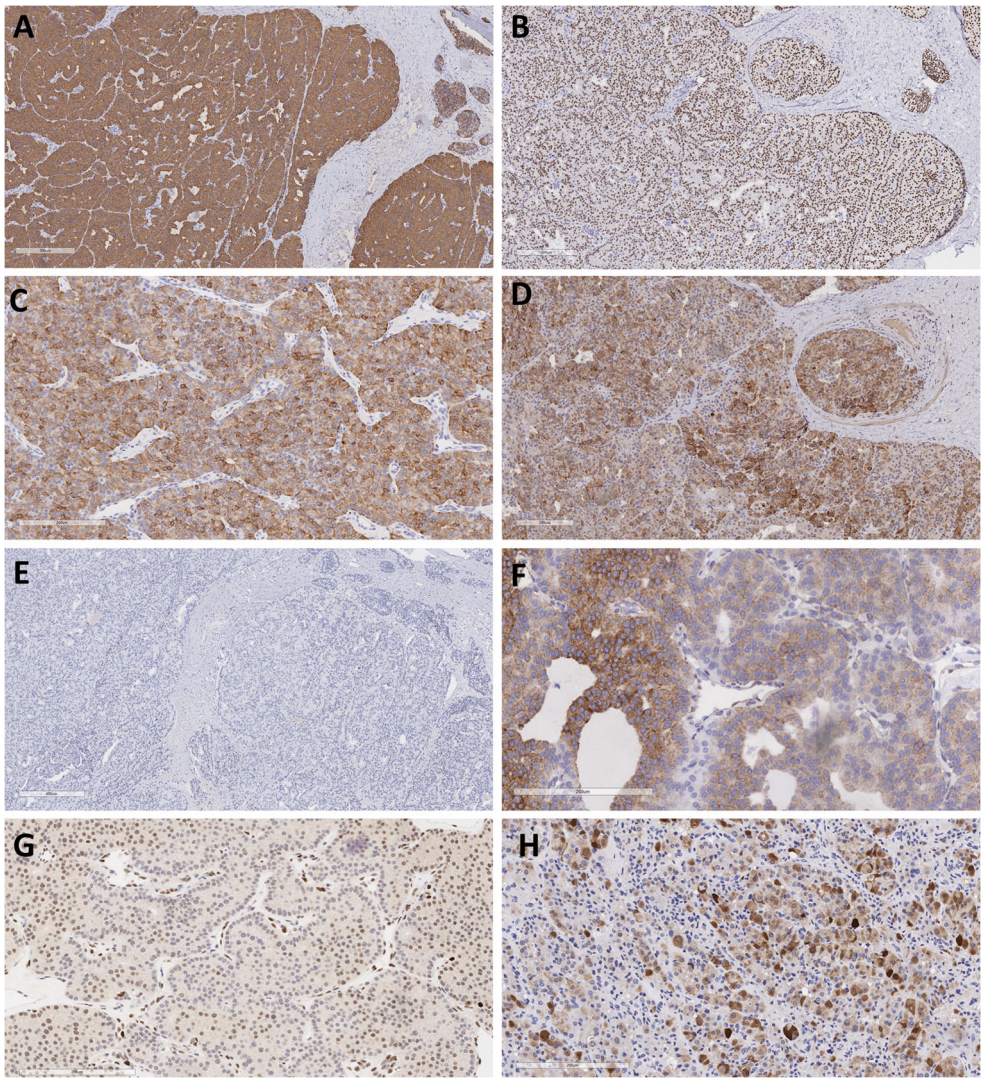

Fig. 3 Immunohistochemical features of the tumor. The tumor cells were diffusely positive for PTH (**a**) and GATA-3 (**b**), confirming parathyroid origin. Interestingly, calcitonin (**c**) and CGRP (**d**) were also positive while monoclonal CEA (**e**) was negative. Reduced expression for bcl-2 (**f**) and Rb (**g**) proteins was seen. PGP9.5 was variably expressed in the tumor (**h**)

diffuse positivity for PTH and GATA-3 and negativity for TTF-1 and monoclonal CEA confirmed the parathyroid origin in this case, expression for calcitonin and CGRP was an interesting finding. The significance of this finding and its relationship to calcium metabolism in patients with hyperparathyroidism is largely unknown; however, both hyperplastic and neoplastic parathyroid proliferations have been previously documented to express calcitonin and CGRP [7, 8].

Another finding of the presented parathyroid carcinoma was the identification of nucleolar loss of parafibromin expression while nucleoplasm surrounding the nucleoli remained positive for parafibromin. While the biologic significance of this finding cannot be further assessed without somatic and germline *CDC73/HRPT2* testing in the current case, Juhlin et al. reported absence of nucleolar parafibromin immunoreactivity in some *CDC73/HRPT2* mutant-parathyroid carcinomas [9].

In summary, the presented case of parathyroid carcinoma not only expands the spectrum of calcitonin- and CGRP-expressing neuroendocrine neoplasms, but also

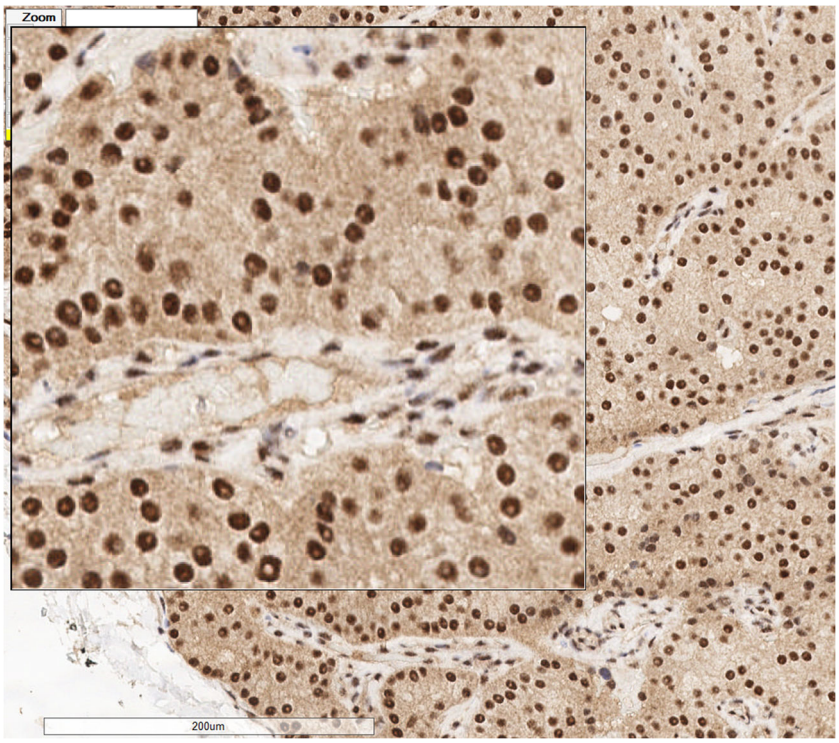

Fig. 4 Nucleolar loss of parafibromin expression in the tumor. Although most *CDC73/HRPT2* mutant-parathyroid neoplasms tend to display global loss of nuclear immunostaining for parafibromin, some tumors have been reported to show nucleolar loss of parafibromin expression while nucleoplasm surrounding the nucleoli remained positive as seen in the presented case

underscores the importance of combined use of hormones and transcription factors in the workup of neuroendocrine neoplasms.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement This report does not contain any research studies with human participants or animals performed by any of the authors. The patient's consent was obtained for publication.

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