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Parathyroid Carcinoma Arising From Four-Gland Hyperplasia

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Abstract

Objective—To report the use of immunohistochemical staining for parafibromin, APC and galectin-3 to evaluate the malignant potential of the resected parathyroid specimen in a patient initially presenting with primary hyperparathyroidism secondary to four-gland hyperplasia who subsequently developed metastatic parathyroid carcinoma.

Methods—We describe a patient with primary hyperparathyroidism who underwent a 3 gland resection of hypercellular parathyroids with post-operative normalization of her serum calcium and parathyroid hormone levels. She returned four years later with recurrent hypercalcemia and underwent partial resection of her remaining hypercellular gland without improvement of her hypercalcemia. Selective venous sampling localized the source as draining into her azygous vein, and she was ultimately diagnosed with metastatic parathyroid carcinoma.

Results—Immunohistochemical staining for parafibromin, APC and galectin-3 suggested the malignant potential of the atypical adenoma removed during the patient's original operation, which is believed to be the source of her metastatic disease. Access to this information by the treating surgeon may have prompted a more extensive en bloc resection or more vigilant follow-up that could have altered the patient's clinical course.

Conclusion—Immunohistochemical staining for parafibromin, APC and galectin-3 can be used to help distinguish the source of metastatic disease in parathyroid carcinoma. Selective venous sampling may help localize metastatic parathyroid carcinoma when it is otherwise not apparent.

Keywords

parathyroid carcinoma; hyperparathyroidism; hypercalcemia; immunohistochemistry; parafibromin; APC; galectin-3

Background

Parathyroid carcinoma is exceedingly rare, comprising 0.1–5% of cases of primary hyperparathyroidism (1). It is difficult to diagnose, with up to 50% of patients with

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metastases initially diagnosed with benign disease (2). Histopathologic criteria used to differentiate between benign and malignant disease overlap considerably, posing a diagnostic challenge. We describe a patient who presented with hyperparathyroidism from multi- gland disease, who four years later was diagnosed with metastatic parathyroid carcinoma not originating from the remaining hypercellular parathyroid gland.

Case Report

A 62- year- old woman presented with calcium of 12.8 mg/dL (reference 8.5–10.5), an intact PTH of 150 pg/mL (reference 10–65), and a vitamin D-25 level of 8 ng/mL (normal > 20) in 2003. She denied neck radiation or a family history of parathyroid or calcium problems, thyroid cancer, brain, pancreatic, or jaw tumors. Sestamibi scan was non-localizing. She underwent bilateral exploration with removal of three enlarged parathyroids weighing 270 mg, 200 mg and 1800 mg, respectively. The fourth gland was visualized and appeared only slightly enlarged. Given the obvious hyperplasia in the three glands removed and the minimal enlargement of the fourth gland, the decision was made to leave the entirety of the fourth gland in-situ rather than perform a partial resection and risk rendering the patient permanently hypoparathyroid. Intra-operative PTH levels fell from 200 pg/mL to 41 post-excision. Pathology showed hypercellularity of all glands with features of atypical adenoma in the largest. The diagnosis of atypical adenoma was made by the presence of mitotic figures and atypical nuclear features, but it was not classified as a parathyroid carcinoma because of the lack of unequivocal vascular, capsular or adjacent tissue invasion, and the lack of known metastatic disease. Her serum calcium normalized to 9.4mg/dL and her PTH to 51pg/mL two weeks post-operatively. The patient failed to return for her subsequent clinic visit, and was ultimately lost to follow-up.

Four years later, she returned with calcium of 18.6 mg/dL, PTH of 723 pg/mL, and an undetectable PTHrp. Neck ultrasound revealed enlargement of the remaining left superior parathyroid. Sestamibi was again uninformative. A CT of the neck and chest revealed no parathyroid tumor, normal lymph nodes, and two sub-centimeter left apical pleural-based lung nodules. Selective venous sampling did not reveal the source of PTH, but was slightly higher in the chest (Table 1).

The patient underwent a partial left superior parathyroidectomy with cryopreservation of a grossly enlarged gland. No parathyroidismosis or lymphadenopathy was seen. Final pathology showed hypercellular tissue without classical signs of malignancy.

Post-operatively, the patient's calcium and PTH remained elevated at 15.2 mg/dL and 746 pg/mL respectively. Repeat selective venous sampling showed an increased PTH gradient in the azygous vein, suggesting a metastatic focus in the chest (Table 1).

CTA of the chest revealed several sub-centimeter non-calcified pleural-based nodules (Figure 1).

CT-guided biopsy of a pleural nodule was performed and showed atypical epithelial cells concerning for malignancy. PTH washings were similar to levels observed in the azygous vein.

An extensive workup including positron emission tomography, endoscopic ultrasound, mammogram, and endometrial biopsy was negative for additional metastases or primary tumors.

The patient underwent thoroscopic lung wedge resection with multiple sub-centimeter nodules removed. Immunohistochemical staining for parathyroid hormone was positive, and a diagnosis of metastatic parathyroid carcinoma was made.

The two hypercellular parathyroids and the atypical adenoma obtained at initial presentation, and the remaining parathyroid resected four years later underwent immunohistochemical staining for parafibromin, APC, and galectin-3 to help determine the source of parathyroid carcinoma (Figures 2&3). Malignant tumors often display absent or reduced parafibromin and APC expression, whereas adenomas usually are positive for both (3, 4, 5). Galectin-3 typically displays strong immunoreactivity in carcinomas as opposed to adenomas. The primary antibodies used were anti-APC EP701Y (Abcam, Cambridge, UK), anti-parafibromin 2H1 (Santa Cruz Biotechnology, Santa Cruz, CA), and anti-galectin-3 NCL-GAL3 clone 9C4 (Novocastra Laboratories, Newcastle upon Tyne, UK). The atypical adenoma from the 2003 specimen displayed positive parafibromin and APC expression in nearly 100% of tumor nuclei in central parts of the tumor, and was strongly positive for galectin-3. However, the expression for parafibromin and APC demonstrated focal loss in the cells engaging the capsule. The hypercellular parathyroids from 2003 and the parathyroid tissue obtained from 2007 were entirely positive for APC and parafibromin without differences between tissue areas, and were negative for galectin-3. The immunohistochemical staining strongly suggests that the parathyroid carcinoma arose from the atypical adenoma resected at initial operation and not from the hypercellular tissue resected initially or four years later.

The patient's hypercalcemia was treated with bisphosphonates and sensipar with improvement in symptoms. She subsequently developed a metastasis to her hip and was treated with radiation.

Her calcium level has been normal for the past 6 months, and she is doing well 7 years after her initial diagnosis of hyperparathyroidism.

Discussion

The rarity of parathyroid carcinoma has slowed progress toward its understanding. Unlike benign hyperparathyroidism, it occurs equally in men and women (6). Patients commonly present in the fifth and sixth decades of life. It is a slow-growing tumor, frequently recurs, and is difficult to eradicate (6). Affected patients often have more pronounced symptoms than those with benign hyperparathyroidism and findings such as markedly elevated calcium (greater than 14 mg/dL), PTH levels five times above normal, palpable neck mass, or hoarseness suggest carcinoma over benign disease (6,7).

Workup of both benign and malignant parathyroid diseases utilizes the same imaging studies, including ultrasound, technetium sestamibi scanning, CT, and MRI. Ultrasound may show a hypoechoic mass with poorly defined margins and local invasion, although benign and malignant diseases are difficult to distinguish (6). Likewise, histopathologic diagnosis of parathyroid carcinoma is extremely challenging because features overlap those of parathyroid adenoma. Even the 'classic' findings including trabecular growth pattern, vascular invasion, and numerous mitotic figures are present in only half the cases of parathyroid carcinoma (8). The most consistent pathological findings include loss of typical lobular architecture, fibrosis with hyaline bands, and the presence of nuclear atypia (6). The only unequivocal features of parathyroid malignancy are vascular-, perineural-, or local tissue- invasion, and metastases (9).

Unfortunately, the diagnosis is often not made until recurrent hypercalcemia occurs or distant metastases are detected (10).

Immunohistochemical markers such as Ki-67, cyclin D1, p27/kip1, CaSR, and galectin-3 have been suggested to aid in diagnosis, but both benign and malignant tumors may be positive (11). Although galectin-3 over-expression typically is specific for parathyroid carcinoma, one study found it highly expressed in benign multi-gland disease (12). In our hands, galectin-3 was helpful in distinguishing carcinoma from hyperplasia. The product of the retinoblastoma gene is a known regulator of cell proliferation and loss of retinoblastoma immunopositive cells has been reported in parathyroid carcinomas (13). However, this finding is not restricted to parathyroid carcinomas, being observed in 11% of adenomas (14).

Hereditary hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare condition associated with germ-line mutations of HRPT2, a tumor suppressor gene that encodes the parafibromin gene product (15). Patients develop hyperparathyroidism, fibro-osseous lesions of the mandible and maxilla and may develop parathyroid carcinoma (6). Loss of nuclear expression of parafibromin is associated with parathyroid carcinoma with good sensitivity (96%) and specificity (99%) (6,11,16). A report by Clark et al. concluded that no single diagnostic marker distinguishes parathyroid carcinoma from adenoma, but loss of parafibromin and Rb expression combined with over-expression of galectin-3 frequently differentiates parathyroid carcinoma from other parathyroid tumors (17).

In our case, focal loss of parafibromin and APC in peripheral tumor cells with positive immunoreactivity for galectin-3 in the 2003 atypical adenoma strongly suggests the carcinoma originated at that time, especially since the other specimens demonstrated positive APC and parafibromin staining and negative galectin-3. It is possible that more extensive evaluation of the tissue removed at initial presentation could have led to more vigilant follow-up or an attempt to return to the operating room for a more aggressive cancer resection (hemithyroidectomy and resection of adjacent soft tissues). Even though presumably she had metastatic parathyroid carcinoma at that time, it is interesting to note the correction of her hypercalcemia and normalization of her PTH after initial surgery. This demonstrates the frequently indolent nature of this malignancy, and that even a few tumor cells remaining in-situ can dwell for years before reaching sufficient quantities to cause recurrent hypercalcemia.

Parathyroid carcinoma is optimally managed by en bloc resection at initial operation with removal of the ipsilateral thyroid lobe, suspicious lymph nodes, and involved structures. The risk of local recurrence and metastasis is high if the capsule is breached (18). Recurrent or metastatic disease warrants resection when possible (6). Radiation therapy has shown some success, and symptoms of hypercalcemia are treated with intravenous bisphosphonates, oral calcimimetics, calcitonin, and corticosteroids. Prognosis is poor with a 50% 10-year survival. Most patients die from severe hypercalcemia, rather than the burden of their metastatic disease (19). Recurrence is common, necessitating close lifelong follow-up to detect early recurrence.

There have been several reports of multi-glandular parathyroid carcinoma, and one in which bilateral parathyroid carcinoma was diagnosed in the setting of multi-glandular hyperplasia (20). However, in that case, the fourth gland exhibited normal histopathologic features. This is, to our knowledge, the first reported parathyroid carcinoma arising from four-gland hyperplasia diagnosed years after first operation in a patient without renal failure. Her initial low vitamin D-25 level may have contributed to the hyperplasia found on histology. Because the metastatic disease was tiny, diagnosis was aided by selective venous sampling demonstrating a gradient in the azygous vein. Furthermore, we retrospectively demonstrated possible malignant potential in one of the initially excised parathyroid lesions using parafibromin, APC, and galectin-3 immunohistochemistry, which could not be detected by standard histopathology alone.

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References

1. Stephenson TJ. Prognostic and predictive factors in endocrine tumours. *Histopathology*. 2006; 48:629–643. [PubMed: 16681678]
2. Sandelin K. Parathyroid carcinoma. *Cancer Treat Res*. 1997; 89:183–192. [PubMed: 9204193]
3. Juhlin CC, Villablanca A, Sandelin K, et al. Parafibromin immunoreactivity: its use as an additional diagnostic marker for parathyroid tumor classification. *Endocr Relat Cancer*. 2007; 14(2):501–512. [PubMed: 17639063]
4. Juhlin C, Larsson C, Yakoleva T, et al. Loss of parafibromin expression in a subset of parathyroid adenomas. *Endocr Relat Cancer*. 2006; 13(2):509–523. [PubMed: 16728578]
5. Juhlin C, Haglund F, Villablanca A, et al. Loss of expression for the Wnt pathway components adenomatous polyposis coli and glycogen synthase 3-beta in parathyroid carcinomas. *Int J Oncol*. 2009; 34(2):481–92. [PubMed: 19148484]
6. Rodgers S, Perrier N. Parathyroid carcinoma. *Curr Opin Oncol*. 2006; 18:16–22. [PubMed: 16357559]
7. Shane E. Clinical review 122: parathyroid carcinomas. *The Jour of Clin Endo and Metabol*. 2000; 86(2):485–493.
8. Bondeson L, Sandelin K, Grimelius L. Histopathological variables and DNA cytometry in parathyroid carcinoma. *Am Surg Path*. 1993; 17:820–829.
9. Cheung C, Rotstein L, Asa S. Pathology Case Review. 2003; 8(1):34–41.
10. Flye M, Brennan F. Surgical resection of metastatic parathyroid carcinoma. *Ann Surg*. 1981; 193(4):425–435. [PubMed: 7212805]
11. Gill A, Clarkson A, Gimm O, et al. Loss of nuclear expression of parafibromin distinguishes parathyroid carcinomas and hyperparathyroidism-jaw-tumor syndrome-related adenomas from sporadic parathyroid adenomas and hyperplasias. *Am J Surg Pathol*. 2006; 30(9):1140–1149. [PubMed: 16931959]
12. Saggiorato E, Bergero N, Volante M, et al. Galectin-3 and Ki-67 expression in multiglandular parathyroid lesions. *Am J Clin Pathol*. 2006; 126(1):59–66. [PubMed: 16753595]
13. Cryns V, Thor A, Xu HJ, et al. Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. *NEJM*. 1995; 330:757–761. [PubMed: 7906387]
14. Tahara E, Smith AP, Gaz R, Cryns V, Arnold A. Genomic localization of novel candidate tumor suppressor gene loci in parathyroid adenomas. *Cancer Res*. 1996; 56:599–605. [PubMed: 8564978]
15. Jackson C, Norum R, Boyd S, et al. Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: a clinically and genetically distinct syndrome. *Surgery*. 1990; 108:1006–1012. [PubMed: 2123361]
16. Tan M, Morrison C, Wang P. Loss of parafibromin immunoreactivity is a distinguishing feature of parathyroid carcinoma. *Clin Cancer Res*. 2004; 10:6629–6637. [PubMed: 15475453]
17. Fernandez-Ranvier G, Khanafshar E, Tacha D, et al. Defining a molecular phenotype for benign and malignant parathyroid tumors. *Cancer*. 2009; 115(2):334–344. [PubMed: 19107770]
18. Wang C, Gaz R. Natural history of parathyroid carcinoma: diagnosis, treatment and results. *Am J Surg*. 1985; 149:522–527. [PubMed: 3985291]
19. Cohn K. Parathyroid carcinoma: the Lahey clinical experience. *Surgery*. 1985; 98:1095–1100. [PubMed: 4071385]
20. Brown J, Mohamed H, Williams-Smith L, et al. Primary hyperparathyroidism secondary to simultaneous bilateral parathyroid carcinoma. *Ear Nose Throat J*. 2002; 81:395–398. [PubMed: 12092283]

Figure 1.
CTA of neck and chest showing pleural nodules.

Figure 2.

Staining of original parathyroid specimens (40X magnification). Solid arrows indicate positive staining. Dashed arrow indicates negative staining.

Figure 3.
Staining of subsequent parathyroid specimens, obtained four years after initial presentation (40X magnification).

Table 1

Results of selective venous sampling procedures

VENOUS LOCATION	INTACT PTH (pg/mL) Initial procedure	INTACT PTH (pg/mL) Repeat procedure
Right subclavian	999	1289
Right internal jugular	1017	1390
Right common facial	999	-
Right azygous	1282	-
Left subclavian	1027	1602
Left internal jugular	1148	1510
Left common facial	876	-
Left brachiocephalic	1073	-
Right atrium	843	-
Superior vena cava	938	1477
Azygous T6	-	4771
Azygous T7	-	4080
Azygous T8	-	2187
Azygous T9	-	6195