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Case Report

Use of a Gamma Probe to Identify and Guide Resection of Recurrent Parathyroid Carcinoma: Report of a Case

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Abstract
Parathyroid carcinoma (PC) accounts for less than 0.005% of all cancers and less than 5% of causes of hyperparathyroidism. This tumor is difficult to identify during surgery, which is detrimental to the oncologic results. Surgery is still the main treatment for the primary tumor and to control parathyroid hormone levels after recurrence. We report a case of recurrent parathyroid carcinoma in a 30-year-old man, identified and managed with the use of a gamma probe during surgery. To our knowledge, this is only the second report of a gamma probe being used to guide resection of a recurrent PC. We discuss the diagnosis and treatment, analyzing the current evidence-based literature.

Key words Parathyroid carcinoma · Hyperparathyroidism · Parathyroid tumor · Hypercalcemia · En bloc resection · Gamma probe

Case Report

A 30-year-old Caucasian man presented with proximal limb weakness and lower limb pain, progressively impairing his walking over the last 4 years. He also complained about upper limb weakness. He had suffered renal and biliary calculosis in the last year. Physical examination revealed hypotrophy of the quadriceps, and pain during internal rotation of the thigh. Cervical examination was unremarkable. His serum ionized calcium level was 8 mg/dl (normal value [NV], 4.4–5.3 mg/dl); total serum calcium, 14.2 mg/dl (NV, 8.6–10 mg/dl); phosphorus, 1.7 mg/dl (NV, 2.5–4.8 mg/dl); parathyroid hormone (PTH), 1251 pg/ml (NV, 11.1–79.5 pg/ml), alkaline phosphatase, 1434 U/l (NV, 90–360 U/l); creatinine, 0.8 mg/dl; 24-h urinary calcium excretion, 714 mg/dl (NV, 100–300 mg/dl); 24-h urinary creatinine excretion, 1911 mg (NV, 800–2000 mg); free thyroxin level, 0.88 ng/dl (NV, 0.8–2 ng/dl); and thyroid-stimulating hormone (TSH), 1.64 μUI/ml (NV, 0.4–4 μUI/ml). Radiological procedures showed moderate bilateral hip joint and hand osteopenia, osteolysis in the left hip and in the right coxofemoral joint, subperiosteal bone resorption in the third part of the left clavicle and in the hands, and a radiotransparent oval area in the proximal phalanx of the first finger of the left hand. Bone scintigraphy demonstrated diffuse hypercaptation, with hyperactivity in the distal third of the left clavicle, right proximal humeral diaphysis, 11th left rib, right sacroiliac joint, bilateral necks of femur, proximal left tibia, and left calcaneus. These findings were compatible with hyperparathyroidism. Sestamibi (^{99m}Tc-methoxyisobutylisonitrile scintigraphy) scan showed focal hypercaptation in the lower left thyroid lobe, compatible with parathyroid adenoma. Thus, the patient underwent a lower left parathyroidectomy, at which time we found an irregular lesion, 2.5 cm in diameter, firmly attached to the esophagus and profound planes. The left thyroid lobe, the esophagus, and the left recurrent laryngeal nerve were dissected and preserved. Frozen-section biopsy findings were suggestive of a parathyroid adenoma or hyperplasia. Histopathologic analysis showed capsular invasion (Fig. 1A), mitotic figures (Fig. 1B), and vascular invasion (Fig. 1C). Immunohistochemical staining revealed positivity to cell cycle-associated antigen Ki-67 (Fig. 2A) and D1 cyclin (Fig. 2B), and negativity to retinoblastoma protein. The Ki-67 labeling index was 5%. The histopathology and immunohistochemical findings were compatible with well-differentiated parathyroid carcinoma. After surgery, the patient gained muscle strength and his pain subsided. Although his PTH levels decreased, they did not return to normal. In the 2-year postoperative period, laboratory

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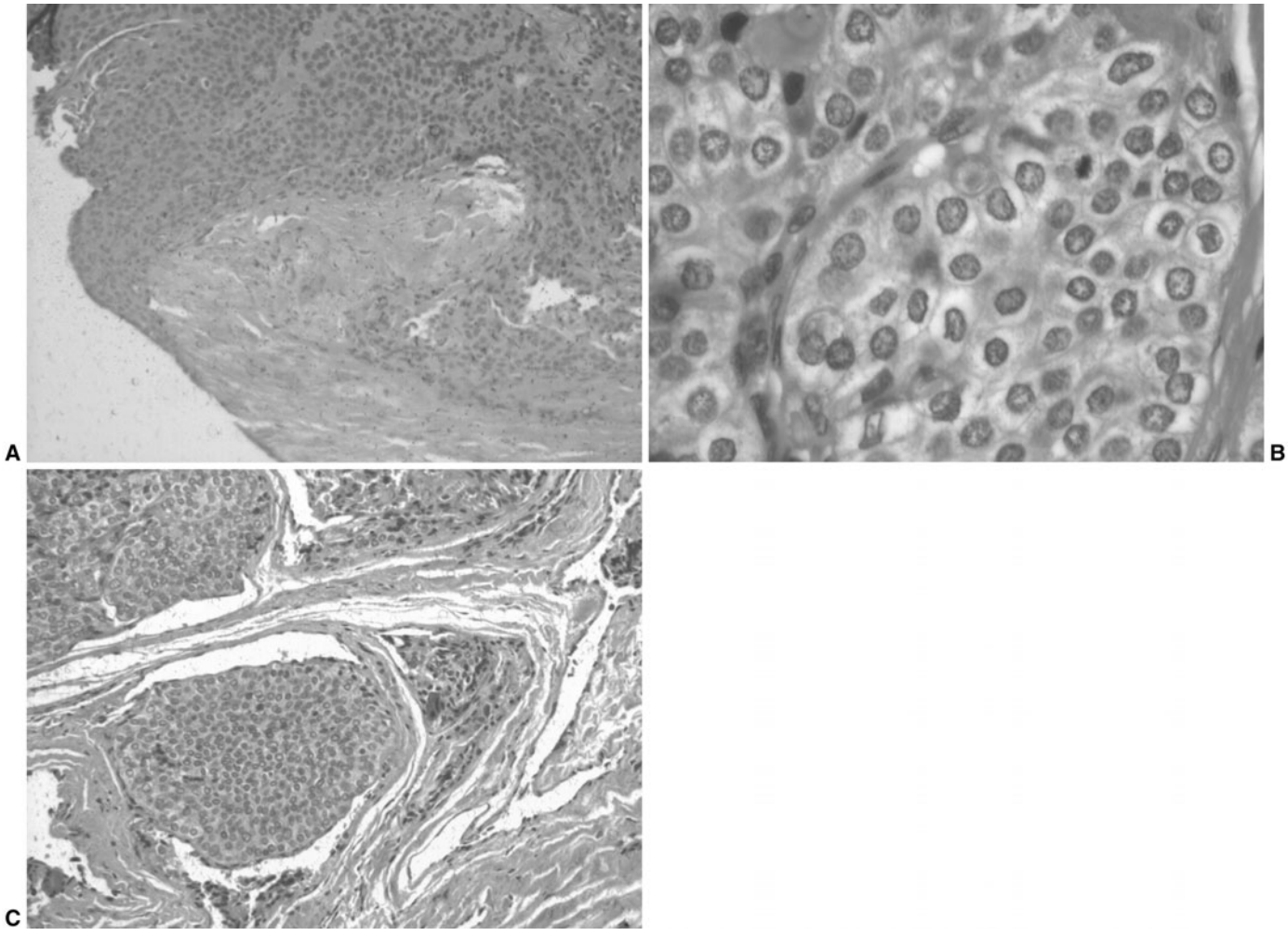

Fig. 1. Microscopic examination of the resected specimen showed capsular invasion (**A**; hematoxylin–eosin, ×200), mitotic figures (**B**; hematoxylin–eosin, ×400), and vascular invasion (**C**; hematoxylin–eosin, ×200)

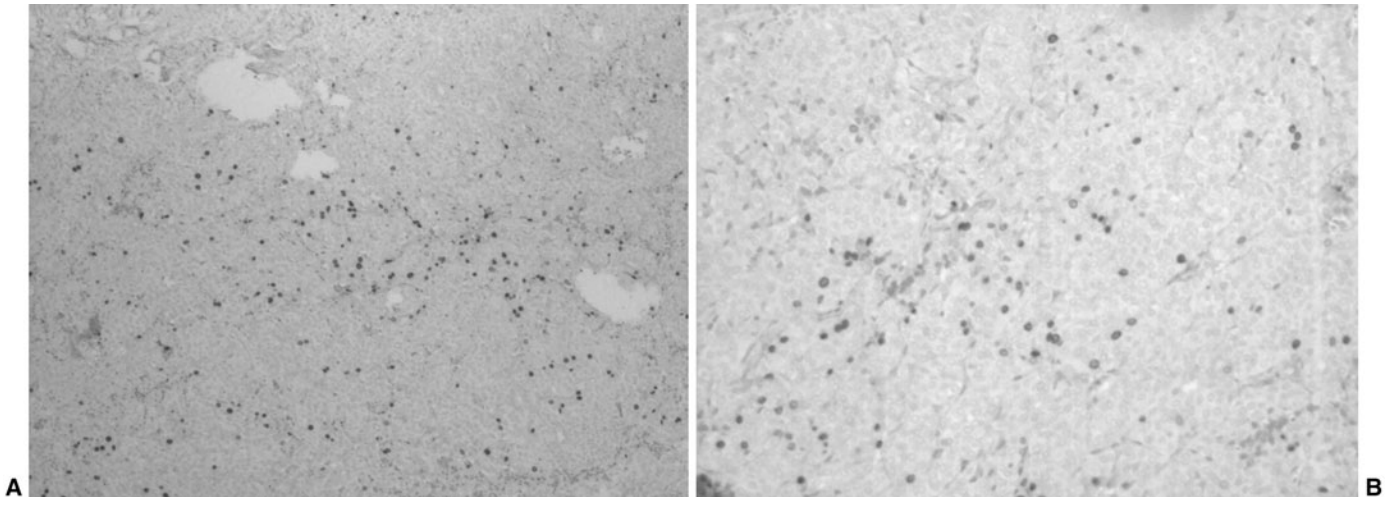

Fig. 2. Immunohistochemical staining of the resected specimen revealed cell cycle-associated antigen Ki-67 positivity, around 12 cells per high magnification field (**A**) and D1 cyclin positivity (**B**)

monitoring showed increasing PTH and serum total calcium levels, followed by a decline in phosphorus levels. The PTH reached a value as high as 1178 pg/ml. The patient again became symptomatic, complaining of bone pain and weak limbs. Cervical ultrasonography showed two well-delineated hypoechogenic oval images, each measuring 0.8 cm and located near the lower left thyroid lobe. However, cervical, thoracic, and abdominal computed tomography (CT) scans were unremarkable. Sestamibi scintigraphy was performed three times after surgery, but it was only on the last examination that we detected a hypercaptation area adjacent to the lower left thyroid lobe, finally defining the localization of the tumor recurrence. No distant metastasis was found. Thus, we performed a second operation using a gamma probe to help identify the tumor, after administering 25 mCi (925 MBq) of ^{99m}Tc-MIBI radioisotope about 3 h before the procedure. Adherences between the tissues were found, with involvement of the strap muscles and esophagus. A small fat-like tissue between the internal jugular vein and carotid artery was appointed by the gamma probe and sent for frozen section. Histopathologic examination revealed a mitotic pattern and nuclear atypia. We performed a left thyroid lobectomy, skeletonization of the trachea, excision of the surrounding strap muscles, and left neck lymph node dissection. After identifying and preserving the left recurrent laryngeal nerve, the gamma probe demonstrated a hypercaptation area inside the en bloc-dissected neck content, even 5 h after the radioisotope injection. This area corresponded to a purple nodule, which was later confirmed as parathyroid carcinoma. After surgery, the patient's PTH level was 147 pg/ml, and again the bone pain resolved, but there was some residual hoarseness. Pathology revealed one hyperplastic parathyroid gland, designated the upper left parathyroid, and disseminated PC cells throughout the tissues, with strap muscle commitment, but a normal thyroid lobe. No lymph node involvement was identified. Four months after the last procedure, the patient still had high PTH levels and persistent hoarseness.

Discussion

Most knowledge of parathyroid carcinoma is based on case reports and retrospective studies. Parathyroid carcinoma is a rare neoplasm that develops in 0.1%–5% of patients with primary hyperparathyroidism.[1–13] The National Cancer Database registered 286 cases treated in the United States between 1985 and 1995, representing an incidence of 0.005% of all registered cancer cases in the United States during that period.[10,14]

The etiology is unknown and until now, there was no evidence that parathyroid adenoma predisposes to parathyroid carcinoma.[11] Most PCs are irregular, and they are frequently described as lobulated and surrounded by a dense, fibrous, grayish-white capsule that adheres to adjacent tissue and makes the tumor difficult to separate from contiguous structures.[4,5,7,10,15] They usually reach 3 cm in diameter, and may be palpable.[5,14] In one series, 48% of the parathyroid tumors were found in the lower left parathyroid gland and the remainder were distributed equally among the other parathyroids.[8] Other studies, however, have described a lower right gland predominance.[16,17] Local invasion is common, with involvement of the ipsilateral thyroid lobe in 89%, strap muscles in 71%, recurrent laryngeal nerve in 26%, esophagus in 18%, and trachea in 17%.[5,8] Lymph node metastasis is present in 15%–32% of parathyroid carcinomas at the time of presentation, and around 30% of patients have distant metastases, usually to the lung and bone.[4,5,7,14,18]

Differentiating between adenoma and carcinoma may be difficult. Schantz and Castleman proposed the following histological diagnostic criteria to differentiate PC from adenomas: the presence of a fibrous capsule or fibrous trabeculae, the presence of mitotic figures, trabecular or rosette-like cellular architecture, and capsular or blood vessel invasion.[1] A retrospective analysis indicated that invasion, a fibrotic capsule, and nuclear atypia were the best malignant histology predictors.[8] Other studies showed that the most valuable single criterion to differentiate these tumors was the presence of mitoses in parenchyma cells.[1,5,19] However, mitotic activity may also be seen in adenomas and hyperplastic glands.[2,7] Immunohistochemical staining for retinoblastoma protein, cell cycle-associated antigen Ki-67 and PTH may be used, but is of limited value.[5,7] Recently, mutations in *HRPT2*, the gene responsible for hyperparathyroidism with jaw-tumor syndrome, has been related to sporadic PC.[20]

Parathyroid carcinomas can be classified as functioning or nonfunctioning. The majority of these tumors are functioning, producing raised levels of serum PTH, as well as calcium. Image examinations include ultrasonography, CT, magnetic resonance imaging (MRI), and ^{99m}Tc-sestamibi. For neck tumor detection, ultrasonography has 57% sensitivity,[15] and sestamibi shows 85% and 95.5% sensitivity and specificity, respectively.[5,10] Whitson and Broadie reported that a combination of different image exams can increase tumor localization accuracy.[21] Although not specific for malignancy, sestamibi scanning is also an excellent modality to detect distant metastasis.[10] Fine-needle aspiration cytology biopsy is not recommended because it does not preclude a diagnosis of carcinoma and it carries a potential risk of needle track seeding.[5,10–12]

Treatment is mainly surgical; however, about 25% of PCs are not recognized by the surgeon during surgery, making the decision about more extensive resection dif-

ficult.[4,5,18] Hence, some investigators have reported inadequate initial surgical resection in about 86% of patients.[4,14] Frozen-section analysis is of little value, especially for well-differentiated lesions, because it is often difficult to distinguish between adenomatous, hyperplastic, and malignant lesions.[5,7,9,13] Frozen section was not helpful in our patient. The most effective treatment is en bloc resection of the primary lesion. This procedure involves ipsilateral thyroid lobe resection, reducing the risk of tumor cell spillage and achieving better local disease control, lower recurrence rates, increased survival rates, and resolution of symptoms related to tumor and hypercalcemia.[1,3,4,7–9,11,12,14,15] This surgical procedure has a 50% cure rate.[7,18] Koea et al. reported a 10% local failure rate and 90% long-term survival rate.[8] However, some authors reported that radical or prophylactic neck dissection does not improve survival but that it increases morbidity.[4,16,19] Thus, although aggressive treatment is advised by some authors, there is still doubt about its results for tumors with locoregional extension found at initial surgery. Moreover, persistently elevated serum calcium levels have been reported even after en bloc resection.[8]

Another challenge in the treatment of PC involves its management when diagnosed after initial simple parathyroidectomy, which is associated with a recurrence rate of 50% and increased mortality of 46% versus en bloc resection.[8,10] Fujimoto et al. suggested reoperation only when recurrence has become obvious.[6] Even after primary curative resection, the recurrence rate is higher than 50%, usually occurring within 2–3 years.[1,4,7,10] Because of the high recurrence and mortality rates, another surgical procedure after initial simple parathyroidectomy should be an option when considering curative resection.

Recurrence rates range between 33% and 78% [5,10,12,15,19] and surgery remains the most effective treatment for recurrent disease.[5,7,8,10–13,19] However, reoperation is rarely curative in the long term and is associated with surgical complications.[4,12] Medical management of hypercalcemia includes calcimimetics (cinacalcet HCL) and bisphosphonates.[4] We found only one case report documenting the use of a gamma probe in surgery for PC.[22] The PC was recurrent and the gamma probe was a success. We described how we performed a major resection guided by hand-held probe, diminishing complication risks and optimizing tumor cell resection, placing an implant between the internal jugular vein and the carotid artery. Unfortunately, nests of small tumor cells may not have been found by gamma probe during surgery.

Until recently, radiotherapy was considered ineffective.[5,7,8,15,19] However, there are now some reports of satisfactory results with adjuvant radiotherapy treatment,[2,3,10,11] although there is insufficient evidence to support the use of radiation therapy as standard adjuvant treatment. Chemotherapy for parathyroid carcinoma is usually ineffective.[4,8,9,11,14]

Some studies have shown survival rates of 85.5% and 49% at 5 and 10 years, respectively.[7,14,16] Another study attributed 5- and 10-year survival rates of 85% and 77%, respectively, to better medical support and hypercalcemia control.[2]

In summary, PC is a rare disease, which is difficult to diagnose and treat. The use of a gamma probe to guide tumor resection is not well documented in the literature, and further reports are needed. Continued reporting and discussion are important for improving our understanding of PC and establishing the best treatment for this cancer.

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