

Case Report

Ectopic secretion of parathyroid hormone in a neuroendocrine tumor: a case report and review of the literature

Emad Kandil¹, Salem Noureldine¹, Mohamed Abdel Khalek¹, Philip Daroca²; Paul Friedlander³

¹Division of Endocrine and Oncologic Surgery, Department of Surgery; ²Department of Pathology, Tulane University School of Medicine, New Orleans, LA; ³Department of Otolaryngology; Tulane University School of Medicine, New Orleans, LA, USA.

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Abstract: Very few cases have been reported in which the production and secretion of intact PTH by a non-parathyroid tumor has been authenticated. This paper describes the case of a 73 year old white female with a clinical and biochemical profile characteristic of primary hyperparathyroidism. Sestamibi scan and comprehensive neck ultrasonography failed to localize a cervical lesion. Because the clinical manifestations were striking, neck exploration was performed. Dissection of the central compartment identified a lesion. PTH levels dropped to normal within ten minutes after its removal. Intraoperative parathyroid hormone assays facilitated the successful surgical removal of the lesion. Pathological examination yielded a diagnosis of a neuroendocrine tumor. These results document the ectopic production of intact PTH by a neuroendocrine tumor and present a novel neoplastic cause of primary hyperparathyroidism. This is the second report of an ectopic neuroendocrine tumor in the head and neck which secreted intact PTH.

Keywords: Ectopic neuroendocrine tumor, ectopic PTH, primary hyperparathyroidism, intraoperative PTH assays

Introduction

Primary hyperparathyroidism is a common disease, with approximately 100,000 new cases per year in the United States [1]. The majority of cases are sporadic, and only a small number of patients have a hereditary component [2]. The underlying abnormality in sporadic hyperparathyroidism is typically a single hyper-functioning adenoma that produces an inappropriately high level of parathyroid hormone (PTH) relative to the serum calcium [2]. Hyperplasia, multiple gland adenoma, and parathyroid carcinoma follow in order of decreasing incidence [3]. Surgical intervention is the mainstay of treatment, providing relief of symptoms and improving patients' overall quality of life while correcting the underlying metabolic complications [4, 5].

Recent decades have seen a shift away from the traditional bilateral four gland exploration toward a less invasive approach [6]. Improvements in pre-operative radiological localization studies and the use of intra-operative PTH assays have facilitated this change [7-9]. Initial studies have demonstrated that the focused

approach has an equivalent rate of complications as well as of persistent and recurrent disease when compared to bilateral cervical exploration [6, 10]. Preoperative parathyroid Tc-99 sestamibi scintigraphy routinely identifies specific areas of overactive parathyroid [11]. Secondly, intraoperative parathyroid hormone levels are measured as a baseline immediately after induction of anesthesia, before excision, and 10 minutes after excision of parathyroid tissue. If the initial excision is not sufficient to adequately lower serum PTH levels [12], the surgeon can take more tissue until the hormone levels fall to an appropriate level. Intraoperative PTH assays have replaced tissue analysis by frozen section and provided a more effective screen for surgical success [8].

The current approach to the surgical treatment of primary hyperparathyroidism is based on the concept that hypercalcemia associated with increased levels of intact PTH is limited to primary parathyroid lesions, rather than production by an ectopic source. This paper proves this concept incorrect by describing a hypercalcemic patient whose increased PTH secretion was due

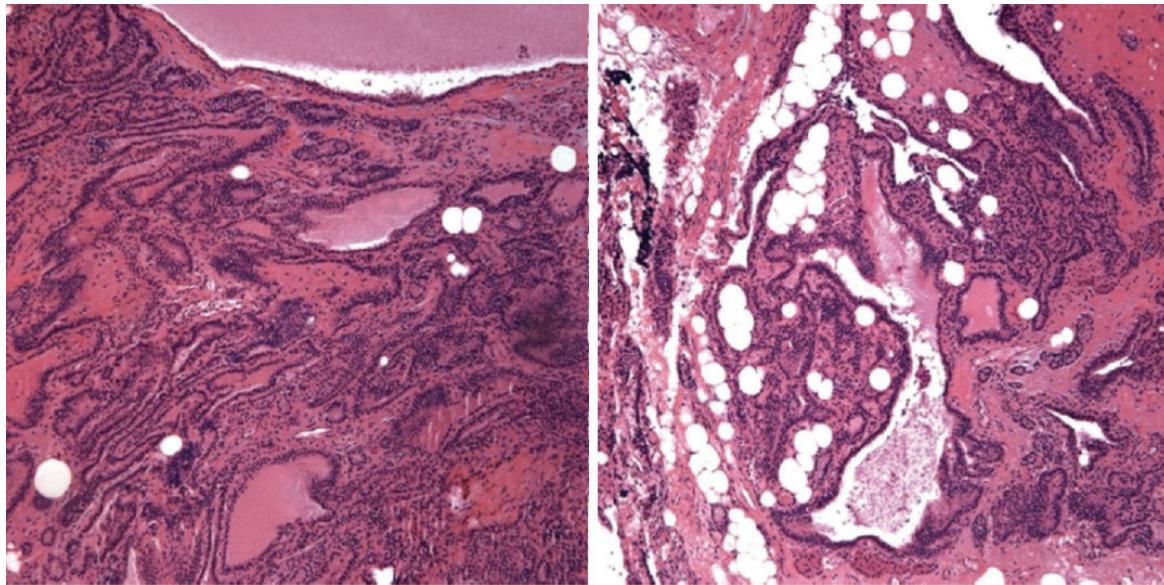


Figure 1. The lesion is unencapsulated multicystic endocrine tissue admixed with fat. Foci of definitive parathyroid tissue are also identified within the lesion.

to an ectopic neuroendocrine tumor in the neck.

Case description

A 73 year old white female was referred to Tulane University Medical center endocrine surgery clinic, for surgical management of recurrent primary hyperparathyroidism. She previously underwent left thyroid lobectomy and parathyroid surgery at age 31. No records were available from her surgery 42 years ago. The patient had history of multiple hospitalizations for nephrolithiasis. She complained of depression and recent onset of fatigue. Her past medical history also included osteopenia treated with Fosamax and Boniva as well as hypertension. Preoperative laboratory data included elevated levels of intact PTH (126 pg/ml) and calcium (10.6 mg/dl). There was no evidence of bone metastasis or increase in parathyroid hormone-related protein. Preoperative sestamibi scan and comprehensive neck ultrasonography failed to localize a source of the disease. A 1.1 cm hypoechoic nodule was identified in the right thyroid lobe. Fine aspiration cytology under ultrasound guidance was performed and revealed evidence of a benign thyroid nodule.

Bilateral neck exploration was performed. The patient's baseline PTH was 93 pg/ml. Normal parathyroid tissue was found on the left side and confirmed on frozen section. Exploration of

both carotid sheaths failed to identify ectopically-located parathyroid tissue. Completion thyroidectomy was performed with removal of the right thyroid lobe because of the possibility of intrathyroidal parathyroid [13, 14]. Intraoperative PTH level increased to 126 pg/ml. Dissection of the right central compartment identified a 1.5 cm lesion in the thyrothymic ligament behind the right sternoclavicular joint. The lesion weighed 520 mg. PTH levels dropped to 12 pg/ml ten minutes after removal of the lesion. Frozen section analysis revealed evidence of a multicystic neuroendocrine tumor, with no parathyroid tissue. The diagnosis of a functional parathyroid lipoadenoma was also considered. The operation was considered successful because of a sufficient fall in intraoperative PTH levels. Postoperative pathological examination of the specimens confirmed the presence of unencapsulated multicystic endocrine tissue admixed with fat (**Figure 1**). Foci of normal parathyroid tissue were also identified within the lesion which exhibited diffuse cytoplasmic staining for parathyroid hormone and diffuse strong immunohistochemical cytoplasmic staining for chromogranin A. (**Figure 2A and B**). A remote and separately sampled parathyroid gland was histologically normal.

The patient's postoperative course was uneventful and she was discharged home after an overnight stay. Since the operation, she has

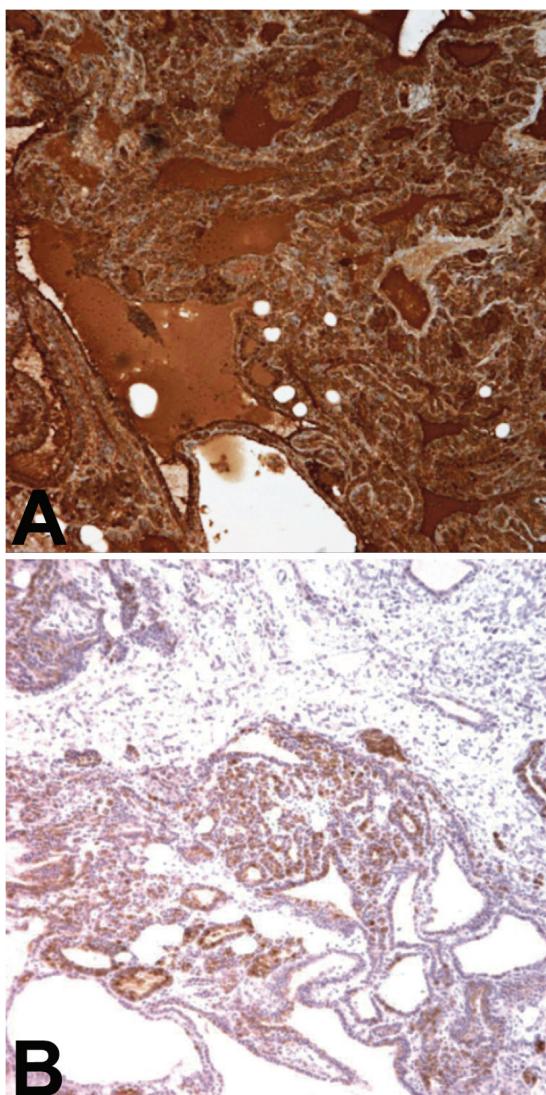


Figure 2. **A.** Diffuse strong cytoplasmic staining for chromogranin by immunohistochemistry; **B.** Diffuse cytoplasmic staining for parathyroid hormone by immunohistochemistry.

been asymptomatic and had no further episodes of nephrolithiasis. She has also felt significantly more energetic. At six months follow up, the patient continued to be eucalcemic with serum calcium levels of 8.0 mg/dl.

Discussion

Albright [15] first proposed that humoral factors produced by cancer cells increased bone resorption and impaired renal calcium excretion. PTH was initially implicated as the hypercalcemic agent. However, after the identification and

cloning of PTH-related peptide [16], subsequent studies demonstrated an essential role for this molecule, and not PTH, as the primary mediator of tumor-induced hypercalcemia.

Primary hyperparathyroidism has classically been defined as overactivity of one or multiple parathyroid glands. Hypercalcemic patients may present with a variety of health problems, including renal stones, osteoporosis, bone fractures, acute pancreatitis, hypertension, headache, polydipsia, dizziness, transient paralysis, gout, peptic and duodenal ulcers, and psychiatric symptoms [17]. Most patients, however, remain asymptomatic. Surgical resection of abnormal tissue provides the only known cure to hyperparathyroidism and is often the method of treatment in symptomatic hyperparathyroidism patients [18].

Hypercalcemia is commonly observed in patients with cancer and bone metastases. Humoral hypercalcemia of malignancy is defined as hypercalcemia associated with a malignant tumor and induced by the production of a hypercalcemic factor by the tumor cells. PTH-related peptide is now considered to be its mediator [16], rather than parathyroid hormone (PTH). Levels of the PTH-related peptide are increased in the serum of most patients with squamous carcinoma [19], and through its binding to a common receptor for PTH and PTH-related peptide, it produces the biochemical features of hyperparathyroidism [20]. Immunoradiometric assays for PTH can distinguish between patients with humoral hypercalcemia of cancer and those with primary hyperparathyroidism, despite the structural homology between the amino termini of the two hormones [21]. Typically, in this syndrome, plasma PTH-related peptide and cyclic AMP levels are elevated, while plasma PTH and active vitamin D₃ levels are suppressed. The once well-accepted and central role of PTH-related peptide in mediating the process of breast cancer metastasis to bone has been disproved [22, 23]. In these cases, the hypercalcemia is secondary to direct bone resorption and release of calcium and phosphorus into the blood stream. The concept of ectopic-PTH-producing tumors in patients without bone metastasis has been suggested, but this idea has been rejected since PTH-related peptide has been identified. Cases of malignant tumors associated with high plasma PTH levels should be suspected as malignant tumors in patients with primary hyperparathyroidism. The

Table 1. Cases in the literature reporting ectopic PTH secretion in the head and neck

Authors	Year	Ectopic PTH Origin
Demura et al [33]	2010	Medullary Thyroid Carcinoma
Morita et al [34]	2009	Papillary Thyroid Carcinoma
Bhattacharya et al [35]	2006	Cervical Paraganglioma
Wong et al [36]	2005	Nasopharyngeal rhabdomyosarcoma
Iguchi et al [37]	1998	Papillary Thyroid Adenocarcinoma
Strewler et al [31]	1993	Non-parathyroid Malignancy
Samaan et al [38]	1983	Squamous Tonsil Carcinoma

Table 2. Cases in the literature reporting ectopic PTH secretion in the thorax:

Authors	Year	Ectopic PTH Origin
Botea et al [39]	2003	Lung Carcinoma
Uchimura et al [24]	2002	Lung Carcinoma
Nielsen et al [40]	1996	Lung Carcinoma
Rizzoli et al [41]	1994	Thymoma
Yoshimoto et al [42]	1989	Lung Carcinoma
Schmelzer et al [43]	1985	Lung Carcinoma
Palmieri et al [44]	1974	Squamous cell carcinoma of lung (renal metastasis)
Palmieri et al [44]	1974	3 cases of Squamous cell carcinoma of lung

diagnosis of an ectopic-PTH-producing tumor should be made only after primary or secondary hyperparathyroidism have been ruled out [24].

Batsakis and colleagues [25] classified neuroendocrine tumors as peripheral primitive neuroectodermal tumors. They can generally be classified into two categories [26], an organ-specific group arising from neuroendocrine organs such as pituitary gland, thyroid, pancreas, and adrenal gland, and a group which arises from diffuse neuroendocrine cells (Kulchitsky cells) widely distributed throughout the body and concentrated in the pulmonary and gastrointestinal systems [27]. Neuroendocrine tumors contain dense neuroendocrine secretory granules and express specific hormones or proteins that can be detected by immunohistochemistry [28]. Chromogranin A and neuron-specific enolase are commonly expressed in neuroendocrine neoplasms [29, 30], and these two proteins are generally included in the immunohistochemical panel to diagnose neoplasms with neuroendocrine differentiation [26].

Although they are rare, a few cases of hypercalcemia due to ectopic intact PTH production have been described in previous reports. They originate in the head and neck (**Table 1**), thorax (**Table 2**), gastrointestinal tract (**Table 3**), and female urogenital system (**Table 4**). Strewler

and colleagues [31] described the first patient with hypercalcemia and elevated levels of intact PTH which originated from a neuroectodermal tumor in the neck. The remaining lesions which caused hypercalcemia associated with elevated levels of intact PTH were malignancies from solid organs.

This paper reports a patient with elevated serum PTH concentrations caused by ectopic production of this hormone by a neuroendocrine tumor in the neck found during neck exploration. Pathological examination of the lesion confirmed the diagnosis of a neuroendocrine tumor. Using immunohistochemistry, the tumor stained positive for PTH (**Figure 2B**), which confirmed the ectopic PTH secretion by the tumor. After removal of the lesion, the patient's serum PTH and calcium levels decreased to normal.

Conclusion

It is often difficult to control humoral hypercalcemia associated with malignant tumors. The most effective treatment is surgical resection of the lesion [32]. This case demonstrates the challenge surgeons face in managing recurrent disease and highlights the rare phenomenon of a neuroendocrine tumor causing recurrent hyperparathyroidism. These results support the ectopic production of intact PTH by a neuroen-

Table 3. Cases in the literature reporting ectopic PTH secretion in the GI tract and pelvis

Authors	Year	Ectopic PTH origin
VanHouten et al [45]	2006	Pancreatic Malignancy
Mahoney et al [46]	2006	hepatocellular carcinoma
Koyama et al [32]	1999	Liver Carcinoma
Arps et al [47]	1986	Pancreatic Endocrine Tumor
Mayes et al [48]	1984	Rhabdoid Kidney Tumor
Grajower et al [49]	1976	Esophageal carcinoma
Robin et al [50]	1976	Small intestine leiomyosarcoma
Deftos et al [51]	1976	Gastric Carcinoid
Deftos et al [51]	1976	Pancreatic islet cell carcinoma
Palmieri et al [44]	1974	Pancreatic islet Cell carcinoma (Liver metastases)
Palmieri et al [44]	1974	Gall bladder adenocarcinoma (Liver metastases)

Table 4. Cases in the literature reporting ectopic PTH secretion in gynecological and other sites.

Authors	Year	Ectopic PTH Origin
Ohira et al [52]	2004	Ovarian carcinoma
Buller et al [53]	1991	Adenosquamous Endometrium Carcinoma
Nussbaum et al [54]	1990	Ovarian Carcinoma
Palmieri et al [44]	1974	Malignant Melanoma
Mavligit et al [55]	1971	Breast carcinoma (Liver metastasis)

docrine tumor and indicate a novel neoplastic cause of hyperparathyroidism.

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Disclosure

Conflict of Interest: None

Address correspondence to: Dr. Emad Kandil, Department of Surgery, Tulane University School of Medicine Tel: 504.988.7407; Fax: 504.988.4762; Email: ekandil@tulane.edu

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