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Case Report

Parathyroid Carcinoma Presented as a Consumptive Syndrome with Diarrhea

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Abstract

Parathyroid carcinoma (PC) is a rare condition in which severe hypercalcemia is frequently associated with a palpable cervical mass. The great challenge in diagnosis is the differentiation of PC from other benign conditions that present with hyperparathyroidism, mainly when unusual symptoms highlight several features. We report a case of a 49-year-old male who complained of diarrhea, non-intentional 20 kg weight loss and low back pain. A palpable nodule was discovered at the left pole of the thyroid gland. Neck ultrasound revealed a 4 cm cervical mass. Laboratory tests showed serum calcium of 17.1 mg/dL, PTH of 2627 pg /mL and serum phosphate of 1.96 mg/dL. En bloc tumor excision with ipsilateral thyroid lobectomy was performed. Progressive improvement in clinical and laboratory conditions were observed. Follow-up at year 2 showed normal serum calcium levels and improvement of quality of life.

Keywords: Parathyroid carcinoma; Hypercalcemia; Hyperparathyroidism; Diarrhea; Consumptive syndrome

Introduction

Parathyroid Cancer (PC) is the least commonly seen endocrine malignancy worldwide. Similar to other causes of primary hyperparathyroidism, PC induces symptoms by an excessive, autonomous release of Parathyroid Hormone (PTH) and severe hypercalcemic related features. Despite its rarity, unusual symptoms like gastrointestinal disturbances and neurocognitive issues may be masking the diagnosis. The objective of this report is to describe the importance of high clinical suspicion associated to a detailed physical examination in order to reveal cervical masses, and to perform an *en bloc* resection that represents the only chance for cure.

Case Presentation

We present the case of a 49-year-old male first admitted to the ER unit with a history of joint pain, difficulty in walking, weakness of both lower limbs for 3 months. He also complained of nausea, episodes of diarrhea and a 20 kg unintentional weight loss. His medical and family histories were unremarkable and he was not on any drugs. On physical examination he was awake, alert, and seemed well oriented to time and place and not confused on general questioning. He was also afebrile, not pale or icteric. A painless, smooth, fibro-elastic, non-adherent, 4 cm nodule was palpable at the left lobe of the thyroid gland. He presented an unsteady gait and the neurologic examination was intact except for a delay in the relaxation phase of the deep tendon reflexes. There was some tenderness on abdominal palpation, mainly on the right hypochondrial and lower thoracic regions with no joint swelling, warmth, or effusion. Laboratory studies showed a PTH level of 2627 pg/mL (12 pg/mL-88 pg/mL), serum calcium of 17.1 mg/dL (8.8 mg/dL-10.3 mg/dL), phosphate of 1.96 mg/dL (3.5 mg/dL-4.5 mg/dL). Calcidiol level was at 24 ng/mL (20 ng/mL-30 ng/mL), and he showed an elevated alkaline phosphatase of 558 U/L (50 U/L-120 U/L). Serum creatinine, albumin and urea were within normal range. Laboratory workup to investigate unintentional weight loss was also unremarkable. He was managed with intravenous rehydration, pamidronate and loop diuretics. A cervical ultrasound identified a heterogeneous 4.0 cm left cervical mass with a regular outline, presenting gross calcifications, fibrous echogenic layers and sharing a cleavage plane with the thyroid. Skull (Figure 1), chest and abdominal CT (Figures 2 and 3) scan also showed trabecular bone reabsorption, innumerable expansive osteolytic bone masses on bilateral iliac wings, acetabulum, and ribs. Calyceal renal lithiasis (< 10mm) on both kidneys were also detected. The case was defined as a primary hyperparathyroidism with tumor etiology and the cervical mass excision via exploratory cervicotomy was proposed. He was referred for surgery after calcitriol (2 mcg/day) and a 3-day colecalciferol (50.000 IU/d) supplementation. During exploratory surgery of the neck, a large 4 cm tumor of the left upper parathyroid gland was found, firmly adhered to the ipsilateral sternocleidomastoid muscles. Central node compartment dissection and en bloc resection of the parathyroid mass was performed. On gross inspection, the 4.0 cm × 3.5 cm × 3.0 cm tumor presented with a greyish-brown hue and a fibrous-elastic capsule. Final histopathology, however, revealed a parathyroid carcinoma, characterized by enlarged uniform hyper chromatic nuclei, prominent nucleoli dimension, with capsular and vascular space invasion and 3 mitotic figures per mm^2. Immunohistochemical (IHC) staining showed tumor expression of CD31, ERG, GATA-3, Ki-67, and PTH. While thyroglobulin, thyroid transcription factor-1 and chromogranin-A yielded negative. There was immediate decrease of intact PTH to 325 pg/mL 6 hours after surgery, and on the seventh Postoperative Day (POD) intact

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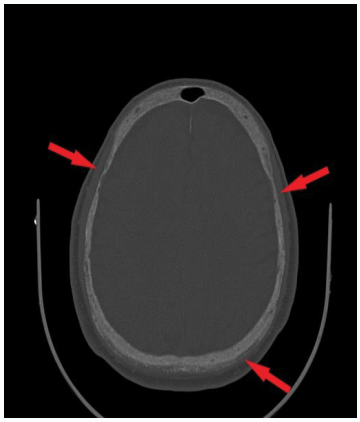

Figure 1: Loss of definition of the inner and outer plates of the skullcap, associated with diffuse bone demineralization with a ground-glass appearance.

PTH returned to the normal range (26 pg/mL). Hypocalcemia, hypophosphatemia and hypomagnesaemia developed from POD 1. The electrolyte abnormalities were treated with a combination of IV and oral calcium and magnesium, as well as calcitriol. He became asymptomatic and was discharged on POD 42 on a normal diet with 3 g/d of calcium carbonate oral supplementation and calcitriol. At a 2-month follow-up the patient gained 4 kg and was asymptomatic. At a 2-year review his serum calcium, calcidiol, magnesium, phosphate and PTH levels had returned to normal levels without supplementation. These characteristics are summarized in Table 1. The patient is currently under follow-up. Informed consent was obtained from the patient for this case report.

Discussion

Parathyroid carcinoma (PC) is an endocrine malignancy and until recently has been regarded as an exceedingly rare condition. It may occur sporadically or as a part of a genetic syndrome including hyperparathyroidism jaw tumor syndrome (HPT-JT), MEN1, MEN2A, and isolated familial hyperparathyroidism [1]. PC is a slow-growing tumor of low malignant potential related to gene mutations on HRPT2/CDC73, a tumor suppressor gene that encodes parafibromin [2]. CDC73 germline mutations occur in 20-40% of patients with sporadic PC and may reveal unrecognized HPT-JT [3]. Our understanding of the molecular pathogenesis of parathyroid tumors has significantly increased over the last two decades. Conversely, we are still lacking the identification of clinical and laboratory markers capable of predicting the outcome of patients [4]. The preoperative diagnosis of PC can be extremely challenging. It only becomes evident if during the exploratory surgery adherence to

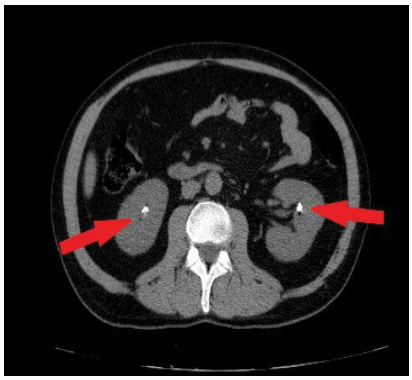

Figure 3: Bilateral non-obstructive nephrolithiasis up to 10 mm.

adjacent structures is found [5]. No single laboratory finding is a definitive diagnostic of PC. However, hypercalcemia above 15 mg/dL and PTH level 10 times the upper limit of the normal range have a positive predictive value of 81% [6]. A solid malignancy diagnosis of a parathyroid lesion is based on histological analysis when invasion of vascular, adjacent structures or distant metastasis are detected [1]. PC symptoms and signs are generally associated with high calcium and extremely high PTH levels. Patients are more likely to be symptomatic at the time of diagnosis, and usually present renal colic, painful joints or lower back pain, nausea, constipation, abdominal pain and neuromuscular complaints, such as weakness and fatigue [6]. Most frequent digestive manifestations in hyperparathyroidism are constipation, heartburn, nausea and appetite loss that occur in 33%, 30%, 24% and 15% of cases, respectively [7]. Interestingly, in this case, the patient's main complaint was about diarrhea, which first made us suspicious of a gastrointestinal pathology. Diarrhea and steatorrhea are frequently related to hypoparathyroidism, not hyperparathyroidism [8]. The exact pathophysiological mechanism is not fully understood. However, hypocalcemia is reported to drive insufficient endogenous cholecystokinin release by the duodenal mucosa during a meal stimulus, leading to gallbladder relaxation and inadequate pancreatic enzyme secretion [9]. It is noteworthy that calcium administration has been prescribed and considered effective in "halting" viral and parasitic diarrhea in children [10]. In human adult volunteers calcium supplementation can reduce the severity and duration of bacterial diarrhea caused by *Escherichia coli* [11]. Thus, if calcium administration is considered a general anti-diarrheal agent, one might assume that low calcium levels are bad to digestion. Alterations in gene expression secondary to mildly sustained stimulation of PTH receptor in parathyroid adenomas or hyperplasia are believed to indirectly

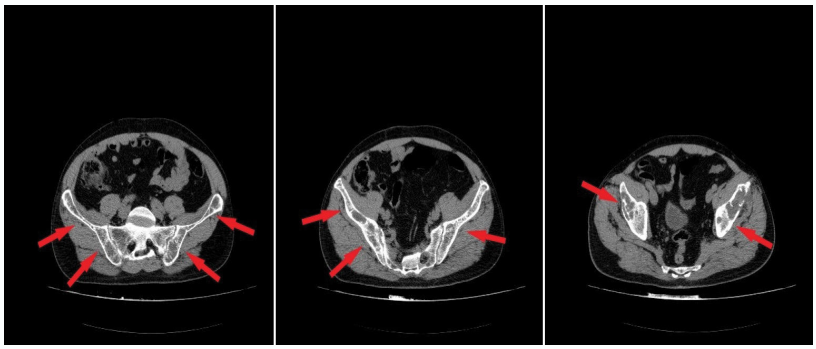

Figure 2: Diffuse osteolytic lesions with an insufflative appearance on bilateral iliac bone wing.

Table 1: Summary of laboratory investigation at admission, surgery-related management and at follow up.

	tCa (mg/dL)	iCa (mg/dL)	$(PO_4)^{3-}$ (mg/dL)	Mg^{2+} (mg/dL)	PTH (pg/mL)	25(OH) VD (ng/mL)
Admission	17.1	9.2			2627.0	24.0
Preoperative	13.7**	7.4**	2.35	1.30		
Postoperative	9.0		1.56	1.06	325.0	36.0
POD 1	7.4		1.46	1.90		
POD 4	9.0	4.9	1.59	1.06		
POD 7	7.1	4.1	1.46	1.92	26.0	36.3
POD 12	7.5	4.3	2.05	2.28		
POD 42*	8.8		1.96	1.52		
Follow up (10m)	9.3		2.90	2.40	35.0	28.6
Follow up (18m)	9.4		3.10	1.90	36.0	29.5
Follow up (24m)	9.1		2.30		57.0	

tCa: total calcium (n.v. 8.8 - 10.3 mg/dL); iCa: ionized calcium (n.v. 4.6 - 5.4 mg/dL); $(PO_4)^{3-}$: phosphate (n.v. 2.5 - 4.8 mg/dL); Mg: magnesium (n.v. 1.6 – 2.4 mg/dL); PTH (n.v. 12 - 88 pg/mL); 25(OH) VD (n.v. 20 - 60 ng/mL).

* hospital discharge

** post pamidronate

explain the nausea and obstipation complaints [7]. As a result, also in a state of mild hypercalcemia, calmodulin, a calcium binding protein, regulates smooth muscle cell responses to neurogenic inputs and causes smooth muscle contraction, translating in a gut atonic state. Both mechanisms can explain obstipation in 66.7% of the subjects with serum calcium >11.5 mg/dL. They were reported as having fewer than 3 evacuations per week compared to 9.1% of the studied patients that evacuate 1 or more times a day [12]. Indeed, people with high-calcium diets or taking excessive calcium are often constipated as are patients with hypercalcemia [13]. In the light of the present case, we propose that a direct exposure to chronic and higher levels of PTH, higher than those seen in adenomas and parathyroid hyperplasia, may pose to some adaptive mechanisms. We should keep in mind that PTH is not only a calcium absorption enhancer but also promotes transport of other ions, e.g., potassium, chloride and bicarbonate, across the intestinal epithelium [14]. Therefore, PTH, a pleiotropic hormone that maintains mineral homeostasis, is also essential for controlling pH balance and ion transport across renal and intestinal epithelial [14]. Its action, directly on the basolateral side of enterocytes, in a non-calciotropic path, regulates anion secretion through a Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) [15]. Recently, not only PTH but also calcitonin have been implicated in intestinal chloride secretion, an important player in body fluid homeostasis and diarrhea [16]. A new class of drugs, the guanylate cyclase-C receptor agonists (GC-Cra), acting through CFTR has revealed a therapeutic potential in treating GI disorders, including chronic idiopathic constipation and irritable bowel syndrome–constipation [17]. CFTR, when activated by GC-Cra, induces epithelial cells to secrete Cl^- and HCO_3^-, inhibits Na^+ absorption, and thus promotes intestinal water secretion. As a proof of concept, when listing side effects of the 2 recently FDA approved GC-Cra use in chronic constipation – Linaclotide and Plecanatide - diarrhea scored the most [18]. Another possible mechanism that could be disrupted by chronic elevated PTH levels in PC and malignant leveled hypercalcemia involves the extracellular calcium-sensing receptor (CaSR). CaSR is a highly conserved G protein-coupled cell surface receptor (GPCR). However, CaSR is an unusual GPCR. Not only senses calcium but also uses extracellular nutrients (e.g., polyamines, certain amino acids and peptides) as its ligands [19]. Some studies predict that over-activation of CaSR may contribute to constipation whereas under-activation of CaSR may contribute to diarrhea [20]. To corroborate those hypotheses, recent studies in knockout mice ($CaSR^{-/-}$) showed a marked increase in expression of IL-1β, TNF-α, INF-γ, IL-6, IL-12 [21]; similar changes in expression of those factors were also noted *in vitro* in cultured colonic epithelial cells [22]. Taking all this together, it is tempting to assume that the consumptive syndrome our patient presented is also a disruptive endocrine disease. In the period the patient was recovering from surgery, rapid postoperative decrease of PTH levels and prolonged hypocalcemia, most likely due to 'hungry bone syndrome', were also correlated with the improvement of his gastrointestinal complaints. Resuming regular daily bowel movements just after surgery may reveal the success of the treatment and another main evidence that the disease was confined to the neck. Although our patient has been free of the disease for 2 years, the high recurrence rate of PC is expected to be up to 49%–60% of cases after the initial operation. Accordingly to the newest edition of the American Joint Committee on Cancer guidelines PC staging system our patient is classified as T1 (tumors are localized to the parathyroid gland with extension limited to the soft tissue), N0 (Lymph node disease absent) and M0 (no distant metastatic disease is described). Since the panel showed a demonstrable difference in cancer-specific survival between patients with disease localized to the neck and those with distant metastatic disease, we could stage our patient as low risk PC. Opposing to our optimism, Silva-Figueroa combining adverse variables into a prognostic scoring system, stratified patients into 3 risk groups of recurrence-free survival (RFS) rates: low (0 variable; 2-year RFS rate, 93%), moderate (1 variable; 2-year RFS rate, 72%), and high (2 variables; 2-year RFS rate, 27%) [23]. Older age (>65y), higher serum calcium before surgery (>15 mg/dL) and the presence of vascular invasion correlated with shorter periods of remission with more frequent relapses of the disease. Taking this score into account, our patient would have been classified as a high risk, with only a 27% chance of being disease free 2 years after the tumor removal. In addition to studies evaluating remission survival rates a panel of IHC markers may prove most useful as an adjunct in the evaluation of challenging parathyroid tumors [4] In this case, expression of parathyroid hormone instead of thyroglobulin, and thyroid transcription factor-1 can help differentiate parathyroid from thyroid tissue. Chromogranin A also known as a parathyroid secretory protein 1, is specific but not sensitive for neuroendocrine cells. GATA-3 expressions as well as Ki-67 add value to the diagnosis of carcinoma since both markers are common to many other neoplasms [24]. Neither specific IHC signature nor a reliable prognostic scoring system stratification of patients are available.

Since, the most common relapse pattern after the initial surgery is local recurrence and distant metastases (e.g., lung, bone and liver metastases), this patient being free of disease up to now may be due to an early identification, appropriate initial surgery, medical treatment for hypercalcemia and correct management of "hungry bone syndrome".

Conclusion

PC is a challenging hypersecreting malignant tumor that can be presented by unusual symptoms, like diarrhea, and its treatment is primarily surgical. We describe a case in which the main complaint was related to malabsorption leading to relevant weight loss. Adequate management of hypercalcemia at the diagnosis and of hunger bone syndrome after surgery, are important goals in reducing mortality. Intensive surveillance will be considered here since male patients in whom preoperative serum calcium levels are >15 mg/dL and tumors that demonstrate vascular invasion are more prone to disease recurrence.

References

1. Sharretts JM, Simonds WF. NIH Public Access. 2011;24;491-502.
2. Wang O, Wang C, Nie M, Cui Q, Guan H, Jiang Y, et al. Novel HRPT2/CDC73 Gene Mutations and Loss of Expression of Parafibromin in Chinese Patients with Clinically Sporadic Parathyroid Carcinomas. PLoS One. 2012;7(9):e45567.
3. Cardoso L, Stevenson M, Thakker R. Molecular genetics of syndromic and non-syndromic forms of parathyroid carcinoma. Hum Mutat. 2017;38(12):1621-48.
4. Cetani F, Marcocci C, Torregrossa L, Pardi E. Atypical parathyroid adenomas: Challenging lesions in the differential diagnosis of endocrine tumors. Endocr Relat Cancer. 2019;26(7):R441-R464.
5. Leonard-Murali S, Ivanics T, Kwon DS, Han X, Steffes CP, Shah R, et al. Local resection versus radical surgery for parathyroid carcinoma: A National Cancer Database analysis. Eur J Surg Oncol. 2021;47(11):2768-73.
6. Machado NN, Wilhelm SM. Parathyroid Cancer: A Review. Cancers (Basel). 2019;11(11):1676.
7. Kandil E, Alabbas H, Tufaro AP, Carson KA, Tufano RP, Kandil E, et al. The impact of baseline intact parathyroid hormone levels on severity of primary hyperparathyroidism and outcomes in patients undergoing surgery. Arch Otolaryngol Head Neck Surg. 2010;136(2):147-50.
8. Abboud B, Daher R, Boujaoude J. Digestive manifestations of parathyroid disorders. World J Gastroenterol. 2011;17(36):4063-6.
9. Cheng SX. Calcium-sensing receptor: A new target for therapy of diarrhea. World J Gastroenterol. 2016;22(9):2711-24.
10. Sayyahfar S, Sadeghian M, Amrolalaei M. The effect of calcium on the duration of acute gastroenteritis in children: A randomized clinical trial. Med J Islam Repub Iran. 2021;35:83.
11. van Hoffen E, Mercenier A, Vidal K, Benyacoub J, Schloesser J, Kardinaal A, et al. Characterization of the pathophysiological determinants of diarrheagenic Escherichia coli infection using a challenge model in healthy adults. Sci Rep. 2021;11:6060.
12. Ragno A, Pepe J, Badiali D, Minisola S, Romagnoli E, Severi C, et al. Chronic constipation in hypercalcemic patients with primary hyperparathyroidism. Eur Rev Med Pharmacol Sci. 2012;16(7):884-9.
13. Kim S, Park E, Park J. Effects of Calcium Fortified Beverage Intake on Insulin Sensitivity and Antioxidant Metabolism in Healthy Elderly. Clin Nutr Res. 2021;10(4):303-13.
14. Laohapitakworn S, Thongbunchoo J, Nakkrasae LI, Krishnamra N, Charoenphandhu N. Parathyroid hormone (PTH) rapidly enhances CFTR-mediated HCO3-secretion in intestinal epithelium-like caco-2 monolayer: A novel ion regulatory action of PTH. Am J Physiol Cell Physiol. 2011;301(1):C137-49.
15. Jantarajit W, Lertsuwan K, Teerapornpuntakit J, Krishnamra N, Charoenphandhu N. CFTR-mediated anion secretion across intestinal epithelium-like Caco-2 monolayer under PTH stimulation is dependent on intermediate conductance K+ channels. Am J Physiol Cell Physiol. 2017;313(1):C118-C129.
16. Tang L, Jiang L, McIntyre ME, Petrova E, Cheng SX. Calcimimetic acts on enteric neuronal CaSR to reverse cholera toxin-induced intestinal electrolyte secretion. Sci Rep. 2018;8(1):7851.
17. Waldman SA, Camilleri M. Guanylate cyclase-C as a therapeutic target in gastrointestinal disorders. Gut. 2018;67(8):1543-52.
18. Layer P, Stanghellini V. Review article: Linaclotide for the management of irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2014;39(4):371-84.
19. Katie L, Tracy MJ, Andrew NK, Donald TW, Rebecca SM, Hans B. Europe PMC Funders Group International Union of Basic and Clinical Pharmacology XXX : Calcium-sensing receptor Nomenclature, Pharmacology, and Function. Pharmacol Rev. 2020;72(3):558-604.
20. Breitwieser GE. Minireview: The intimate link between calcium sensing receptor trafficking and signaling: Implications for disorders of calcium homeostasis. Mol Endocrinol. 2012;26(9):1482-95.
21. Daniel López, Hera Vlamakis, Richard Losick. Genetics chances NIH Public Access. Bone. 2012;23:1-7.
22. Nishitani Y, Zhang L, Yoshida M, Azuma T, Kanazawa K, Hashimoto T, et al. Intestinal Anti-Inflammatory Activity of Lentinan: Influence on IL-8 and TNFR1 Expression in Intestinal Epithelial Cells. PLoS One. 2013;8(4):e62441.
23. Silva-Figueroa AM, Hess KR, Williams MD, Clarke CN, Christakis I, Graham PH, et al. Prognostic Scoring System to Risk Stratify Parathyroid Carcinoma. J Am Coll Surg. 2017;S1072-7515(17)30179-5.
24. Cakir B, Polat SB, Kilic M, Ozdemir D, Aydin C, Süngü N, et al. Evaluation of preoperative ultrasonographic and biochemical features of patients with aggressive parathyroid disease: Is there a reliable predictive marker? Arch Endocrinol Metab. 2016;60(6):537-44.