A case report of a patient with parathyroid carcinoma and a CDC73 germline mutation

Nuno Cordeiro Raposo[1]*, Nádia Mourinho Bala[2], Sónia Pratas[2], Cristina Valadas[2]

European Journal of Medical Case Reports
Volume 5(12):341–344
https://doi.org/10.24911/ejmcr/173-1629190180

ABSTRACT

Background: Parathyroid carcinoma (PC) is an uncommon cause of primary hyperparathyroidism (pHPT). Mutations of the cell division cycle protein 73 homolog (CDC73) gene are associated with both sporadic and familial pHPT and PC, including hyperparathyroidism-jaw tumor (HPT-JT) syndrome.

Case Presentation: A 38-year-old man presented with severe hypercalcemia and acute renal injury due to pHPT. He had a palpable left cervical mass of 50 mm, characterized by both ultrasound and ^{99m}Tc-sestamibi scintigraphy as an enlarged hyperfunctioning parathyroid gland. Histological diagnosis after parathyroidectomy was of PC. During follow-up patient developed metastasis of the skin, mediastinal lymph-nodes, and lungs. Even after surgical excision of all detectable metastasis parathyroid hormone (PTH) remained elevated. Genetic analysis found a germline mutation (c.766_767delGT) of the CDC73 gene, which was not previously reported in PC.

Conclusion: Germline CDC73 analysis may be considered in HPT-JT syndrome, familial isolated pHPT, PC, and young individuals with pHPT.

Keywords: Parathyroid carcinoma, hyperparathyroidism, CDC73 mutation, case report.

Received: 17 August 2021 **Accepted:** 02 December 2021 **Type of Article:** CASE REPORT **Specialty:** Endocrinology

Correspondence to: Nuno Cordeiro Raposo
*Assistant Physician of Endocrinology, Department of Endocrinology, Hospital Beatriz Ângelo, Loures, Portugal.
Email: nunofilipecordeiroraposo@gmail.com
Full list of author information is available at the end of the article.

Background

Parathyroid carcinoma (PC) is a rare cause of primary hyperparathyroidism (pHPT) and represents only 0.005% of all cancers [1]. Given its rarity there is a relative paucity of literature regarding pathogenesis of PC. It may occur sporadically or as a part of a genetic syndrome, such as multiple endocrine neoplasia type 1 (MEN1) and type 2a (MEN2a), hyperparathyroidism-jaw tumor (HTP-JT) syndrome, and isolated familial HPT [2,3].

HPT-JT syndrome (OMIM phenotype number #145001) is a rare autosomal dominant familial cancer syndrome of variable and incomplete penetrance, which ensues from inactivating germline mutation of the cell division cycle protein 73 homolog (CDC73) gene that encodes a tumor suppressor protein known as parafibromin [4]. CDC73 gene, previously known as hyperparathyroidism type 2 gene, is mutated in over 80% of patients with HPT-JT syndrome and up to 15% of patients with HPT develop PC [5]. More than 100 germline mutations have been reported in HPT-JT syndrome, of which 50% were frameshift deletions or insertions [6]. Here we present a case of PC in a patient with a CDC73 frameshift mutation (c.766_767delGT) that was previously reported in pHPT [7] but not in PC.

Case Presentation

We present a 38-year-old man who was admitted to the emergency room for myalgia, arthralgia, dehydration, and left cervical swelling with 18 months' progression. Previous history included non-specific cervical surgery at infancy for unknown reasons and since then he had no clinical surveillance.

Patient had a short stature (158 cm) and had large cysts on both his elbows and arms. Physical examination also revealed a large left cervical nodule that was stiff and adhering to adjacent structures.

Lab analysis confirmed pHPT [PTH = 1,953 pg/ml (reference values = 14.0-72.0 pg/ml)] with severe hypercalcemia [corrected calcium for serum albumin = 19.1 mg/dl (reference values = 8.5-10.1 mg/dl)] and acute renal injury [creatinine = 3.6 mg/dl (reference values = 0.7-1.3 mg/dl)]. Cervical ultrasonography revealed a heterogeneous hypoechogenic nodule of 66 × 31 mm next to the left thyroid lobe. There were no enlarged cervical lymph-nodes and thyroid structure was homogenous. These features were confirmed on computed tomography (CT) scan, which confirmed a right displacement of the trachea. The nodule was compatible with hyperfunctioning parathyroid tissue on ^{99m}Tc-sestamibi scintigraphy.

After stabilization of calcium levels with intravenous hydration and zoledronic acid, patient was submitted to left parathyroidectomy, with monitoring of intra-operative PTH levels (4,678 pg/ml at $t = 0$ and 470 pg/ml at $t = 20$ minutes). The histological diagnosis was PC with 55 mm and direct invasion of adjacent skeletal muscle (pT3 cN0 cM0).

In order to maintain normal serum calcium after surgery patient received oral calcium supplementation for three years. During this time PTH was elevated (100-200 pg/ml) but stable and there was no evidence of disease recurrence on imaging tests. Kidney function remained stable [creatinine = 1.63 mg/dl; glomerular filtration rate [estimated by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) equation] = 51.9 ml/minute/1.73 m^2)], and symptoms of muscle and joint aches were reduced.

Regarding the possibility of familial PC, prolactin, plasma metanephrines, gastrin, calcitonin, and chromogranin A were evaluated and were all normal. Genetic analysis of the CDC73 gene found an heterozygotic frameshift mutation (c.766_767delGT) that leads to a premature stop codon and a truncated protein. The patient was referred to a genetic specialist and first-degree family members were evaluated for the gene mutation. The results are unknown at the time of writing.

Five years after surgery patient presented with recurrent pHPT (PTH = 1,145 pg/ml and corrected calcium for serum albumin = 15.7 mg/dl) and cervical examination revealed a subcutaneous left cervical nodule. Cervical ultrasonography exposed a 12 mm subcutaneous non-pure cyst over the scar of previous parathyroidectomy, whose fine needle aspiration confirmed it was a metastasis of PC. Full staging was performed with CT scan, which confirmed the presence of diffuse bilateral pulmonary nodules, and one large lymphadenopathy of the anterior mediastinum with 27 × 18 × 34 mm. Patient was referred to surgery: excision of subcutaneous metastasis and bilateral atypical pulmonary resection with mediastinal lymphadenectomy (Figure 1). PTH and calcium levels were controlled after surgical treatment (Figure 2) and the patient is under active surveillance.

Timeline

Discussion

PC has a low incidence of 1.5 per 1,000 and men and women are equally affected [1].

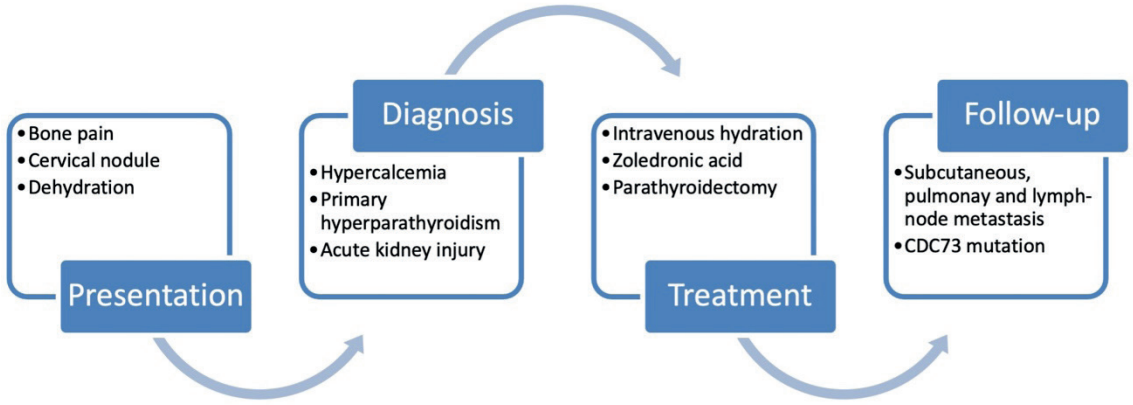

Figure 1. *Timeline of the case report.*

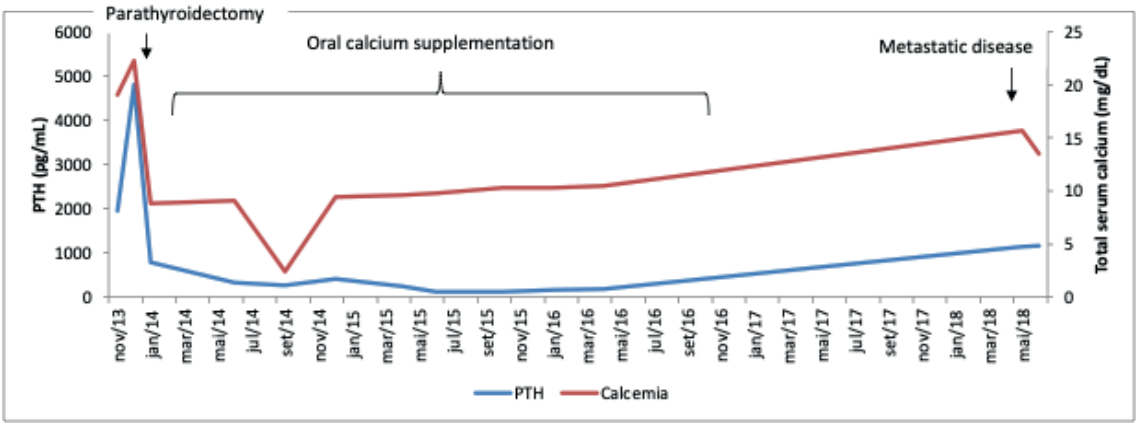

Figure 2. *PTH and total calcium corrected to serum albumin evolution since diagnosis of pHPT.*

Most patients with PC present with pHPT and a large parathyroid lesion [8]. However, there are no reliable clinical diagnostic criteria and histological examination is indispensable [9]. Neck ultrasound may reveal a parathyroid lesion and ^{99m}Tc-sestamibi scintigraphy shows a hyperfunctioning parathyroid nodule, but these techniques cannot distinguish preoperatively a PC from a benign parathyroid tumor [8,9]. Fine-needle aspiration cytology should not be performed because it cannot distinguish a benign from a malignant lesion and may be associated with tumoral seeding [10].

Clinical manifestations are related to pHPT and its consequences (nephrolithiasis, nephrocalcinosis, reduced renal function, osteopenia, pathologic fractures, bone pain, peptic ulcer, and pancreatitis) [11,12]. Fatigue, malaise, polydipsia, polyuria, nausea, vomiting, abdominal pain, and constipation may also occur [9]. Physical examination may reveal a neck mass and osteitis fibrosa cystica are related to long-standing uncontrolled pHPT, as was described in our patient [5].

The etiology of PC is not completely understood, but risk factors include external radiation exposure and specific genetic defects [9]. Familial PC is associated with HPT-JT syndrome, MEN1, MEN2a and familial isolated HPT [2-4]. However, sporadic cases are more common and up to 70% of those are associated with CDC73 mutations [13].

CDC73 is a tumor suppressor gene, located at 1q31, that encodes parafibromin [6]. Parafibromin has a role in the control of cell proliferation, apoptosis, and chromosome stability [14]. CDC73 mutations that lead to a loss/reduction of parafibromin expression are associated with HPT-JT syndrome and sporadic PC [15]. HPT-JT syndrome is an autosomal dominant disorder characterized by parathyroid tumors and ossifying fibromas of the maxilla and/or mandible [6]. Renal and uterine tumors may also occur [16]. Parathyroid tumors are often uniglandular and affect 95% of individuals, 15% of which develop PC [8]. Thirty-eight germline mutations are linked to familial PC and most of them are frameshift mutations, followed by nonsense and missense mutations [6]. Here we present the first case of PC related to a specific frameshift mutation (c.766_767delGT), that leads to premature stop codon and a truncated parafibromin.

Surgery is the standard of care, with *en bloc* resection of the primary lesion, and excision of adjacent ipsilateral thyroid lobes and of the adjacent involved structures [5]. Recurrences occur in >50% of patients with PC [9]. Surgery remains the first option for local recurrences and lymph node metastasis in the neck and mediastinum [1]. Surgical excision of distant metastasis is also indicated when possible [17]. Postoperative adjuvant radiation therapy is not routinely recommended, and its efficacy is not established in PC [9]. Chemotherapy for systemic disease is often unsuccessful on arrest of disease progression and control of hypercalcemia [8]. Saline infusion and loop diuretics may ameliorate hypercalcemia, but calcium-sensing receptor agonists, such as cinacalcet, are often needed in metastatic disease [5].

Negative prognostic factors are age older than 65 years, serum calcium level >15 mg/dl, and vascular invasion [18]. Five-year survival range from 85% to 91% and 10-year survival from 49% to 87.6% [18]. Patients with metastatic disease and tumors >3 cm have worse cancer-specific survival [19]. CDC73 mutations-related PC may have a less favorable clinical outcome (more frequent locoregional recurrences and shorter survival interval), reflecting the potential benefit of testing all patients with newly diagnosed PC [20].

Conclusion

PC is a rare cause of pHPT but should be considered in patients with severe hypercalcemia and large parathyroid mass. Surgical excision is the mainstay in the management of PC and close lifelong follow-up is necessary. Genetic screening for CDC73 germline mutations should be contemplated in patients with suspected HPT-JT syndrome, familial isolated pHPT, PC, and young individuals with pHPT [16]. Patient's family members may be offered genetic counselling [16].

What is new

PC is a rare cause of pHPT and mutations of the CDC73 gene are associated with a poorer prognosis. The authors describe a novel mutation of the CDC73 gene in a patient with a metastatic advanced PC.

List of Abbreviations

CDC73	Cell division cycle protein 73 homolog
HPT-JT	Hyperparathyroidism-jaw tumor
MEN1	Multiple endocrine neoplasia type 1
MEN2a	Multiple endocrine neoplasia type 2a
PC	Parathyroid carcinoma
pHPT	Primary hyperparathyroidism

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this case report.

Funding

None.

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

Author details

Nuno Cordeiro Raposo[1], Nadia Mourinho Bala[2], Sonia Pratas[1], Cristina Valadas[1]

1. Assistant Physician of Endocrinology, Department of Endocrinology, Hospital Beatriz Ângelo, Loures, Portugal.
2. Resident of Endocrinology, Department of Endocrinology, Hospital Beatriz Ângelo, Loures, Portugal.

References

1. Cetani F, Pardi E, Marcocci C. Parathyroid carcinoma. Front Horm Res. 2019;51:63–76. https://doi.org/10.1159/000491039
2. Simonds WF. Genetics of hyperparathyroidism, including parathyroid cancer. Endocrinol Metab Clin North Am. 2017;46(2):405–18. https://doi.org/10.1016/j.ecl.2017.01.006
3. Cetani F, Saponaro F, Borsari S, Marcocci C. Familial and hereditary forms of primary hyperparathyroidism. Front Horm Res. 2019;51:40–51. https://doi.org/10.1159/000491037
4. Gill AJ. Understanding the genetic basis of parathyroid carcinoma. Endocr Pathol. 2014;25(1):30–4. https://doi.org/10.1007/s12022-013-9294-3
5. Salcuni AS, Cetani F, Guarnieri V, Nicastro V, Romagnoli E, de Martino D, et al. Parathyroid carcinoma. Best Pract Res Clin Endocrinol Metab. 2018;32(6):877–89. https://doi.org/10.1016/j.beem.2018.11.002
6. Newey PJ, Bowl MR, Cranston T, Thakker RV. Cell division cycle protein 73 homolog (CDC73) mutations in the hyperparathyroidism-jaw tumor syndrome (HPT-JT) and parathyroid tumors. Hum Mutat. 2010;31(3):295–307. https://doi.org/10.1002/humu.21188
7. Cavaco BM, Guerra L, Bradley KJ, Carvalho D, Harding B, Oliveira A, et al. Hyperparathyroidism-jaw tumor syndrome in Roma families from Portugal is due to a founder mutation of the HRPT2 gene. J Clin Endocrinol Metab. 2004;89(4):1747–52. https://doi.org/10.1210/jc.2003-031016
8. Schulte KM, Talat N. Diagnosis and management of parathyroid cancer. Nat Rev Endocrinol. 2012;8(10):612–22. https://doi.org/10.1038/nrendo.2012.102
9. Goswamy J, Lei M, Simo R. Parathyroid carcinoma. Curr Opin Otolaryngol Head Neck Surg. 2016;24(2):155–62. https://doi.org/10.1097/MOO.0000000000000234
10. Xue S, Chen H, Lv C, Shen X, Ding J, Liu J, et al. Preoperative diagnosis and prognosis in 40 parathyroid carcinoma patients. Clin Endocrinol (Oxford). 2016;85(1):29–36. https://doi.org/10.1111/cen.13055
11. Ryhänen EM, Leijon H, Metso S, Eloranta E, Korsoff P, Ahtiainen P, et al. A nationwide study on parathyroid carcinoma. Acta Oncol. 2017;56(7):991–1003. https://doi.org/10.1080/0284186X.2017.1306103
12. Ferraro V, Sgaramella LI, Di Meo G, Prete FP, Logoluso F, Minerva F, et al. Current concepts in parathyroid carcinoma: a single centre experience. BMC Endocr Disord. 2019;19(Suppl 1):46. https://doi.org/10.1186/s12902-019-0368-1
13. Guarnieri V, Battista C, Muscarella LA, Bisceglia M, de Martino D, Baorda F, et al. CDC73 mutations and parafibromin immunohistochemistry in parathyroid tumors: clinical correlations in a single-centre patient cohort. Cell Oncol (Dordr). 2012;35(6):411–22. https://doi.org/10.1007/s13402-012-0100-x
14. Ciuffi S, Cianferotti L, Nesi G, Luzi E, Marini F, Giusti F, et al. Characterization of a novel CDC73 gene mutation in a hyperparathyrodism-jaw tumor patient affected by parathyroid carcinoma in the absence of somatic loss of heterozygosity. Endocr J. 2019;66(4):319–27. https://doi.org/10.1507/endocrj.EJ18-0387
15. Gill AJ, Lim G, Cheung VKY, Andrici J, Perry-Keene JL, Paik J, et al. Parafibromin-deficient (HPT-JT type, CDC73 mutated) parathyroid tumors demonstrate distinctive morphologic features. Am J Surg Pathol. 2019;43(1):35–46. https://doi.org/10.1097/PAS.0000000000001017
16. van der Tuin K, Tops CMJ, Adank MA, Cobben JM, Hamdy NAT, Jongmans MC, et al. CDC73-related disorders: clinical manifestations and case detection in primary hyperparathyroidism. J Clin Endocrinol Metab. 2017;102(12):4534–40. https://doi.org/10.1210/jc.2017-01249
17. Rozhinskaya L, Pigarova E, Sabanova E, Mamedova E, Voronkova I, Krupinova J, et al. Diagnosis and treatment challenges of parathyroid carcinoma in a 27-year-old woman with multiple lung metastases. Endocrinol Diabetes Metab Case Rep. 2017;2017:16–0113. https://doi.org/10.1530/EDM-16-0113
18. 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;15: 30179–5. https://doi.org/10.1016/j.jamcollsurg.2017.01.060
19. Lo WM, Good ML, Nilubol N, Perrier ND, Patel DT. Tumor size and presence of metastatic disease at diagnosis are associated with disease-specific survival in parathyroid carcinoma. Ann Surg Oncol. 2018;25(9):2535–40. https://doi.org/10.1245/s10434-018-6559-6
20. Cetani F, Banti C, Pardi E, Borsari S, Viacava P, Miccoli P, et al. CDC73 mutational status and loss of parafibromin in the outcome of parathyroid cancer. Endocr Connect. 2013;2(4):186–95. https://doi.org/10.1530/EC-13-0046

Summary of the case

1	**Patient (gender, age)**	Male, 38-year-old
2	**Final diagnosis**	Parathyroid carcinoma
3	**Symptoms**	Myalgia, arthralgia, left cervical nodule, dehydration
4	**Medications**	Normal saline, zoledronic acid
5	**Clinical procedure**	Parathyroidectomy, excision of subcutaneous and pulmonary metastasis, mediastinal lymphadenectomy
6	**Specialty**	Endocrinology