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CASE REPORT

Challenges in the treatment of parathyroid carcinoma: a case report

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Abstract

Introduction Parathyroid carcinoma (PC) is a rare neoplasm with a high rate of recurrence and an indolent course. It is frequently functional, causing nearly 1% of the cases of primary hyperparathyroidism (HPT), and in some cases, it may be complicated by brown tumors, mimicking bone metastases. Synchronous parathyroid and papillary thyroid carcinomas are rare.

Case report We present a patient with HPT due to PC, misdiagnosed at first evaluation, which exhibited multiple hypermetabolic lytic lesions in the skeleton, suggesting bone metastases. Their regression after PTH reduction suggested the diagnosis of brown tumors due to severe HPT. Given the persistence of HPT, the patient underwent a number of neck surgeries, and a papillary thyroid microcarcinoma with a nodal metastasis was diagnosed. A genetic test discovered a previously unreported mutation of the CDC73 (HRPT2) gene, codifying for parafibromin and resulting in a premature stop codon (c.580A>Tp.Arg194). Because of the persistence of HPT, cinacalcet therapy was started in order to control hypercalcemia.

Conclusion This is a very unusual patient with a newly discovered variant of the CDC73 gene and a phenotype characterized by recurrent PC, brown tumors, and N1a metastasized thyroid carcinoma. The present case confirms that PC may not exhibit clear malignant properties at first assessment, contributing to inadequate initial surgical treatment. Although infrequently, PC can be associated with papillary thyroid cancer. The diagnosis of brown tumor should be considered in patients with severe HPT and multiple destructive bone lesions mimicking metastases on PET/CT imaging.

Keywords Parathyroid carcinoma · Hyperparathyroidism-jaw tumor syndrome · Brown tumors · Papillary thyroid cancer

Introduction

Parathyroid carcinoma (PC) is one of the rarest malignancies, accounting for less than 1% of patients with primary hyperparathyroidism (HPT) [1]. It is difficult to diagnose because of its rarity, absence of clear diagnostic markers, and overlapping clinical features with benign HPT [2]. Frequently, a complete surgical cure is not achieved, and recurrence is common. Prognosis is poor and mortality is usually due to complications of hypercalcemia [3, 4]. High PTH levels are also responsible for osteitis fibrosa cystica characterized by the presence of brown tumors, benign lesions that may mimic bone metastasis [5]. PC may occur sporadically or as a part of a genetic syndrome, such as hyperparathyroidism-jaw tumor syndrome (HPT-JT) characterized by the occurrence of HPT and fibro-osseous tumors of the jaw bones [6].

Coexistence of PC and thyroid carcinoma is extremely rare, with few cases reported in the scientific literature [7]. Here, we report a HPT-JT patient with multiple brown tumors mimicking bone metastases, synchronous PC, and papillary thyroid cancer (PTC) which developed a voluminous ossifying fibroma of the maxilla. To our knowledge, this association has not previously been reported.

Case report

A 42-year-old female was admitted to our clinic, after two surgical procedures performed at other medical centers, for persistent parathyroid carcinoma (PC) complicated by multiple lytic and destructive lesions in the skeleton. Two years before admission to our department, the patient experienced severe asthenia, nausea, and weight loss, together with acute renal failure and severe hypercalcemia (14.7 mg/dl, normal

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range 8.4–10.2); neck ultrasonography exhibited a 40-mm mass contiguous to the right thyroid lobe. The patient underwent parathiroidectomy, and histological diagnosis was an atypical parathyroid adenoma. Because after surgery, PTH persisted at elevated levels, 1 year later, the patient underwent additional surgery, and the histopathological diagnosis was PC with invasion of thyroidal and soft perithyroidal tissues. Postoperative exams revealed low serum calcium (7.9 mg/dl) and high PTH values (399 pg/ml, normal range 12–65), while CT scan showed multiple lytic and destructive lesions in the dorsal column (Fig. 1a), ninth right rib, and right iliac wing (Fig. 1b), suggesting bone metastases. All these bone lesions displayed high uptake at 18FDG-PET (Fig. 1a, b). After the radiological assessment, the patient was admitted to our medical center with a diagnosis of persistent PC with multiple bone metastases. No history of neck irradiation or familiar endocrine disease was reported. Serum laboratory tests at admission showed calcium 7.9 mg/dl, phosphorus 2.3 mg/dl (normal range 2.3–4.7), PTH 410 pg/ml, and vitamin D 9.9 ng/dl (normal range 15–60). Neck ultrasonography revealed residual tumor tissue in the right thyroidal bed and in the isthmus. Treatment with calcium carbonate (3 g/die) and cholecalciferol (800UI/die) was started. After a few days, PTH decreased to 260 pg/ml, while calcium and phosphorus increased to 8.9 and 2.5 mg/dl, respectively. Three months after the previous CT scan, a new radiological evaluation revealed an evident change of the bone lesions, characterized by bone restructuring aspects without the previous lytic features (Fig. 1c). Consistently, 18FDG PET did not show the hypermetabolic lesions previously reported (Fig. 1d). However, hypercalcemia recurred soon and, a few weeks subsequent to hospital discharge, calcium was 10.9 mg/dl, phosphorus 2.2 mg/dl, and PTH 743 pg/ml. Given the persistence of HPT and the spread of local disease, a third neck surgery was performed with resection of residual tumor tissue in the right thyroidal bed and completion thyroidectomy. The PC diagnosis was confirmed (with invasion of adipose and muscle tissues and thyroid isthmus), and an incidental 4-mm papillary thyroid carcinoma (PTC) was found in the left thyroid lobe with a nodal metastasis in the central compartment. The

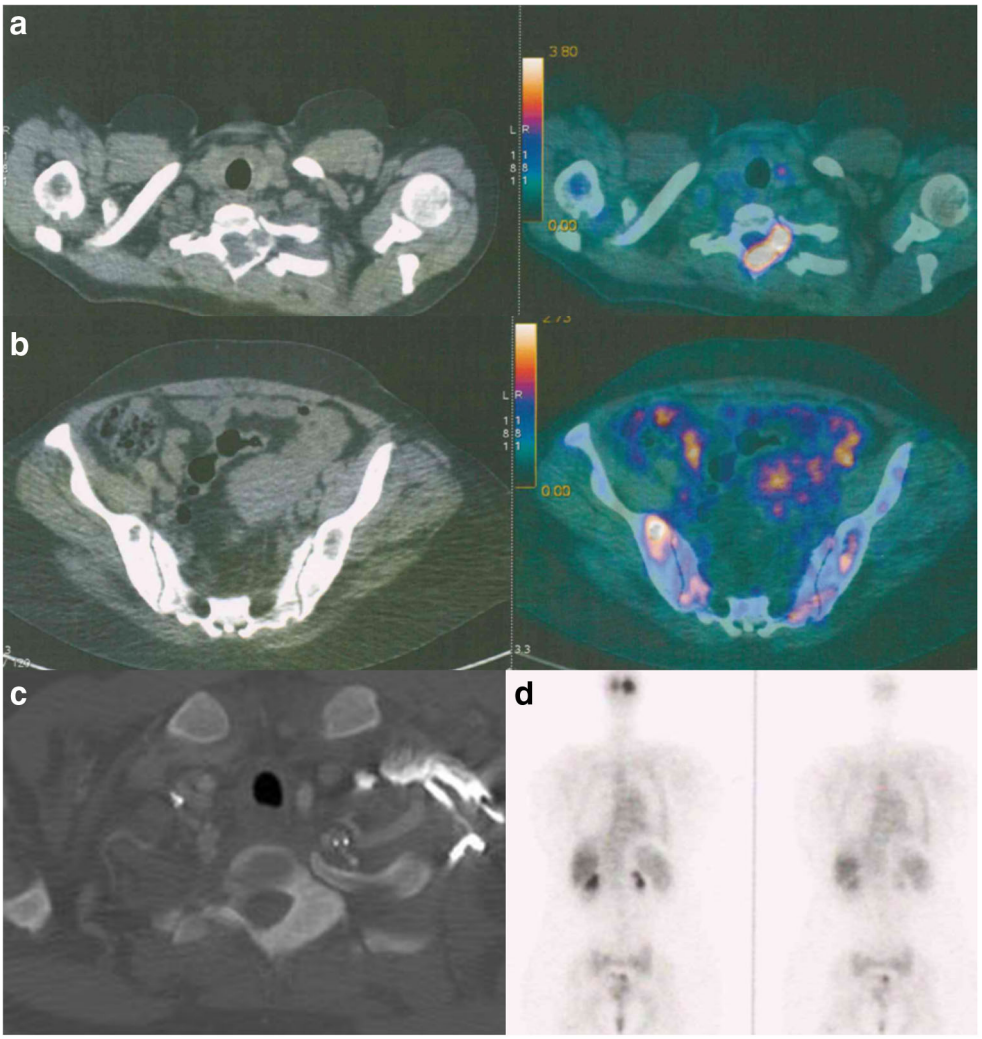

Fig. 1 Initial 18FDG PET/CT scan shows hypermetabolic and lytic bone lesion in D2 (**a**) and in the right iliac wing (**b**). Evident change of aspect of the vertebral lesion, with bone restructuration and absence of lytic features (**c**), and disappearance of uptake of 18FDG in osseous lesions (**d**)

patient underwent radioiodine treatment with 3.7 GBq of 131-iodine and, at subsequent follow-ups, she invariably showed undetectable thyroglobulin levels. To control persistent hypercalcemia, treatment with cinacalcet was started at 60 mg/die. Since serum calcium levels steadily increased during the follow-up (up to 12.9 mg/dl), stepwise dose titration of cinacalcet (up to 270 mg/die) allowed achievement of a stable calcium level between 10.9 and 11.4 mg/dl, but PTH levels still continued to be elevated (469–743 pg/ml). Three months after the last neck surgery, the patient developed a large and rapidly growing maxillary tumor of 50 × 30 × 40 mm in the anterior region of the maxilla. Enucleation of the mass revealed an ossifying fibroma. A genetic test performed on genomic DNA purified from peripheral blood lymphocytes identified a mutation, to our knowledge never reported before, of the CDC73 (HRPT2) gene, which codifies for parafibromin, resulting in a premature stop codon (c.580A>Tp.Arg194). Two additional surgical procedures were performed after 4 and 10 months to remove a metastatic lymph node package of 6 cm on the right side, at level VI of the neck, and a 3-cm retropharyngeal mass. Thereafter, external beam radiotherapy was carried out (cumulative dose 60 Gy). Fifty months following the diagnosis, the patient is alive, with high serum calcium on cinacalcet therapy and persistent structural disease in the neck without distant metastases.

Discussion

We present the case of a woman with HPT-JT, who was affected by PC initially misdiagnosed as atypical adenoma, complicated by brown tumors mimicking diffuse bone metastases, synchronous PTC, and ossifying fibroma of the maxilla.

PC is a rare tumor characterized by a challenging preoperative and pathological diagnosis [1]. Some clinical features may suggest only PC (markedly elevated calcium and PTH levels and palpable neck mass), while differential diagnosis between adenoma and carcinoma is not feasible merely through evaluation of clinical and biochemical features [2, 7]. Histopathological diagnosis of PC is also difficult given that many pathological features (mitotic figures and trabecular architecture) are not unique to PC, being present in benign lesions, while other pathological characteristics, like capsular and vascular invasion or necrosis, are not always present in PC [2].

Recurrence is very common (up to 82% within 5 years), and resection of the primary tumor rarely results in a definitive cure of PC; moreover, multiple surgical procedures are often required, as in our patient's case [3, 4, 8, 9]. Restoration of normocalcemia after surgery indicates that all hyperfunctioning tissue has been removed; however, in the early postoperative period, patients should be strictly monitored because of the risk of symptomatic hypocalcemia due to "hungry-bone syndrome," as was experienced by our patient [3]. Survival rate is < 50% at 10 years and mortality is usually due to complications of hypercalcemia caused by high PTH levels [9]. Medical therapy is the main treatment to manage hypercalcemia, while calcimimetics represent a more effective treatment for controlling this disorder [8, 10].

The severe HPT caused by PC is responsible for osteitis fibrosa cystica, which can affect the whole skeletal system with the presence of brown tumors [5]. The presence of multiple skeletal lytic lesions in a PC patient demands an arduous differential diagnosis between bone metastases and brown tumors. On first observation, our patient manifested severe bone involvement, as revealed by CT scan and FDG-PET images, suspicious for diffuse metastatic disease. Brown tumors are not true neoplasms, but reactive osteolytic lesions related to long-standing HPT and caused by excessive PTH secretion, which stimulates bone resorption, accompanied by fibrovascular replacement. These osteolytic cavities occur in spongiose bone in which hemorrhages and proliferation of soft tissue result in a red-brown elastic mass, known as osteitis fibrosa cystica [5]. Brown tumors display a high uptake of 18FDG in PET, secondary to the presence of giant cells and macrophages, images of difficult interpretation when skeletal lesions are present in PC patients. [11] These lesions have also been reported to be detectable by bone scan and MIBI scintigraphy [12]. The bone lesions tend to recover spontaneously after reduction of PTH levels, and FDG-PET imaging can be useful to monitor response to treatment and the osteoblastic changes in brown tumors [13], as occurred in our patient.

PC may occur sporadically or as a part of genetic syndrome, such as multiple endocrine neoplasia (MEN), familial HPT, and HPT-JT [3, 14]. In our report, the genetic test identified the patient as affected by HPT-JT syndrome, which is an autosomal dominant disease, characterized by the occurrence of HPT and fibro-osseous tumors of the jaw bones [15]. HPT-JT pathogenesis involves a germline inactivating mutation of the HRPT2/CDC73 tumor suppressor gene located on chromosome 1q25-32 encoding a 531 amino acid protein termed parafibromin. This protein is an inhibitor of cellular proliferation via cell cycle arrest, and in HPT-JT syndrome, there is a loss of parafibromin expression and/or function [16]. We found a novel mutation that results in a premature stop codon, which means it is likely pathogenetic. Since about one-third of patients with apparently sporadic PC carry germline mutations in the HRPT2/CDC73 gene, mutation testing is warranted in patients with PC. Moreover, PC is more frequent in HPT-JT patients, occurring in 15% of cases, while about 30–40% of HPT-JT subjects develop ossifying fibroma of the maxilla and mandible [15]. Ossifying fibroma is often misdiagnosed as osteoclastic brown tumors, which may be localized at the same sites and do not regress after reduction of PTH levels [15]. Genetic testing for HRPT2/CDC73 offers important

clinical opportunities, since, in this syndrome, PC shows more aggressive behavior and a higher rate of recurrent/persistent disease; moreover, the presence of comorbidities in these subjects points to the need for jaw imaging studies; finally, the family members of the patient affected with HPT-JT syndrome should be tested for the presence of the germline mutation.

The association between thyroid carcinoma and PC is extremely rare, and only eight cases have been described in the literature [6]. The unicity of our case consists in the synchronicity of PTC and PC in a context of HPT-JT syndrome. In the previous reports, PC was functional with high PTH and calcium levels in 7/8 cases, F:M ratio was 3:1, and papillary/follicular ratio was 7:1. Lymph node metastases from thyroid carcinoma, with the involvement of the central neck compartment (as in our patient), were reported in 2/8 cases [6]. It is difficult to hypothesize the existence of a pathogenetic association between PC and PTC in our patient, and, considering that PTC is the most common endocrine malignancy, its presence could be considered incidental. However, despite its small size, this PTC metastasized to the regional lymph nodes, suggesting aggressive biological behavior. In any case, accurate thyroid imaging before neck exploration for HPT appears to be critical.

The diagnostic and therapeutic difficulties that arose in this case are paradigmatic of the complexities inherent in the management of malignant parathyroid disease.

Compliance with ethical standards

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest The authors declare that they have no conflict of interest.

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