CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 42 (2018) 214–217

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Parathyroid carcinoma: From a case report to a review of the literature

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ARTICLE INFO

Article history:
Received 28 September 2017
Received in revised form
14 November 2017
Accepted 16 November 2017
Available online 22 November 2017

Keywords:
Parathyroid carcinoma
Primary hyperparathyroidism
Endocrine surgery
Oncology

ABSTRACT

INTRODUCTION: Parathyroid carcinoma is a rare endocrine malignancy. The reported incidence is from 0.5 to 5% of primary hyperparathyroidism cases in various series. Consideration of parathyroid carcinoma in the differential diagnosis of hypercalcaemic disorders is important because the morbidity and mortality are substantial and the best prognosis is associated with early recognition and surgical resection.
PRESENTATION OF CASE: We report a case of parathyroid carcinoma occurring in a 60-year-old woman who presented to our institution with persistent hyperparathyroidism and hypercalcemia 3 years after being submitted to one gland parathyroidectomy in another hospital.
DISCUSSION AND CONCLUSION: A review of the related literature follows.

1. Introduction

Parathyroid carcinoma (PC) is a rare endocrine malignancy, which usually accounts for less than 1% of all cases of primary hyperparathyroidism (pHPT) [1]. PC was first described in 1904 by the Swiss surgeon, de Quervain [2] in a patient who presented with a non-functioning lesion, and since then, studies on PC have been published successively in the literature worldwide.

We report, according to the SCARE criteria [32], a case of parathyroid carcinoma in a patient with persistent pHPT and review the related literature.

2. Presentation of case

Our patient was a 60-year-old woman with a previous medical history of primary hyperparathyroidism. She was studied in another hospital, where three years before she had hypercalcemia detected in routine laboratory and underwent a left parathyroidectomy (one gland). Histopathological examination of the gland showed "benign parathyroid tissue".

In a routine control by her family doctor, hypercalcemia with persistent hyperparathyroidism was detected and she was referred to our hospital two years after surgery. She complained of bone disease (osteoporosis), hypertension, constipation, and neuropsychiatric symptoms (irritability and depression). She had no family history of hypercalcemia or metabolic diseases. Physical examination did not reveal any palpable neck masses.

Laboratory data showed increased serum concentrations of parathyroid hormone (PTH; 301 *pg/mL* [normal range, 15–65 *pg/mL*]) and calcium (2,8 *mmol/L* [normal range, 2.09–2.42 *mmol/L*]), phosphorous 0.88 *mmol/L* (normal range, 0.87–1.45 *mmol/L*), albumin 5.12 *g/dL* (normal range, 3.5–5.0 *g/dL*), magnesium 0.9 *mmol/L* (normal range, 0.6–1.1 *mmol/L*). Serum levels of 25-hydroxyvitamin D, creatinine and urea were within normal range.

A neck ultrasonography had been performed, which revealed a thyroid nodule on right lobe with 22 *mm* and an enlarged nodule (35 *mm*) on the posterior face of the left thyroid lobe.

The computed tomography (CT) scan of the neck revealed a heterogeneous mass with approximately 5 cm in diameter, located posterior to the left inferior pole of thyroid gland and extending to the mediastinum – adenoma versus PTC. A ^{99m}Sestamibi-CT scan confirmed increased uptake in the topography of left inferior PT, corresponding to CT scan findings. Therefore, the patient was referred for formal cervical exploration with parathyroidectomy. At surgery, the inferior left PT was a polycystic gland of about 5 cm, adherent to the posterior face of left thyroid and close to the esophagus. The gland was easily dissected from esophagus and *en bloc* removal of the gland with the left thyroid lobe and all involved tissue was performed. The left recurrent nerve was free of disease. There was no gross involvement of regional lymph nodes. A decrease of serum levels of intact PTH of 81% was observed 10 min after removal of the PT (final value of 53 *pg/mL*). Both superior and inferior right PT had normal size and shape and were preserved.

Abbreviations: PC, parathyroid carcinoma; pHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PT, parathyroid; FNA, fine-needle aspiration; CT, computed tomography.

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https://doi.org/10.1016/j.ijscr.2017.11.030

Pathological examination of the PT revealed, on gross inspection, a hard mass measuring $6.5 \times 4 \times 2.5\,cm$ and weighting 26 g. The cut surface was mostly occupied by a heterogeneous whitish nodule, with hemorrhagic and cystic areas. Microscopically, the PT was occupied by a partially encapsulated nodular tumor, with trabecular and pseudo follicular solid pattern. It was composed of uniform cells which variated in size and shape, and areas of thick fibrous bands. It had a low mitotic index (less than 2 mitoses per 10 high-power fields). There was partial capsular invasion with extension to the thyroid and cervical soft tissues. There were also some images that suggested neural and vascular invasion. Based on these findings the diagnosis was a PTC. Free margins (less than 1 *mm*) were found.

Postoperatively, the patient did well, without complication. In the first day after the surgery, PTH and serum calcium had returned to normal levels, 40 *pg/mL* and 2.28 *mmol/L*, respectively. She was discharged home uneventful at the 7th postoperative day.

At 12-month follow-up, the patient is asymptomatic with normal serum calcium.

3. Discussion

The clinical diagnosis of PC is often difficult and is almost always obtained, as in the present case, only after a postoperative histopathological examination.

PC is a rare disease responsible for 0.1% to 5% of cases of pHPT. Higher incidence is seen in Japan, with reports reaching 5%. In Western countries, it is usually responsible for less than 1% of cases of pHPT [3], however, an Italian study has reported a PC incidence of 5.2% in patients operated for pHPT [4].

PC incidence has mostly remained unchanged, with a small increase in the number of patients with mildly symptomatic PC, probably secondary to detection of hypercalcemia on biochemistry analysis [5].

PC is a disease of middle life (fifth decade of life) and occurs equally in men and women [5,6]. This contrasts with benign parathyroid lesions which are more prevalent in women.

The etiology of parathyroid cancer is unknown. There is an increased risk of PC in families with endocrine diseases (such as familial hyperparathyroidism and multiple endocrine neoplasia type 1) [7–10].

Prior neck radiation and end-stage renal disease have been associated with increased incidence of parathyroid cancer [11]

Several different mutations have been implicated in the pathogenesis of parathyroid cancer. These include the retinoblastoma (Rb), p53, breast carcinoma susceptibility (BRCA2) and cyclin Dl/parathyroid adenomatosis gene 1 (PRAD1) genes. None of these have been assigned a primary role in pathogenesis [12].

The overwhelming majority of parathyroid cancers are functioning tumours. Therefore, patients most often present with symptoms and signs of hypercalcaemia, such as fatigue, malaise, weakness, weight loss and anorexia; psychiatric manifestations (i.e. depression) and digestive symptoms (e.g. nausea, vomiting, abdominal pain, peptic ulcer, pancreatitis and constipation), some of them were seen in our patient.

More prominent are symptoms of renal and skeletal involvement. Patients quite often complain of polyuria, renal colic and nephrolithiasis. Bone pain and pathological fractures are also reported.

Most patients manifest evidence of both renal and skeletal involvement at the time of presentation, contrary to benign adenomas.

The clinical criteria for suspicion of malignant parathyroid neoplasm as said by Obara et al., are: (1) age below 55 years; (2) marked hypercalcaemia and hyperparathormonaemia (more than 10 times over the limit); (3) severe bone symptoms (fibrocystic osteitis in 40%–70% of cases) and kidney symptoms (nephrocalcinosis, nephrolithiasis in 30%–60% of cases); (4) recurrent laryngeal paralysis due to tumor invasion; (5) palpable cervical swelling, that is rare in benign disease [3,12]. Up to 50% of patients present with a palpable neck mass related to either advanced local or regional metastatic disease [13].

Although imaging studies (ultrasound, CT scan, MRI, PET) are not definitive in the differential diagnosis between adenoma and parathyroid carcinoma [14], in cases where malignancy is suspected, higher-resolution anatomical studies are of considerable value. Computed tomography (CT) with contrast will provide excellent details on the location of the lesion and its relation with other structures [15] and can also reveal invasion of surrounding structures and enlarged lymph nodes. Magnetic resonance imaging (MRI) with gadolinium and fat suppression will give the best detail on soft tissues of the neck, and can supplement further information, specifically in the setting of preoperative assessment.

Technetium–99 m sestamibi is a lipophilic isotope that is taken up by abnormal parathyroid tissue, preferably attaches to parathyroid tissue due to the inherent high metabolic activity seen within this tissue [16]. However, sestamibi scan is a localization study, and provides little benefit in differentiating benign from malignant parathyroid lesions. Nevertheless, sestamibi scan has been described as useful in diagnosing and localising metastatic parathyroid carcinoma [17].

Fluorodeoxyglucosepositron emission tomography (FDG-PET) has mainly been used in adenoma cases, and very few reports exist on its use in parathyroid carcinoma. A practical point to remember is that the lytic bone lesions (Brown tumours) appear FDG avid on PET. In cases of parathyroid carcinoma, they can be mistaken as bone metastases [18].

Fine needle aspiration cytology is not recommended due to both the high probability of false negatives (which may influence the surgical approach incorrectly) and to the obvious disruption of the neoplastic capsule with subsequent neoplastic spread [16,19].

Laboratory criteria to distinguish parathyroid adenoma from carcinoma are nonspecific.

The average serum calcium level in patients with parathyroid carcinoma is higher (15.9 mg/dL) than that reported in patients with parathyroid adenomas (12 mg/dL). Only 10 per cent of patients with carcinoma had serum calciums of less than 13 mg/dL and 75% had serum calciums of 14 mg/dL or higher. In contrast, 50% of patients with adenomas have serum calciums of 12 mg/dL or less.

Serum levels of alkaline phosphatase and a and b subunits of human chorionic gonadotrophin are also raised [20].

Non-functioning carcinomas are exceedingly rare (19 cases since 1929), and usually present with signs and symptoms of local growth and invasion (e.g. neck mass, hoarseness, dysphagia) [21].

From a histopathological point of view, the differential diagnosis may not be simple. WHO criteria for PC include demonstration of an invasive growth pattern or distant metastasis.

PC, in contrast to the soft, reddish-brown adenoma, has a hard consistency and is surrounded by a dense fibrous reaction that gives the tumor a whitish hue. It is often adherent to or infiltrating adjacent structures. At operation, the presence of a mass adherent to surrounding structures is the most valuable information the surgeon has to know that he may be dealing with a carcinoma. However, only as much as 50% of cases are adherent to or invading adjacent structures [22].

Grossly, tumours are usually quite large with an average diameter of >3 cm [23] and can weigh between 2 and 10 g, being often irregular, firm to hard, and have a greyish-to-white colour.

They are difficult to diagnose microscopically. With the exception of invasion of surrounding structures, lymph node metastases, or the presence of mitotic figures, there are no histological features

that alone can distinguish between an adenoma and carcinoma. Although Shantz and Castleman described the principle histologic features that distinguished parathyroid carcinoma as a trabecular patter, mitotic figures, thick fibrous bands, and capsular and blood vessel invasion [24], later investigators showed that none of these criteria are sufficiently sensitive or specific to confirm or discard the diagnosis reliably. Mitotic activity and trabecular patterns can be seen in benign lesions, as reported by McKeown et al. [25]. On the other hand, capsular invasion can only be seen in a portion of specimens, and vascular invasion in even fewer cases. These difficulties, naturally, have intensified interest in developing other methods such as immunohistochemistry and DNA analysis. No single marker thus far has shown to be perfectly sensitive and specific. Staining for parafibromin, Rb expression, Ki-67 and galectin-3 have all been used [12].

Pathological diagnosis of parathyroid carcinoma continues to be a challenge. In the absence of a gold standard test, a multidisciplinary approach, considering all clinical, biochemical and structural aspects of the disease, offers the best chance for accurate diagnosis.

The purpose of surgery is not only oncological but also to control endocrine function. In fact, the morbidity and mortality associated with PC are generally more related to various functional aspects (PTH hypersecretion and severe persistent hypercalcaemia) than to oncological aspects [26].

The majority of studies recommend en bloc resection of the tumor together with the ipsilateral thyroid lobe, and excision of any adjacent structures involved, at the time of the initial surgery to offer the best opportunity for better local disease control and significantly improved long term-survival [13,22]. Every effort should be made not to rupture the capsule of the tumor and spill tumor cells in the field.

As it is possible to encounter both adenoma and carcinoma synchronously, a formal cervical exploration should be done all four glands found and examined [9].

Prophylactic or radical neck resection is usually performed only if enlarged or abnormal-appearing lymph nodes are found to be involved, as unnecessary prophylactic radical neck dissection may increase the risk of surgical complications [22,27].

Use of intra-op PTH test has been reported in parathyroid cancer. If this tool is available, its use can be helpful. After surgery, close monitoring of calcium levels and adequate replacement is necessary to avoid severe hypocalcaemia due to 'hungry bone syndrome'.

Adjuvant therapy with RT or QT was not deemed effective in the treatment of parathyroid carcinoma [12], although some small studies and case reports challenged this notion [13,22,26,28].

In spite of all technological and technical advances, recurrence is very common in parathyroid carcinoma [29]. Patients who had a complete en-bloc tumor resection at the time of initial surgery have a lower recurrence rate–with survival rates as high as 90% at 5 years and 67% at 10 years [30]. Unfortunately, a significant proportion of patients are not diagnosed at initial surgery and do not undergo complete resection. On average, recurrence occurs 2–3 years after initial surgery [29]. Much longer time lapses, up to 23 years, have been reported previously [1].

The most common relapse pattern after the initial surgery is local recurrence and distant metastases (e.g., lung, bone and liver metastases). Patients present with gradually increasing PTH and serum calcium levels. Severe hypercalcaemic crisis is rare. The treatment strategy consists of controlling hypercalcaemia, localising studies and surgical excision of resectable disease when feasible [3].

Many patients may require multiple operations and this approach, in fact, is justified as it offers the best palliative option [31].

The aim of follow-up is early detection of potentially curable loco-regional recurrence and/or secondary tumours. That's why it should include clinical examination with calcium levels and PTH monitored every 3 months for the first 3 years [12], 6/6 months till 5th year and yearly lifelong after that. When there is any suspicion it should be confirmed afterward with imaging studies.

In conclusion, Parathyroid carcinoma is an extremely rare tumor that continues to present formidable challenges in diagnosis and treatment which are often difficult. This is associated with delayed diagnosis when the tumor is already palpable, that decreases the possibility of achieving a histological margin-negative resection, as this is the patient's only hope for cure and prolonged disease-free survival. Effort should be taken to establish more reliable diagnostic tools.

Conflict of interest

The authors have no conflict of interest.

Funding

The authors have no funding.

Ethical approval

Being a Case Report, with written consent from the patient, our institution doesn't require formal Ethical Approval.

Consent

Consent was given and signed by the patient.

Author contribution

All author contributed to data collection, data analysis or interpretation and writing the paper.

Registration of research studies

This paper is a clinical report, no research involved.

Guarantor

José Miguel Presa Fernandes.

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