



## Two case reports of parathyroid carcinoma and review of the literature

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### ABSTRACT

Parathyroid carcinoma is an infrequent endocrine malignant neoplasm with an aggressive behavior. Two cases of parathyroid carcinoma are described, one with a late diagnosis after previous surgeries for parathyroid hyperplasia, and the other diagnosed after pathologic fracture. The aim of this article is to make a review on recent parathyroid carcinoma literature and discuss these two illustrating cases. There has not been established any etiology for parathyroid carcinoma and no predisposing factors were identified. Parathyroid carcinoma may occur sporadically or as part of a genetic syndrome. The clinical features of parathyroid carcinoma are similar to benign cases of hyperparathyroidism and the pathologic diagnose is difficult. In the absence of metastatic disease in addition to a similar clinical setting, it can be difficult to distinguish benign and malignant hyperparathyroidism. Parathyroid carcinoma is a rare disease which diagnose can be challenging. Recent advances in immunohistochemical analysis may have helped in histopathologic evaluation, but pre-operative detection relies on imaging exams that may not differentiate malignant from benign hyperparathyroidism. The first surgical approach is paramount for disease control. There is still few effective therapeutic options for recurrent and metastatic disease, and these patients' prognostic status remain poor. Promising results were observed with denosumab and PTH immunization, and they may be a useful therapy for advanced cases in the future, but further investigation is required.

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## 1. Introduction

Parathyroid carcinoma is an endocrine malignant neoplasm with an aggressive behavior. It was first described in 1904 by Fritz De Quervain, when he reported a case of non-functioning neoplasm, and then, 26 years later, Sainton and Millot described the first functioning parathyroid carcinoma.<sup>1,2</sup> It is an infrequent neoplasm, with a prevalence of 0,005% of all cancers and accounting for 0,4–5% of all cases of primary hyperparathyroidism.<sup>3</sup> There is no gender dominance in parathyroid carcinoma and its onset is usually a decade earlier than parathyroid adenomas, with a mean age of 45–59 years.<sup>4,5,6</sup> It has not been described any

preponderance concerning race, income level or geographic region in the literature.<sup>5</sup>

## 2. Objective

The aim of this article is to make a review on recent parathyroid carcinoma literature and discuss two illustrating cases.

### 2.1. Etiology

There has not been established any etiology for parathyroid carcinoma and no predisposing factors were identified, it seems to be a result of a complex interaction of environmental factors and inherited genetic predispositions. There have not been established a definite progression sequence of benign to malignant lesions. The absence of conclusive data is attributed to the rarity of this tumor.<sup>7</sup> Neck radiation, adenoma, secondary and tertiary hyperparathyroidism have been reported in patients with parathyroid

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carcinoma.<sup>8</sup>

Parathyroid carcinoma may occur sporadically or as part of a genetic syndrome. Multiple endocrine neoplasia type 1, 2A and isolated familial hyperparathyroidism are syndrome describes to be associated with parathyroid carcinoma. Additionally, 15% of patients with hyperparathyroidism jaw tumor syndrome may develop parathyroid carcinoma.<sup>9</sup> Somatic genes mutations have been associated with parathyroid carcinoma, such as HRPT2 (CDC73, or Parafibromin) gene mutation, abnormal expression of the retinoblastoma and p53 proteins, and tumor suppressor gene on chromosome 13 on the surroundings of retinoblastoma gene. Sporadic cases have also been associated with HRPT2 mutations in up to 25%. Albeit these discoveries, these molecular changes have been identified in studies with small cohort of tumor samples and further investigations is required.<sup>10–12</sup>

## 2.2. Clinical and laboratory features

The clinical features of parathyroid carcinoma are similar to benign cases of hyperparathyroidism and the pathologic diagnose is difficult. These factors make parathyroid carcinoma a challenge. Aside from that, less than 10% of parathyroid carcinoma cases are nonfunctional. The majority presents as functioning tumors with hypercalcemia and its symptoms, such as depression, anxiety, weight loss, weakness, bone disease, renal involvement, abdominal pain, and peptic ulcer disease. Skeletal involvement includes osteopenia, bone pain, osteoporosis, osteofibrosis and pathologic fractures (found in up to 90%) of patients. Renal disease manifest as nephrolithiasis and renal insufficiency (seen in up to 80%).<sup>3,13–16</sup> Other clinical signs that may help are palpable neck mass and hoarseness.<sup>7</sup> Serum calcium levels are frequently higher than 14mg/dL and PTH serum levels are commonly 3 to 10 times higher than the upper limit of normal.<sup>6,17,18</sup> It has been described recently the method which third to second generation parathormone (PTH) ratio is calculated and a result higher than one can predict whether the tumor is malignant with a sensitivity of 75–82% and a specificity of 97–98%. This result relies on the tendency of the parathyroid carcinoma in producing more amino-PTH, which is identified by third generation assays.<sup>19–22</sup> Levels of alkaline phosphatase and alfa and beta subunits of human chorionic gonadotropin may be higher in malignant primary hyperthyroidism than in benign cases.<sup>23,24</sup>

## 2.3. Imaging

The absence of metastatic disease in addition to a similar clinical setting, it can be difficult to distinguish benign and malignant hyperparathyroidism. Aside from that, all patients with hyperparathyroidism need to have their disease extension evaluated for treatment planning.<sup>7</sup> The diagnostic sensitivity and accuracy are increased when more than one imaging method is used.<sup>4</sup> The imaging modalities that have been used are ultrasonography, sestamibi scanning, computed tomography (CT), single-photon emission CT, magnetic resonance imaging (MRI), and positron emission tomography.<sup>25–28</sup>

Ultrasonography is a noninvasive and inexpensive method and for this reason is the most commonly used method.<sup>9</sup> Despite not being able to definitely discern malignant from benign cases, some sonographic features may suggest carcinoma.<sup>29</sup> Parathyroid carcinoma usually presents as lobulated, hypoechoic and relatively large and ill-defined borders when compared to adenomas,<sup>30,31</sup> associated to local infiltration, calcification, suspicious vascularity and a thick capsule have been predictive of malignancy. Ultrasonography can also detect lymph node enlargement and invasion of the tumor to adjacent structures.<sup>9</sup>

Other imaging modality frequently used along with cervical ultrasonography is Technetium-99m sestamibi scintigraphy.<sup>32</sup> Increased and prolonged uptake of this isotope is generally found in hyperfunctioning parathyroid tissue,<sup>7</sup> thus sestamibi scanning is a localization study that cannot differentiate benign from malignant cases, but it may be useful in diagnosis and localizing ectopic hyperfunctioning tissue and metastatic disease.<sup>7,32,33</sup> Nonetheless, this method is not completely specific for parathyroid tissue and thyroid nodules can have proeminent and delayed imaging.<sup>33</sup> Single photon emission computed tomography (SPECT) can simplify the localization of a parathyroid lesion, improving the sensitivity of 99mTc sestamibi scintigraphy.<sup>34</sup>

Computed tomography (CT) is an additional diagnostic method because it lacks sensitivity in detecting parathyroid carcinoma.<sup>35</sup> The same can be applied to MRI. These method may provide anatomical description of the lesion and its extent and also can detect other involved regions, making them useful for determining recurrence and metastatic spread.<sup>9,4</sup> When these modalities are used, it is useful to have an additional method such as ultrasonography and sestamibi scanning to determine the most likely site of abnormal glands and differentiate normal gland from lymph nodes and other unrelated structures.<sup>36</sup>

The sensitivity for localizing parathyroid carcinoma in the neck using ultrasonography, 99mTc sestamibi scan, CT and MRI were, respectively, 83%, 79%, 69% and 93%.<sup>37</sup>

Other diagnostic method that can localize functioning parathyroid tissue is selective venous catheterization with PTH measurement, and some studies have shown that it can demonstrate high sensitivity in localization.<sup>38,39</sup> Albeit its sensitivity, this is an invasive and not commonly available studies, being recommended only when other noninvasive studies fail to localize the disease or results are questionable.<sup>40</sup>

In the set of recurrence suspicion, when there is laboratory suggestion, imaging studies is essential. It is recommended two concordant studies, that may include ultrasound, CT, MRI, sestamibi scan, PET CT and/or highly selective venous sampling for PTH assay.<sup>4</sup>

## 2.4. Cytology and histopathology

Fine-needle aspiration cytology should be avoided,<sup>41</sup> because discerning between malignant and benign disease on cytology is challenging<sup>4</sup> and this procedure may cause tumor disruption and its seeding through the needle tract, leading to higher chances of recurrence.<sup>4,35</sup> However, it may be useful in distinguishing thyroid from parathyroid tissue or identifying metastatic parathyroid carcinoma.<sup>42</sup>

Intraoperative findings that suggest carcinoma are large grayish to white tumors, usually with 3cm or more. They are firm and can be adherent or invade surrounding structures, and it has been described a cystic component in 21% of the cases.<sup>4</sup> In the absence of preoperative or intraoperative clear signs of carcinoma, frozen section analysis may not help, since carcinoma and adenoma histopathological features are similar and sometimes indistinguishable.<sup>43,7</sup> It has been described morphologic features that may suggest parathyroid carcinoma,<sup>4</sup> which include fibrous band with a trabecular architecture (90%), capsular invasion (60%), vascular invasion (15%) and mitotic activity (80%).<sup>4</sup> Nonetheless, not all parathyroid carcinoma display these finding and they are not specific for malignancy.<sup>44–48</sup> In the absence of vascular invasion, perineural invasion, invasion to adjacent structures and metastasis, parathyroid carcinoma should not be yielded.<sup>7</sup>

Some borderline cases have been previously described as atypical parathyroid adenomas, but recent disclosures concerning biomarkers in molecular pathology have helped distinguishing

parathyroid carcinoma from adenomas.<sup>44,49</sup> Immunohistochemical positivity to loss of expression of parafibromin, retinoblastoma protein (Rb), p27, Bcl-2a, mdm-2 and APC, combined with positivity for galectin-3, overexpression of p53, and increased Ki67 proliferation index (>5%) have been implied to confirm malignancy in parathyroid tumor.<sup>7,46</sup>

## 2.5. Case reports

### 2.5.1. Case one

A 35 year-old male, was admitted in Brazilian Nacional Cancer Institute on August, 10th of 2002 asymptomatic with a history of urinary tract lithiasis and hypercalcemia since 1999 and a cervical ultrasonography that suggested parathyroid adenoma. He had a personal history of systemic arterial hypertension, rheumatic fever treated at eleven years, and partial nephrectomy in the left kidney when he was thirteen years for unknown reasons. He had family history of parathyroid disorders, which included hyperparathyroidism on his mother, aunt, a cousin, a nephew and two sisters.

Complementary evaluation laboratory and sestamibi scintigraphy was performed and there wasn't sestamibi uptake outside the parathyroid and a total serum levels of calcium of 11.09 mg/dL (upper limit of 10.4 mg/dL), parathormone (PTH) of 148.7 pg/mL (upper limit of 54 pg/mL), creatinine of 1.0 mg/dL (upper limit of 1.3 mg/dL) and a phosphorus of 1.6 mg/dL (lower limit of 3.0 mg/dL) with no other abnormalities. On October, 31st of 2002 he was submitted to exploratory cervicotomy which found 4 parathyroids, two in each side, with the bigger one in the right presenting 15 × 10mm, with normal colour and macroscopic features. There was no invasion of adjacent organs and no suspicious lymph nodes. He was submitted to subtotal parathyroidectomy, with auto-transplantation of half parathyroid in the left arm muscles. At frozen section, the pathologist was only able to identify that they were formed by parathyroid tissue. Postoperative histopathology result demonstrated parathyroid hyperplasia in all parathyroids resected.

On follow-up, three years after the resection, he presented asymptomatic with PTH serum level of 201 pg/mL (upper limit of 65 pg/mL) and serum total calcium level of 11,4 mg/dL (upper limit of 10,2mg/dL). Sestamibi scintigraphy demonstrated no abnormal uptake and cervical ultrasonography was normal as well. Nonetheless, he was submitted to resection of the parathyroid implant in left arm muscles, which histopathological analysis demonstrated normal parathyroid tissue. He remained with high calcium (12,7 mg/dL) e PTH (370 pg/dL) serum levels one month after the latest surgery. Another sestamibi scintigraphy was performed and now it demonstrated an abnormal uptake in the lower aspect of the right thyroid lobe.

On June, 2nd of 2006 it was performed another exploratory cervicotomy, and intraoperative findings demonstrated a tumor adjacent to the lower aspect of the right thyroid lobe. There was no changing in PTH and calcium levels, and they remained high.

He lost follow-up and returned on 2012 with a history of three cervicotomies and tumor resection in other institutions, on 2007, 2010 and 2011. During this period he also had been submitted to four nephrolithotomy, five parathyroid alcoholization and hospitalization with PTH serum level higher than 2000 pg/dL and the need for hemodialysis. The last histopathological report related a tumor with 37mm and other mass (referred a paratracheal tumor) with 25mm with necrosis, vascular invasion and local invasion to thyroid, strap muscles and a segment of the cervical esophagus. The surgical margins were positive, and there was one metastatic lymph node from three resected. The immunohistochemical analysis demonstrated positivity to chromogranin A, synaptophysin, CD31, CD34 and ki-67 (10%). With these findings the diagnose of

parathyroid carcinoma was made and he returned to our institution for external beam radiation.

He was submitted to external beam radiation with a total dose of 5940cGy in 33 fractions. He lost follow-up again in our institution, and came back in 2014 with a PET CT result reporting focal high metabolism in the neck and high metabolism pulmonary nodules in the right and left lungs. The CT reported bilateral pulmonary nodules. He was submitted then to pulmonary metastasectomies twice in 2014 due to persistent elevated serum calcium levels.

There was still high serum levels of parathormone and calcium in 2015. A PET CT scan demonstrated high metabolism on cervical lymph nodes in level II bilaterally. CT imaging demonstrated no abnormal lymph nodes or masses in the neck, but there was right pulmonary nodes. He was again submitted to pulmonary metastasis resection, but calcium control was not achieved. He was evaluated for systemic chemotherapy, but the clinical oncology group did not found it to be beneficial.

On 2016, his calcium levels are being clinically controlled, but there has been persistent high levels and another metastatic investigation is being made.

### 2.5.2. Case two

A 33 year-old male presented in Brazilian Nacional Cancer Institute on July of 2015 with a two-year history of bone pain and pathologic fracture of the right clavicle one year before (Fig. 1). He had no personal pathologic history, and the only family pathologic history was type 2 diabetes in his mother and type one diabetes in his father. A previous MRI demonstrated a 7.0 cm lesion in the right uerum and dorsal spine CT showed litic lesions in vertebrae bodies and ribs.

Laboratory findings demonstrated total serum calcium of 13.1 mg/dL (upper limit of 10.2 mg/dL) and serum PTH of 1985 pg/mL (upper limit of 65 pg/mL). There was no renal function impairment. Bone scintigraphy showed abnormal uptake in



Fig. 1. Right clavicle assymetry due to previous fracture.

multiple areas of axial and appendicular skeleton. Sestamibi scintigraphy found abnormal uptake only in the right humerus bone. Cervical ultrasonography demonstrated a solid, hypoechoic and irregular nodule with some hyperechoic points suggestive of psammomas bodies and a higher central blood flow, measuring  $34 \times 44 \times 18$  mm in thyroid's right lobe topography.

On August of the same year, he was submitted to an exploratory cervicotomy which findings were a tumor with around 3.5 cm adjacent and invading the right thyroid lobe with extension to the right tracheo-esophageal groove. A total thyroidectomy with levels VI and VII dissection was performed (Fig. 2). Post-operative histopathological reported parathyroid carcinoma with 32 mm infiltrating the right thyroid lobe without vascular invasion (Figs. 3 and 4). All lymph nodes and the left thyroid lobe were free of malignancy. Parathormone levels dropped from 2646 to 91.58 pg/dL on the first day after surgery.

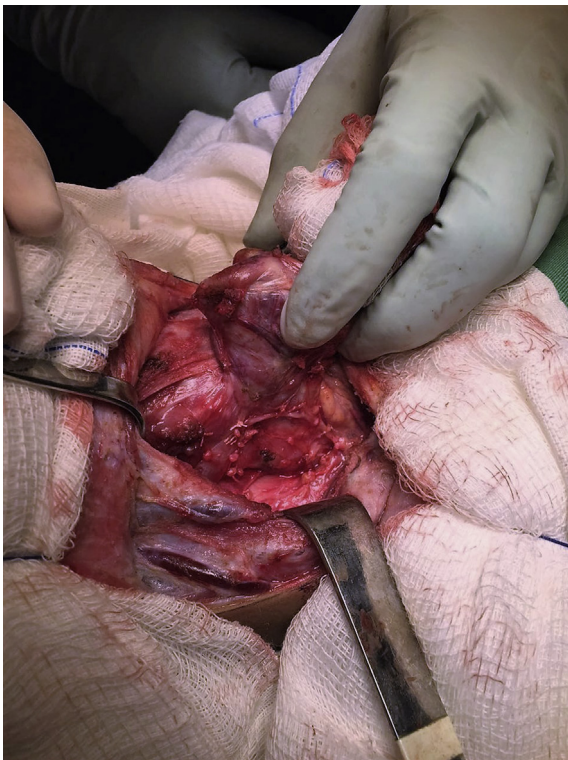
One month after surgery, serum PTH levels became to rise again, and so did serum total calcium levels. Cervical, thorax and abdomen CT scans showed multiple spine litic lesions, deformity in costal arches with multiples litic lesions and two left lung nodules with 9 and 6 mm.

Thoracic surgery department did not indicate metastasis resection due to costal arches lesions, and radiotherapy was also ruled out.

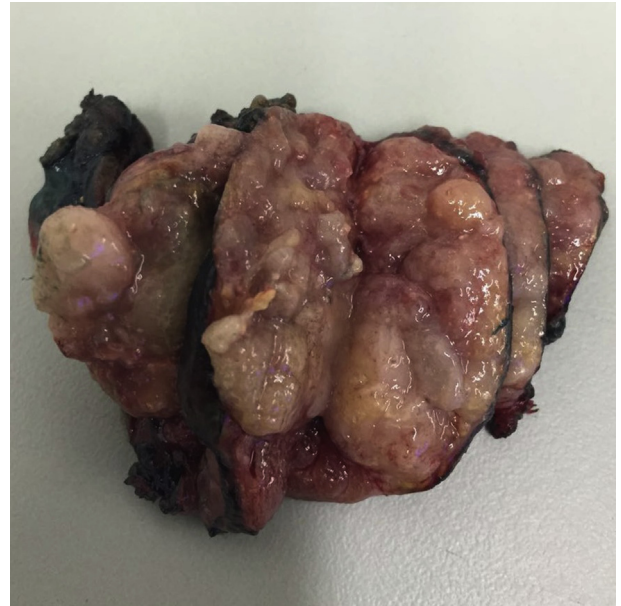
On the last follow-up consultation on May 2016, patient complained about bone pain, serum PTH level was 250 pg/dL, but with normal calcium levels.

### 3. Discussion

We report two different cases of parathyroid carcinoma but consistent with literature.<sup>7,43,50</sup> Both demonstrate de clinical and morphological variability of parathyroid carcinoma, which can



**Fig. 2.** The tumor adherent to the right thyroid lobe, without recurrent laryngeal nerve involvement.

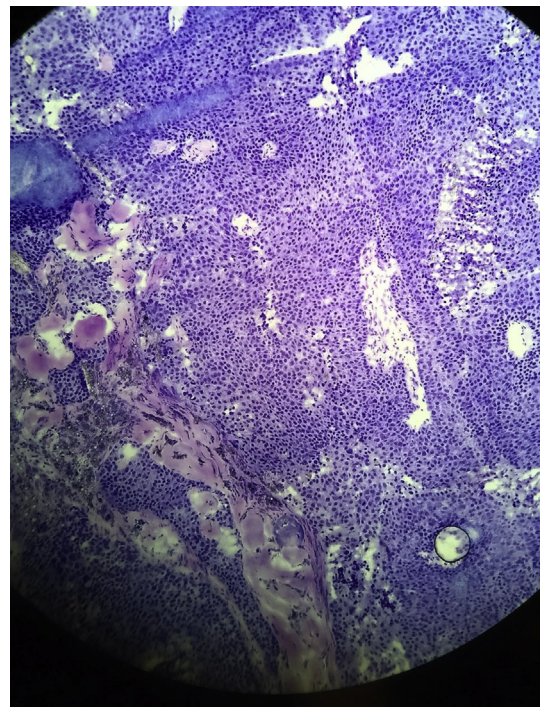


**Fig. 3.** Tumor macroscopic and microscopic overview.

make diagnose of this neoplasm challenging.

The reported median ages in the largest series range from 54,5 years (14–88 years) to 57 years (10–89 years).<sup>5,51</sup> Although our patients were younger than the reported median ages, they were within the age range of these reports.

The first case was diagnosed as parathyroid hyperplasia on 2002, when immunohistochemical analysis of parathyroid neoplasm wasn't fully developed.<sup>7</sup> Even though it hasn't been found any evidence that parathyroid carcinoma arises from malignant transformation of preexisting benign lesions, hyper-



**Fig. 4.** Tumor macroscopic and microscopic overview.

functioning parathyroid glands and/or familial disease have previously been associated with parathyroid cancer.<sup>7,52,53</sup> Another consistent finding was his past of familial hyperparathyroidism, which has been associated to parathyroid carcinoma.<sup>4,54</sup> Serum calcium and PTH levels weren't high enough and intra-operative findings didn't help on leading to malignancy suspicion.<sup>4,7,9,43</sup> The presence of increased mitotic activity, atypical mitoses and nuclear atypia should raise the suspicion for an underlying malignancy.<sup>7</sup> Based on the current evidence, loss-of-expression of parafibromin, retinoblastoma protein (Rb), p27, Bcl-2a, mdm-2 and APC, along with positivity for galectin-3, overexpression of p53 and increased MIB-1 (Ki67) proliferation index (>5%) in immunohistochemical staining has been suggested to confirm a diagnosis of malignancy in a parathyroid tumor. Parafibromin, galectin-3 and bcl-2 are the most helpful ancillary biomarkers.<sup>7</sup>

On the other hand, the second case had clinical and laboratory findings that highly suggested parathyroid carcinoma. He presented with bone pain and lesions, PTH levels 30 times the normal upper limit, and a primary lesion with typical ultrasonography features, such as hypoechoic appearance, ill-defined borders, suspicious vascularity and size larger than 15mm.<sup>3,15,25,30,31,55</sup>

The oncologic surgical approach that has been advocated as the treatment of choice is en bloc resection with ipsilateral hemithyroidectomy and, despite being controversial, central neck dissection has been recommended as well on the grounds that central compartment metastasis may occur in 15–30% of patients and the procedure does not inflict significant risk.<sup>7</sup> Nonetheless, the second case presented with gross thyroid invasion involving the right lobe entirely, thus it was performed total thyroidectomy with neck dissection of the central compartment.

There is no formal AJCC/UICC TNM staging system for parathyroid cancer, and prognostic factors for this disease have not been defined. The American National Cancer Database report have not found any prognostic value in tumor size and lymph node status.<sup>56</sup> Two staging systems were elaborated based on histopathologic criteria, regarding capsular invasion, invasion to surrounding soft tissues, invasion of vital organs such as hypopharynx, trachea, esophagus, larynx, recurrent laryngeal nerve and carotid artery, and presence or absence of lymph node and distant metastasis.<sup>57,23</sup> In a study evaluating prognostic factors, intraoperative tumor rupture, locally advanced tumor and/or presence of lymph node metastasis, and the presence of mitotic figures in the tumor parenchyma cells were associated with tumor recurrence.<sup>56</sup> The presence of vascular invasion is probably the single most important predictor of distant recurrence and metastasis.<sup>19,20,56,58</sup> The complete staging and risk assessment for the first case is T4N1M1, stage IV, according to *Shaha and Shah classification*, and for *Differentiated Schulte classification* as well, with all of the high risk features such as vascular invasion, lymph node metastasis and vital organ invasion and distant organ metastasis. The second case, is T3N0M1, stage IV, according to *Shaha and Shah classification*, and T2N0M1, stage IV, for *Differentiated Schulte classification*, with distant organ metastasis (lung) as high risk feature.

Approximately one third of patients have metastatic lesions at presentation and the most common site if metastasis is the lung followed by liver and bone.<sup>4,5,40</sup> When is the metastasis is operable, its resection is recommended, which may include pulmonary resections, hepatectomies, bone resections or craniotomies.<sup>5,43,52</sup> Metastasectomies might not provide curative treatment, but they are justified for the reduction of severe hypercalcemia and it has been associated with improved survival, probably because mortality in advanced metastatic parathyroid carcinoma is associated mainly to severe hypercalcemia rather than mass effect. Even incomplete resections can control calcium levels or facilitate medical control of hypercalcemia.<sup>43,59</sup> In light of these evidences,

the thoracic surgery department carried out with multiples metastasectomies for the first case. The second patient, despite the pulmonary metastasis, presented with multiple bone metastasis to the spine and costal arches which contraindicated lung metastasectomy. In patients with inoperable disease current treatment modalities are limited and the most common measures concern control of hypercalcemia.<sup>20</sup>

There is no large-multicentered randomized studies that corroborates the use of radiotherapy or chemotherapy for parathyroid carcinoma due to the rarity of the disease.<sup>9</sup> Parathyroid carcinoma is believed to be resistant to radiation, with disappointing results. In SEER study, 9,8% of patients with parathyroid carcinoma received radiation therapy and it was not associated with improved survival rate. Nonetheless, several case series reported reduced recurrence in patients submitted to radiation therapy.<sup>3,9,52</sup> Our first case was submitted to neck radiation and so far has no evidence of cervical disease and the second patient was not eligible to radiation therapy.

Chemotherapy is usually used for patients with inoperable disease, unsuitable for surgery, and there is no standard treatment protocol. Some case reports showed benefit with dacarbazine, alone or associated with fluorouracil and cyclophosphamide. However there is no conclusive evidence supporting chemotherapy for parathyroid carcinoma.<sup>43,60</sup> The first patient, despite multiple lung metastasectomies remained with hypercalcemia, however systemic therapy was not indicated due to lack of supporting evidence.

Ablative therapy may be an adjunct to palliation in parathyroid cancer. Ethanol ablation guided by ultrasound with percutaneous injection of 98% ethanol into the tumor can reduce PTH and calcium serum levels. It has minimal side effects, but should be reserved to palliative cases, due to potential tumor seeding along needle tracks and risk of local nerve and tissue injuries.<sup>61</sup> This strategy was not successful for our first case.

Recently, it has been found promising results with denosumab, a monoclonal antibody against receptor activator of nuclear factor κB ligand inhibiting osteoclast development, activation and survival.<sup>62–65</sup> It has been approved for treatment of postmenopausal osteoporosis and for the prevention of skeletal-related events in malignancies bone metastasis. Since denosumab decreases calcium levels, it may counteract the hypercalcemic effect of PTH.<sup>64</sup> Denosumab have been compared with zoledronic acid in patients with advanced malignancies in two randomized trials and denosumab demonstrated a higher rate of hypocalcemia than the latter.<sup>66,67</sup>

Besides, immunotherapy with autoantibodies against human PTH has demonstrated good results in patients with metastatic disease. Bradwel and Harvey induced auto-antibody formation against PTH by using human and bovine PTH-like immunogenic fragments, achieving serum calcium decrease, but without anti-tumor effect. In 2004, Betea et al. reported the first case of successful immunization against PTH in a patient with parathyroid carcinoma with hormonal and biochemical normalization accompanied by tumor regression.<sup>68,69</sup> Yet, Horie and Ando, observed a minimal remission, probably their case was highly aggressive.

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