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Case Report
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Parathyroid Cancer after Surgical Treatment – A Case Report of Radiotherapy Beneficial Effect in Metastatic Disease

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Abstract

Parathyroid cancer is an uncommon endocrine malignancy representing 0.005% of all cancers with the less than 1% frequency in all primary hyperparathyroid patients. The treatment of choice is radical surgical resection – parathyroidectomy and en bloc resection of surrounding tissues. Radiofrequency ablation, radiotherapy and chemotherapy are therapeutic palliative options without evidence of effectiveness. In parathyroid carcinoma hypercalcaemia rather than local infiltration or metastases presence is the main cause of death. At this work we introduce a 10 years case history of a patient with hormonally active disseminated parathyroid cancer in whom the use of radiotherapy allowed for long lasting hypercalcaemia control. The case we present and data reported by others though covering a small number of patients may indicate potential positive role of radiotherapy in parathyroid carcinoma both in case of residual local or metastatic disease.

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Introduction

Parathyroid cancer is an uncommon endocrine malignancy representing 0.005% of all cancers with the less than 1% frequency in all primary hyperparathyroid patients [1]. Its course is indolent but progressive and its hormonal activity leads to clinical manifestation of severe hypercalcaemia including bone, renal, cardiovascular and digestive tract symptoms. Hypercalcaemia is also the main cause of death rather than local infiltration or metastases presence [1].

The treatment of choice is radical surgical resection – parathyroidectomy and *en bloc* resection of surrounding tissues – not always undertaken in this scope due to the lack of clear preoperative diagnostic criteria. In some cases the histopathologic data may also be unreliable so malignant disease recognition is stated when local recurrence or pulmonary/bone metastases are seen [2]. Water diuresis, intravenous bisphosphonates, calcimimetics, glucocorticosteroids and haemodialysis are used for calcium control [3]. Surgery, radiofrequency, radiotherapy and chemotherapy are therapeutic palliative options without evidence of effectiveness [2].

At this work we introduce a 10 years case history of a patient with hormonally active disseminated parathyroid cancer in whom the use of radiotherapy allowed for long lasting hypercalcaemia control.

Case Report

A 59-year-old female patient was diagnosed with the jaw tumor in 2007. She was referred to surgical resection and histological analysis revealed brown tumor. According to that diagnosis biochemical assessment of calcium balance was done confirming primary hyperparathyroidism With PTH level 270 pg/ml (normal range 16 pg/ml to 87 pg/ml) and calcium concentration 2.65 mmol/l (normal range 2.10 mmol/l to 2.55 mmol/l). Subsequently neck CT revealed tumor mass 46 mm × 37 mm × 51 mm localized in the area of left thyroid lobe inferior pole. *En block* resection of the left inferior parathyroid gland and left thyroid lobe with subtotal resection of right thyroid lobe was performed in December 2007. Exploration of the neck showed infiltration of the left common carotid artery and esophagus. Histopathological diagnosis was parathyroid carcinoma with positive surgical margins status.

In March 2008 the patient was admitted to our Department for the first time. Laboratory investigations showed elevated PTH concentration with normocalcemia and vitamin D depletion.

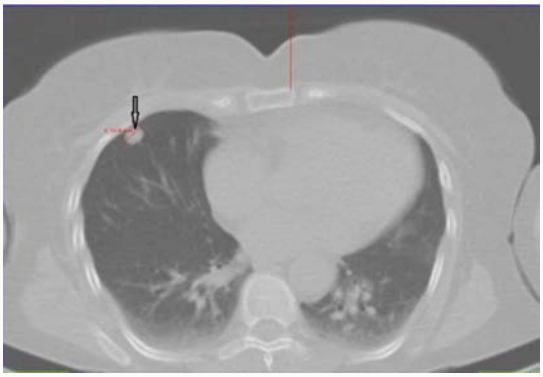

Figure 1: CT scan 2013, the biggest metastatic lesion in right lung - arrow.

In neck CT, ^{99}Tc-MIBI scintigraphy and PET FDG there was no morphologic and functional signs of the persistent disease. Therapy with vitamin D was ordinated leading to normal PTH and calcium level. During the follow up biochemical assessment and CT scan of neck and thorax as well as ^{99}Tc-MIBI scintigraphy was repeated in 6 months intervals. Germline *Cell Division Cycle 73 (CDC73)* gene mutation analysis was negative. Somatic *CDC73* mutation screening was not performed.

Recurrence of PTH-dependent hypercalcaemia was documented in May 2011, 56 months after surgical treatment. PTH concentration was 256 pg/ml (normal range 16 pg/ml to 87 pg/ml) with serum ionized calcium 1.37 mmol/l (normal range 1.05 mmol/l to 1.30 mmol/l). In ^{99}Tc-MIBI scintigraphy the pathologic uptake of the radioisotope in left area of the neck was revealed, which corresponded with 10 mm lesion localized in ultrasonography and CT scan. PET FDG was negative. The possibility of surgical treatment and risk of adverse events was discussed with the patient. She refused further surgery. According to that, treatment with use of cinacalcet in dose 30 mg per day was initiated and conventional radiotherapy as an alternative therapeutic approach was planned. In January 2012 patient received 70 Gy in fractionated doses to the local recurrence area. Unfortunately radiotherapy did not result in decreasing PTH and calcium level but recurrence mass diameter remained stable. Over following year serum calcium was mildly elevated under control of cinacalcet and monthly repeated pamidronate intravenous injections. PTH concentration stayed stable around the level of 300 pg/ml.

In July 2013 CT scans revealed 3 lesions highly suspected about metastatic etiology in right lung, the dominating of 10 mm size localized in segment V (Figure 1). ^{99}Tc-MIBI scintigraphy was positive for the biggest metastatic lesion (Figure 2). Despite the morphologic progression, considering satisfactory biochemical control upon calcimimetic treatment and low risk of organ failure according to small mass of neoplastic lesions, multidisciplinary tumor board proposed closer clinical monitoring rather than subsequent oncologic therapy.

Upon surveillance PTH concentration was gradually increasing and in May 2015 reached 999 pg/ml, which resulted in substantial calcium elevation. Dose adjustment of cinacalcet was necessary and 60 mg per day was applied. According to the deterioration of biochemical markers respiratory-gated stereotactic radiotherapy for the lung metastases was recommended. In July 2015 patient received 15 Gy for each of 3 lesions in one dose. After 3 months fall of PTH level to 541 pg/ml and normalization of serum calcium concentration

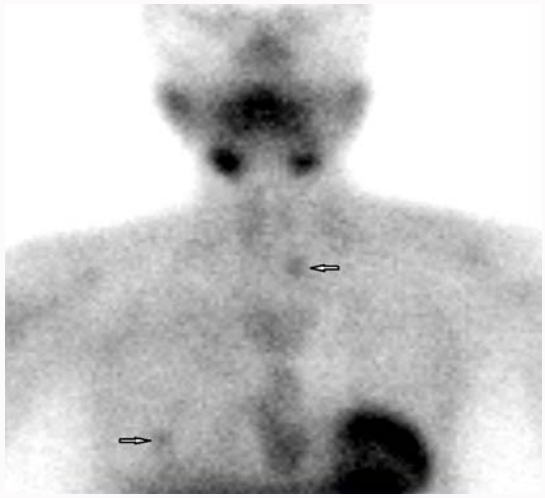

Figure 2: ^{99}TcMIBI scintigraphy 2014, local recurrence, lung metastatic lesion - arrows.

was observed, which allowed withdrawal of cinacalcet.

Though normocalcemia was not permanent and calcium concentration started to rise 10 months after radiotherapy, it stays till nowadays (22 months after radiotherapy of lung metastases) slightly elevated, well controlled with use of cinacalcet in dose 30 mg daily. PTH concentration persisted on the level around 500 pg/ml.

Beneficial effect of lung metastases radiotherapy forced us to retrospective analysis of previous radiation treatment targeted at local recurrence lesion, which did not entail improvement in calcaemia control. Re-assessment of CT scans revealed a single micro lesion in right lung present already in 2010, which suggests possible existing subclinical/microscopic disease spread at the time of first radiotherapy.

Under 22 months surveillance CT scans demonstrated stable picture of the disease (local recurrence mass in left area of the neck and three lesions in right lung size up to 10 mm).

Medical assessment conducted in 2016 confirmed preserved kidney function without presence of kidney stones. Likewise densitometry did not reveal bone mass loss.

Discussion

The clinical manifestation of parathyroid cancer may overlap that caused by parathyroid adenoma. Since only about 10% of parathyroid carcinomas are nonfunctional both mentioned above entities may appear by symptoms of hypercalcemia [2,4]. The typical clinical picture is characterized by nephrolithiasis, impaired renal function or bone involvement including different form of bone resorption [5]. It is worth emphasizing that overt bone disease is unusual in benign hyperparathyroidism [2]. In our patient brown tumor in the jaw was the first symptom of parathyroid carcinoma. Brown tumors are the result of bone resorption and consist of mononuclear stromal cells and multinucleated giant cells with hemorrhagic infiltrates and hemosiderin deposits, localized usually in jaws, pelvis or sternum [6]. Diagnosis of such lesion always requires searching for primary hyperparathyroidism. Tumors localized in jaw accompanied by hypercalcemia need differentiation between mentioned above brown tumors and ossifying fibromas being a component of hyperparathyroidism-jaw tumor syndrome (HPT-JT) – autosomal

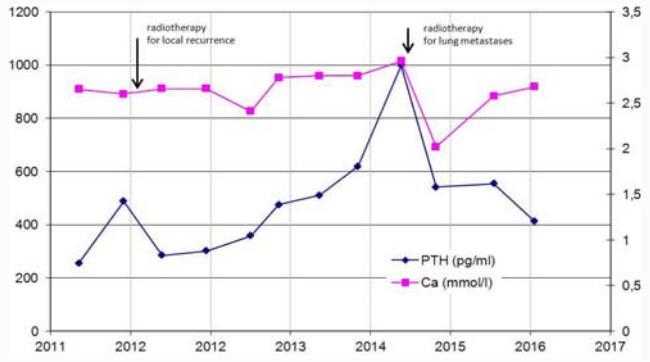

Figure 3: Patient's PTH and calcium serum concentration in follow up period.

disorder caused by germline *CDC73* mutation, in which the risk of parathyroid cancer is rated at 15% [2].

It is reported that serum calcium level is higher in case of parathyroid cancer comparing to its benign counterpart and exceeds 3.5 mmol/l in 60% to 65% [1]. Likewise PTH serum concentration in parathyroid cancer are mostly markedly elevated, 5-10 times above normal limit [1,2]. Contrary, our patient presented at the diagnosis only mildly elevated PTH and calcium concentration which is in line with opinion that no threshold level for malignancy exists and diagnosis of this rare entity needs vigilance (Figure 3) [1,7].

Literature data report mean age of parathyroid cancer onset between 45-59 years, decade earlier than parathyroid adenoma disclosure [5,8]. In our patient first symptom was diagnosed in age of 59, closer to typical age of identification for hypercalcaemia resulting from parathyroid adenoma.

In view of clinical manifestation, which can hamper differentiation of malignant and benign cause of hypercalcaemia it is of important issue to pay attention to other features suggesting malignancy. Parathyroid carcinoma are usually >3 cm and may present as palpable cervical mass. Infiltration of surrounding structures strongly suggests malignant behavior [2]. The 5 cm diameter of tumor revealed in CT scan in case of our patient and evidences of infiltration of adjacent organs prompted the surgeon to *en block* resection. Only radical surgical treatment offers the highest chance of cure in patients with parathyroid carcinoma therefore suspicion of malignancy at the initial surgery is substantial [1].

Making a diagnosis of parathyroid carcinoma by histopathology is also challenging as most of the histological features of parathyroid carcinoma are not specific [7]. It is common that only persistent or recurrent disease or appearance of metastatic lesion give the rise to suspicion of parathyroid carcinoma.

Surgical resection (if possible) is treatment of choice in case of local recurrence though subsequent operations have lower success rates and seldom being curative but may be favorable in lowering serum calcium levels. There is no other oncological therapy with evidenced effectiveness instead of surgery [1,2,7]. There are some studies suggesting beneficial effect of adjuvant radiotherapy. In 1985 Lillemoe and Dudley reported [9], giving the radiotherapy locally to the tumor bed in 3 patients with confirmed soft tissue involvement without recurrence noted in 16-46 months follow up period. In 1998 Chow et al. [10] presented experience of The Princess Margaret Hospital in postoperative radiation therapy for microscopic residual disease in six patients. They reported no recurrence in 12-156 months follow up period. In 2003 Munson et al. reported data of 4 patients received postoperative adjuvant therapy without evidence of disease 53-67 months after treatment. However there are reports do not confirming efficacy of radiotherapy in parathyroid carcinoma [11,12]. Moreover there are no reports considering use of radiotherapy in parathyroid carcinoma local recurrences.

With respect to our patient decision refusing another surgical intervention we decided to apply radiotherapy to the area of local recurrence. We did not observe an improvement in calcaemia control but we achieved stability of neoplastic mass in the neck for long period. Possible disease micro dissemination at time of neck radiotherapy (single micro lesion revealed in lung during re-assessment of imaging studies) we account for a lack of positive biochemical effect.

Distant metastases in course of parathyroid carcinoma rarely appear at the time of first diagnosis. They are mainly localized in cervical lymph nodes and lungs, rarely in liver or bones [2]. Resection of single metastases if technically possible is strongly recommended. The procedure may not be leading to complete remission but usually results in decreasing of PTH and calcium concentration [2,5]. The biochemical improvement is crucial issue in parathyroid cancer management. It is not mass effect but hypercalcaemia most threatening to the patient suffering from parathyroid carcinoma. Therefore in case of reported patient despite the morphologic progression (new lung metastases appearance) we considered necessity of applying new therapeutic modality only at the moment of calcium control deterioration. Nowadays there are no chemotherapy or radiotherapy standard protocols in disseminated parathyroid carcinoma management [7]. According to our own experience, discussing the patient at multidisciplinary board, respiratory-gated stereotactic radiotherapy for the lung metastases area was recommended. It resulted in achieving normocalcaemia of 10 months duration without necessity of additional therapeutic methods as well as a 22 months period of stable disease according to RECIST criteria. According to our knowledge there are no studies reporting using of stereotactic radiotherapy in parathyroid carcinoma metastases.

Though in our patient's calcium serum level for the whole follow up period did not exceed 3 mmol/l to 5 mmol/l, in the majority of parathyroid cancer patients controlling PTH-driven hypercalcaemia is a difficult challenge. The most effective in lowering serum calcium over the wide range of disease severity is cinacalcet-calcimimetic, that modulates Calcium Receptor enhancing its sensitivity to extracellular calcium concentration thus reducing parathyroid cell hormonal secretion [13,14]. The recommended doses range from 30 mg to 360 mg daily. Higher baseline concentrations of serum calcium require higher doses of cinacalcet [13]. Decreasing in serum calcium concentration is not linked with such like dynamic fall in PTH concentration, which is still unexplained phenomenon. The most observed adverse events during cinacalcet therapy are nausea and vomiting [2]. In controlling hypercalcaemia we used as well intravenous bisphosphonates, which role in bone resorption limitation is well established but effectiveness in controlling calcaemia may be transient [2]. In case of parathyroid toxicosis saline infusion, loop diuretics and finally dialyses must be taken in to a consideration.

Conclusions

Parathyroid carcinoma is rare neoplasm demanding medical vigilance. Only early recognition and complete resection at the time of initial surgery provides guarantee of cure. Management of recurrent

or persistent disease remains a challenge. The case we presented and data reported by others though covering a small number of patients may indicate potential positive role of radiotherapy in control of parathyroid carcinoma both in case of residual local or metastatic disease. Undoubtedly further studies are necessary.

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