case report

ISSN 1506–9680

VIA MEDICA

Parathyroid cancer — difficult diagnosis — a case report

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[Received 7 VIII 2015; Accepted 30 XII 2015]

Abstract

Parathyroid cancer is a rare disorder of unclear etiology that is difficult to diagnose and treat. It is most often diagnosed incidentally based on multi-organ non-specific symptoms of hypercalcemia as a consequence of parathyroid hormone oversecretion. We present a case of a male with primary hyperparathyroidism who was diagnosed with parathyroid cancer ectopically located in the mediastinum only after the third surgery. However, due to chronic hypercalcemia, problems with localization and a bad clinical condition, the patient was not able to undergo a radical resection and one year after the first pathological fracture died. Taking into consideration the whole clinical picture we want to emphasize the need to apply comprehensive differential diagnosis of hypercalcemia and localization diagnosis of parathyroid tissue with a use of MIBI scintigraphy accompanied by the computed tomography and magnetic resonance imaging, as the most specific diagnostic tools employed in this pathology.

KEY words: hyperparathyroidism, parathyroid cancer, MIBI scintigraphy, MRI, CT

Nuclear Med Rev 2016; 19, 1: 46–50

Introduction

Parathyroid cancer is characterized by rather slow progression and low malignancy dynamic. It is estimated to comprise from 1% (in the US and Europe) to 5% (in Japan and Italy) of all cases of primary hyperparathyroidism (PHP) and only 0.005% of all tumors [1, 2]. In most cases the disease develops spontaneously though it may occur in patients with family history of the disorder. The diagnosis of parathyroid cancer is mainly based on the symptoms of resistant hypercalcemia caused by autonomous oversecretion of parathyroid hormone (PTH), which leads to disorders of the skeletal system, gastrointestinal tract, kidneys and often neck tumors [3, 4]. Localization tests include ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and parathyroid scintigraphy with 99mTc-hexakis2-methoxyisobutylisonitrile (99mTc-MIBI) [5] and the method of choice is total resection followed by histological tests.

The aim of this report is to present diagnostic difficulties in the localization of ectopic parathyroid cancer and draw attention to the need for accurate differential diagnosis of hypercalcemia.

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Case report

A 49-year-old male with no history of chronic illnesses was admitted to hospital in August 2011 due to the fracture of the shaft of the right humerus and fracture of the neck of the right femur after a fall from standing height. Fractures were surgically treated but the X-ray images showed cysts, which led to a more comprehensive diagnosis in search for abnormalities. Clinical picture and the conducted tests (Tables 1, 2) showed PHP with parathyroid adenoma and the patient was scheduled for parathyroidectomy. After the surgery the patient developed the so-called "hungry bone syndrome" (decrease in PTH and hypocalcemia). Laboratory tests also showed significant deficiency in vitamin D3 (3.7 ng/ml), decrease in urinary calcium (48 mg/24 hrs.) and a slightly higher level of chromogranin A (141 ug/l; n. 19–98). Due to the fact that the patient complained of pain, he underwent radiological examination which showed new fractures of the shaft of the left humerus and numerous fractures of the proximal and medial left femur. After achieving normal calcium level the patient was transferred to the Department of Orthopedics and Traumatology and scheduled for surgery. During the patient's six-week-long hospital stay the levels of calcium (Ca), phosphor (P) and PTH were examined numerously. Both thyroid and adrenal gland disorders were excluded. The patient only manifested slightly higher parameters of inflammation. Due to progressive increase in PTH level observed from December 2011, he was transferred to the Department of Endocrinology for further diagnosis and treatment. The patient manifested typical

Table 1. Laboratory test results

Parameter \ Time	At baseline (August 2011)	After Surgery 1 (October 2011)	December 2011	After Surgery 2 (January 2012)	After Surgery 3 (April 2012)	After Surgery 4 (June 2012)
PTH concentration [pg/ml] (n. 14–72)	> 1900	64	420–913	1113–1899	3930–5570	4730–4090
Total calcium [mg/dl] (n. 8.4–10.4)	14.36	10.45–6.79	9.5–13	10.6–13.2	10.3-17.7	9.4–13.7
Phosphor [mg/dl] (n. 2.4–5.1)	2.6	1.48–1.85	1.7–2.4	1.4–2.1	2.4-2.6	3.8–4.6

Table 2. Imaging and types of surgeries

	Imaging	Type of Surgery	Histopathological results
At baseline August 2011	Neck CT: "parathyroid adenoma within the lower pole of the left thyroid lobe"		
Surgery 1 17 October 2011		Right parathyroidectomy	"parathyroid adenoma, chief cells"
After Surgery 1	MIBI scintigraphy: "no scintigraphic lesions suggestive of enlarged parathyroid glands" SPECT imaging "enlarged parathyroid gland within the area of the central part of the right lobe of the thyroid cannot be excluded" Neck and Chest CT: "in the middle of the right thyroid lobe on the back wall on plain images visible tissue structure of 16 x 11 mm of a slightly lower optical density than the parenchyma of the gland, after administering contrast shows weaker enhancement and faster washout — could be consistent with enlarged parathyroid tissue"		
Surgery 2 20 January 2012		Subtotal resection of the right and left lobe of the thyroid and isthmus with the use of a scintillation detector device	"...the morphological picture does not allow for accurate evaluation whether the parathyroid glands are normal or enlarged"
After Surgery 2	Neck and Chest CT: "below and towards the back from the trachea at Th4 visible focus of tissue, with round curves and diameter of 12 mm with visible deformation of the esophagus — parathyroid gland" PET-CT (FDG): metabolically active lesion in the left area of the trachea below the piriform recess, which could be consistent with enlarged parathyroid Whole body MIBI scintigraphy: "in the projection of the right lobe and in the midline of the body two areas of increased accumulation of MIBI" Somatostatin receptor scintigraphy: "No lesions suggestive of overexpression of somatostatin receptors"		
Surgery 3 25 April 2012		Total strumectomy with left parathyroidectomy	Parathyroid cancer, immunohistochemistry: cyclin D1 (+), Galectin-3, **Ki-64** (MiB1), positive in ca. 2% of the cells
After Surgery 3	Neck and Chest CT: "towards the back from the manubrium to the front from the brachiocephalic vein visible tissue areas contrast enhanced of total size ca. 12 x 32 x 31 mm. Towards the back from the trachea at Th4 visible polycyclic focus of tissue with round curves of size of ca. 19 x 25 x 30 mm contrast enhanced with visible deformation of the esophagus — significant progress as compared with the previous examination. Normal mediastinal and hilar lymph nodes"		
Surgery 4 20 June 2012		Right thoracotomy — resection of mediastinal tumor	Morphological picture is consistent with parathyroid cancer, immunohistochemistry: cyclin D1 (+), Galectin-3, **Ki-64** (MiB1), positive in ca. 2% of the cells
After Surgery 4	Neck and Chest CT: "Behind the trachea on the right side (in the area of previously visible lesions) very small contrast enhanced area. Pathological tissues located behind the sternum, towards the front from the left brachiocephalic vein with no significant change as compared with the previous examination. Single mediastinal lymph nodes as previously"		

symptoms of PHP: severe osteoporosis with numerous pathological fractures (Figure 1), diffuse decalcification of the spine and long bones, an episode of renal colic with kidney obstruction that had to be removed surgically and ulcerous disease. The patient underwent conventional parathyroid 99mTc-MIBI subtraction scintigraphy which showed no accumulation of radiotracer (Figure 2). Only another examination with the use of SPECT imaging (subsequent single-photon emission computed tomography) revealed an area which could be enlarged parathyroid within the area of the central part of the right lobe of the thyroid which was confirmed by chest and neck CT (Table 2). Due to increasing levels of PTH and calcemia the patient was repeatedly and unsuccessfully operated on in the Department of Chest Surgery also with the use of a scintillation detector device (Table 2). Despite aggressive pharmacotheraphy (forced diuresis, steroids, bisphosphonates) the concentration of both PTH and Ca still grew with low levels of phosphor and magnesium. On 17 April 2012 we performed 18F-FDG-PET/CT (fluorodeoxyglucose-positron emission tomography) which revealed a metabolically active lesion in the left area of the trachea below the piriform recess, which could be suggestive of enlarged parathyroid tissue (Figure 3). In the same month the patient underwent another surgery (Table 2) complicated by circulatory arrest followed by successful resuscitation, however due to bad clinical condition the lesion was not removed.

The histological results conclusively confirmed the diagnosis of parathyroid cancer. By reason of persistent very high level of the PTH and hypercalcemia apart from a standard therapy the patient was also treated with Cinacalcet (Mimpara 3 x 60 mg/d), which

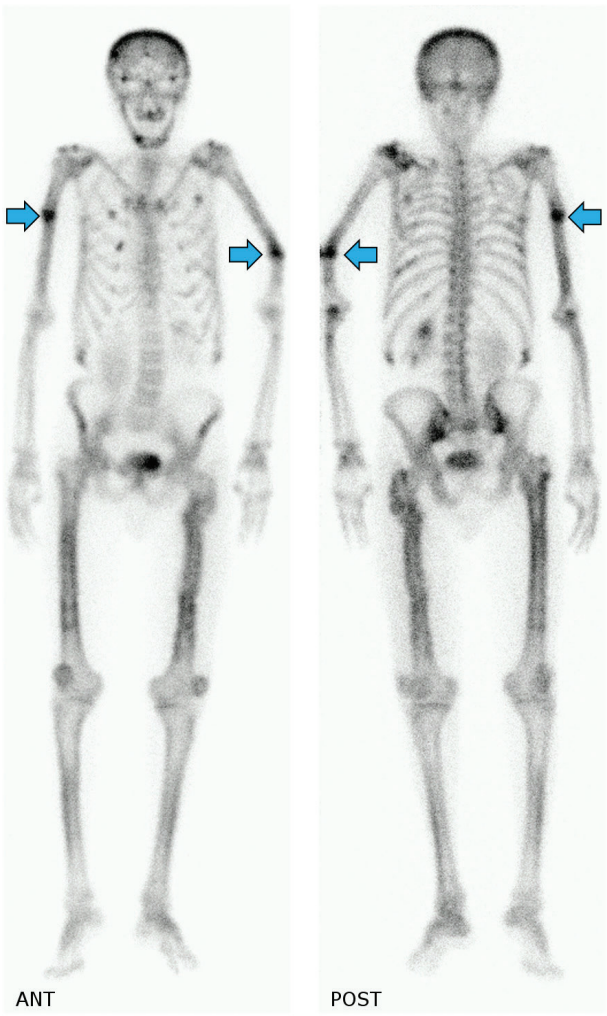

Figure 1. Whole body bone 99mTc-MDP scintigraphy, AP and PA. Visible numerous areas of increased activity and metabolism of bone tissues are suggestive of fractures (arrows)

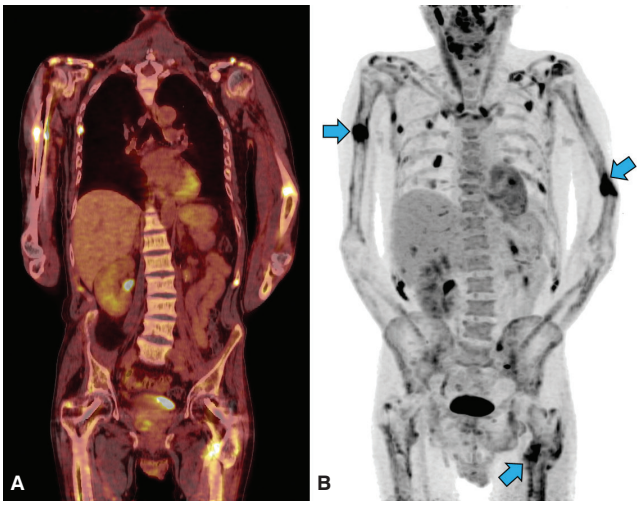

Figure 3. 18F-FDG PET/CT. PET-CT (**A**) and PET-MIP (**B**) Numerous areas of increased glucose metabolism in the skeletal system most probably connected with metastases and bone fractures (arrows)

resulted in lower and more stable calcemia. In the interest of the patient who complained of shortness of breath and dysphagia and due to a rapidly progressing polycyclic mass lesion at Th4 visible in CT imaging in June, he was operated on the fourth time. The mediastinal lesion built from the cells of parathyroid cancer was removed incompletely (Table 2). Moreover, the combination pharmacotheraphy was continued with the level of calcium within the upper normal range. The team of oncologists did not qualify the patient for chemo- and radiotherapy. In August 2012 the patient was transferred to a hospice where he soon died.

Discussion

We report a clinical case of a male-patient whose pathological fractures underlying hypercalcemia were the primary manifesta-

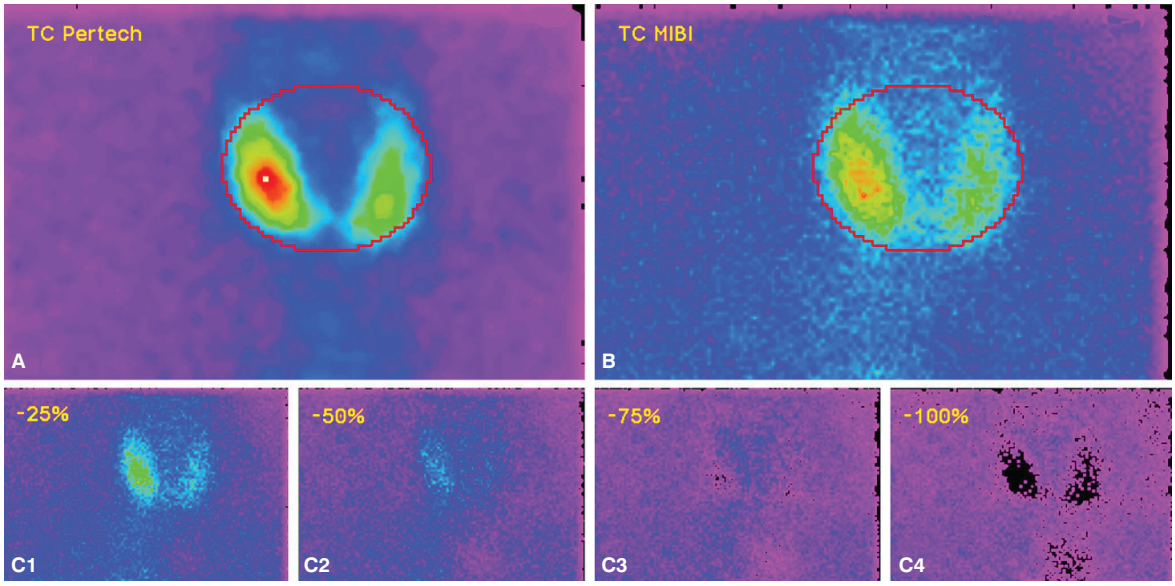

Figure 2. Parathyroid scintigraphy with 99mTc-MIBI (**A**) with pertechnetate (**B**) using subtraction technique (**C**)

tions of parathyroid cancer. Further tests showed a characteristic clinical picture of parathyroid cancer [2, 6] due to hypercalcemia: numerous cysts, diffuse decalcification of the spine, pathological fractures and lower density of the bone structure, calcinosis of the right renal medulla visible in ultrasonography, inflammation and defects in the membrane of the esophagus and stomach and duodenal ulcer visible in gastroscopy. Literature to date has shown that the diagnosis of parathyroid cancer is often incidental and radiographic findings of PHP account for 60–91% of all cases of parathyroid cancers [7]. Moreover, patients may suffer from overall weakness, fatigue, loss of appetite, loss of weight, depression, nausea, vomiting, constipation, polyuria and polydipsia, which were not observed in this patient. However, it should be borne in mind that there may be cases of non-secreting tumors with normal PTH and Ca levels which are more difficult to diagnose [8, 9]. In differentiation of parathyroid cancer and adenoma there are a few factors worth accounting for: the patient's gender (the prevalence of the cancer is the same in men and women, however adenomas are three-fold more frequent in women than in men), the patient's age (younger by 10–20 years than in the case of a benign lesion, i.e. at the age of 40 or 50), acute severe hypercalcemia (> 14 mg/dl), accompanying bone and renal lesions (in 40–60% of the patients) and quite often palpable neck mass [3, 10]. Such elements of differential diagnosis to a large extent can be found in our case.

In case of suspicion of parathyroid cancer a key important stage is localization of the malignant lesion, especially in terms of its size and invasion, in order to allow for a radical, i.e. effective, surgery with a normal tissue margin. The problem of localizing parathyroid cancer is complicated by the fact that in 6–16% of the patients it can be found in non-typical places — most often in the thyroid (18%), the thymus (38%) or behind the esophagus (31%) [11]. One of the simplest, safest and repeatable imaging is ultrasonography, however, its sensitivity (50–60%) is insufficient and it can mainly be used in localizing lesions in the neck and thyroid. A test of choice in the localization diagnosis of enlarged parathyroid glands is 99mTc-MIBI scintigraphy which is also effective in localizing ectopic lesions and distant metastases [12, 13]. But the effectiveness of this method directly depends on the size of the lesion. So, according to Roy et al. the sensitivity of conventional method is 89%, and increase even up to 95% when use MIBI scintigraphy and ultrasonography [12]. Even better results can be obtained by use of hybrid imaging combining MIBI scintigraphy and CT or MRI with contrast and fat suppression which allows for the assessment of the details of the pathological tissues, its relations with other structures and their invasion of neighboring tissues or enlarged lymph nodes [14]. Due to better resolution and more precise localization of the lesion in three dimensions as compared to the classic scintigraphy, the use of SPECT imaging in recent years has increased. To detect remote metastases we use FDG-PET which can give false positive results. In complex cases a patient may undergo catheterization of cervical veins to determine the concentration of PTH [15]. It should be emphasized that in our case no significant pathologies were found in ultrasonography, while a suspicious focus that could be diagnosed as parathyroid lesion was visible only in the CT.

However, only after the second surgery in the chest CT we found the focus of PTH secretion in the mediastinum, which unfortunately could not be completely removed. Unfortunately, this patient did not undergo MIBI scintigraphy before the surgery. The examination performed postoperatively proved to be unreliable due to anatomical and surgical tissue damage. Yet again we would like to underline how crucial it is to employ this type of scintigraphy before applying the right course of action.

Owing to the histological difficulties in diagnosing parathyroid cancer visible in our case where the diagnosis was possible only after the third surgery, there was a need to employ other diagnostic methods based on immunohistochemistry and DNA analysis. These new markers include parafibromin, expression of Rb, Ki-67 and Galectin-3. Unfortunately, none of these has enough sensitivity and specificity on its own, therefore their results need to be interpret the results jointly [3, 16].

The only efficient method of treating parathyroid cancer is a total resection of the primary tumor, which is very demanding owing to the problems with localizing parathyroid tissue. The efficacy of surgery can be evaluated intraoperatively on the basis of the decrease of PTH concentration per minute [17]. It is 50% in comparison with the highest input level. Taken the above into consideration the first surgery performed on the patient should be deemed efficient as we obtained normalization of the parathyroid hormone concentration and the patient even developed hypocalcemia. Unfortunately, quite quickly the parathyroid tissue grew back from the cells which had remained in the mediastinum. This fact proved how crucial it is to localize and assess the invasion of pathological parathyroid tissue and perform complete resection with a margin of healthy tissue. It should be underlined here that all farther images of the neck were more difficult to evaluate because of fibrous tissue which formed after the surgeries. Therefore, it is critically important to localize the pathological lesion at the beginning of the disease. In our case upon the right diagnosis and localization of the tumor the patient did not qualify for a total resection of the lesion due to numerous complications and great extent of the malignant infiltration. After the non-radical resection of the tumor due to its low accessibility the progression of the lesion occurred quickly compressing the respiratory track and the patient needed another surgery.

Conclusions

Parathyroid cancer is a rare and slowly progressing pathology with quite good prognosis when diagnosed quickly and accurately. However, there are no clear diagnostic criteria or no clear courses of treatment. The only confirmed course of treatment that translates into prognosis and morbidity is a total resection with a margin of healthy tissue. The efficacy of the surgery is strictly connected with best localization of the pathological parathyroid tissue. That is why it is crucial to differentiate hypercalcemia and diagnose the patient before embarking on any therapy. In the localization diagnosis a method of choice is parathyroid MIBI scintigraphy accompanied by the computed tomography and magnetic resonance imaging, as together they provide almost 100% detectability. It is important that in every case of incidentally diagnosed hypercalcemia we exclude parathyroid cancer as one of the causes. The differentiation of the malignant process from parathyroid adenoma before the surgery affects the extensiveness of the surgical procedure, which in turn affects the patient's morbidity. The diagnostic difficulties encountered in our case emphasize the fact the right diagnosis should be based on the clinical picture, laboratory and radiological test results.

Conflict of interest

The authors declare that they have no conflict of interest.

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