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Symptomatic Primary Hyperparathyroidism in a Woman in Remission from Breast Cancer: A Case Report from Antananarivo, Madagascar

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Abstract: The occurrence of hypercalcemia in a person with cancer always raises concerns about hypercalcemia of malignancy. A well-conducted diagnostic approach can rule out this possibility and find primary hyperparathyroidism, the other most common cause of hypercalcemia. Few cases of primary hyperparathyroidism have been reported in Madagascar. Our aim is to report a case of it by discussing the circumstances of discovery and its therapeutic management. We report a case of 56 years-old patient, with treated breast cancer in remission, hospitalized for symptomatic hypercalcemia at 3.14 mmol/l. Her serum intact PTH level was elevated to 270 ng/ml and images in favor of osteitis fibrosa cystica were present in the spine and pelvis. Cervical ultrasonography could not locate the pathological parathyroids. Cervico-thoracic CT scan revealed two bilateral para-esophageal parathyroid nodules which were removed by bilateral neck exploration parathyroidectomy and for which the anatomo-pathological examination was in favour of an adenoma. The postoperative course was simple. This observation illustrates that hypercalcemia in subjects with active cancer or cancer in remission is not always related to metastasis but may, indeed, be related to primary hyperparathyroidism. Its curative treatment is based on surgical removal of the pathological parathyroid(s).

Keywords: CT Scan, Hypercalcemia, Osteitis Fibrosa Cystica, Parathyroidectomy, Primary Hyperparathyroidism, Scintigraphy

1. Introduction

Hypercalcemia is defined as an increase in total blood calcium above 2.61 mmol/l (10.5 mg/dl) [1]. Ninety percent of hypercalcemia cases are due to either primary hyperparathyroidism (PHPT) or cancer-related hypercalcemia [2]. Although more than 30% of patients with cancer may develop hypercalcemia during the course of their disease [3], a well-framed diagnostic approach can confirm or refute the role of cancer in the occurrence of hypercalcemia in these patients. Once the cancer etiology has been ruled out, the hypercalcemia generally corresponds to the PHPT, which corresponds to the set of clinical, biological and anatomical manifestations linked to the lesion of one or more parathyroid glands by an autonomous secretion of parathyroid hormone (PTH), causing hypercalcemia [4]. It is the third most frequent endocrine pathology in the world, predominantly in postmenopausal women [5]. Currently, ninety percent of

PHPT are discovered during routine blood calcium measurements in "asymptomatic" patients, i.e., not complicated by nephrolithiasis or ‘‘osteitis fibrosa cystica’’. Rare are the cases of PHPT discovered in front of clinical manifestations [4]. We discovered a case in the Unit of Endocrinology, Joseph Raseta Befelatanana Teaching Hospital, Antananarivo, Madagascar.

We aim to report the case by discussing the circumstances of discovery and its therapeutic management.

2. Observation

It was Mrs R., 56 years old, hospitalized for vomiting in the said unit. Her disease would have started one month before by the appearance of nausea and recurrent vomiting, without abdominal pain nor associated diarrhea. In addition, she had been experiencing severe bone pain for 3 months, located in the right hip and knees. There was no flushing, no flush, no headache.

The personal history was marked by the existence of a total mastectomy with lymph node curage completed with adjuvant radiotherapy and chemotherapy for infiltrating carcinoma of the right breast, 4 years earlier, actually in remission. She had no known metastasis. She was hypertensive since the age of 48 and diabetic since the same age. She was regularly treated and well-controlled for these two pathologies. She was menopausal since the age of 50. She had not taken any medication that could lead to hypercalcemia. Her mother was also hypertensive and diabetic. No family history of hypercalcemia or PTH was reported.

On clinical examination, her blood pressure was 105/65mmHg, heart rate 112 beats per minute, temperature 36.9°C, weight 50 kg for a height of 154 cm. She had clinical signs of mixed dehydration with persistent skin folds and dry mucous membranes. No tumor mass was found. Palpation of the right hip was painful but there was no limitation of movement.

Biologically, in view of the digestive disorders, dehydration and bone pain, a phosphocalcic assessment was requested. The total blood calcium level was increased to 3.14 mmol/l (normal: 2.2 - 2.6 mmol/l), the serum phosphorus level was at the low limit at 0.8 mmol/l (normal: 0.8 - 1.45 mmol/l). In view of the hypercalcemia, a serum intact PTH-measurement was performed, which was increased to 270 pg/ml (Normal: 15 - 68.3 pg/ml). In addition, the value of serum 25-hydroxy-vitamin D (25 OH vitamin D) was 28.8 ng/ml (Normal: 30 - 40 ng/ml). Calciuria was 175 mg/24h or 3.55 mg/kg/24h.

In addition, the diabetes was well controlled with a fasting blood glucose level of 6.4 mmol/l and a glycated hemoglobin (HbA1c) level of 6.8%. There was a slight hypernatremia at 145 mmol/l, a normal glomerular filtration rate at 71 ml/min/1,73m². Blood count, serum protein electrophoresis, liver function tests and thyroid function tests were all normal.

The cervical ultrasonography, showed only two cystic-looking thyroid nodules classified EU - TIRADS 2 measuring respectively 09 x 5.5mm and 07 x 3.5 mm, located in the 2 thyroid lobes. The parathyroids were not reported. Since scintigraphy was not available, a total body injected computed tomography (CT) scan was performed, demonstrating parathyroid nodules, in bilateral para-esophageal position measuring 15×7 mm on the left and 14×9 mm on the right, with vascular kinetics typical of parathyroid adenomas (density at 120 HU at arterial time (Figure 1), with washout at parenchymal time (94 HU) (Figure 2).

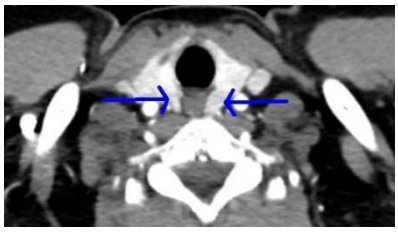

Figure 1. *CT scan with contrast injection at arterial time showing parathyroid nodules in bilateral paraesophageal position.*

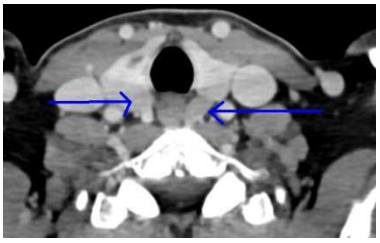

Figure 2. *CT scan with contrast injection showing washout of parathyroid nodules at parenchymal time.*

Inthe spine, there were staged osteophytosis, suggestive of arthrosic lesions, calcification of the yellow ligament in L2 - L3, with moderate bone demineralization compatible with osteoporosis (Figure 3).

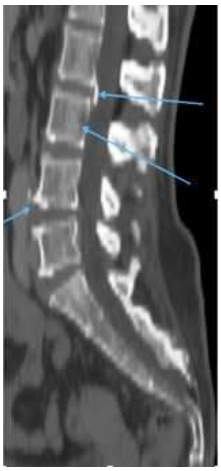

Figure 3. *CT scan in the bone window showing stepped arthrosic lesions suggestive of osteophytosis, calcification of the yellow ligament in L2 - L3, with moderate bone demineralization compatible with osteoporosis.*

In the pelvis, there was also bilateral sacroiliac and coxofemoral arthrosis, and osteocondensation of the right greater trochanter, with a possible gap in continuity and cortical rupture, associated with a subperiosteal bone resorption (Figure 4).

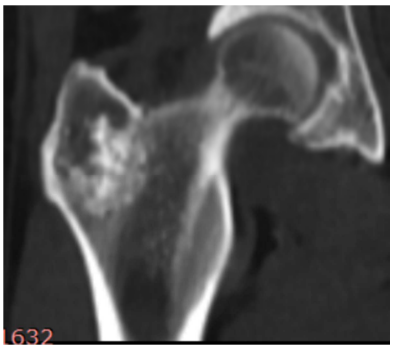

Figure 4. *CT scan in the bone window showing medullary osteocondensation in the right greater trochanter, a line of continuity, a cortical rupture and a subperiosteal bone resorption.*

There was no pathological image in favour of pleuropulmonary or visceral or lymph node metastasis.

An upper gastrointestinal fibroscopy performed at a distance from the acute episode in search of ulcers returned normal.

The diagnosis of a PHPT discovered at the time of a symptomatic hypercalcemia with ‘‘osteitis fibrosa cystica’’ was then retained.

Therapeutically, the patient received symptomatic treatment with antiemetics, parenteral rehydration with 0.9% isotonic saline and a World Health Organization (WHO) level III analgesic.

Removal of the 2 visibly pathological parathyroid glands by conventional bilateral neck exploration surgerywas performed. Rapid determination of serum intact PTH level to ensure successful removal was not available. The postoperative evolution was marked by the appearance of a symptomatic hypocalcemiaat 1.78 mmol/l at twenty-four hours, which benefited from calcium supplementation until normalization. The serum intact PTH level was normalized. In addition, the patient was supplemented with vitamin D. The anatomical-pathological result of the operation was in favor of a parathyroid adenoma.

3. Discussion

The singularity of our observation lay in the patient's history of cancer, making hypercalcemia of malignancy a priori suspect.

The discovery of hypercalcemia requires an serum intact PTH assay [6].

This assay makes it possible to distinguish between hypercalcemia of extra-parathyroidal origin and that of parathyroidal origin.

For the former, the level of serum intact PTH is collapsed. The hypercalcemia is PTH-independent and the causes are mainly neoplastic, including breast, bronchial, kidney and thyroid cancers. The mechanisms most often involve either osteolytic metastases or paraneoplastic production of hypercalcemic factor. In 80% of the cases, it is the PTH-related peptide (PTH-rP), a ubiquitous embryonic peptide, which has a high homology with PTH and binds to the PTH receptor [7].

In the second group, the level of serum intact PTH is increased or normal but "inadequate" to the hypercalcemia. This is PTH-dependent hypercalcemia. PHPT is the most common cause [8]. It results from excessive PTH secretion by one or more parathyroid glands. PHPT is caused by a solitary parathyroid adenoma in 80% of cases, by quadriglandular hyperplasia in 10-15%, by multiple adenomas in 5% and in less than 1% of cases by parathyroid cancer [8]. Other rarer causes of PTH-dependent hypercalcemia are tertiary HPT, familial hypocalciuric hypercalcemia and lithium treatment [9]. The combination of hypercalcemia, hypophosphatemia or normophosphatemia, as in our patient, with an elevated serum intact PTH level suggests PHPT.

Our observation illustrates once again the observation of Fierabracci et al that the association of PHPT and breast cancer is possible and that the prevalence of PHPT would increase even in subjects with treated breast cancer [10].

In Madagascar, PHPT is still very rarely reported. While in other countries the vast majority of PTH is biologically incidental [4], in our country it has been discovered during clinical manifestations.

This reflects the inadequacy of the routine determination of blood calcium levels. Indeed, in our patient, the clinical signs were digestive and bone related to hypercalcemia. For Andriantsoa et al, they were bone pains [11].

Primary hyperparathyroidism is a predominantly female disease, mostly affecting postmenopausal women [12]. Our observation was one such case. This increased prevalence beyond the age of menopause can be explained by the revealing effect of oestrogen deficiency on osteoblastic activity [4, 13].

The clinical signs of PHPT are those of hypercalcemia in general. Our patient had presented with food vomiting, a hallmark of severe hypercalcemia. In addition, all patients with clinically evident hypercalcemia have volume depletion, which is explained by the renal effects of hypercalcemia (polyuria) and decreased oral intake due to nausea and vomiting. Other possible gastrointestinal manifestations include pancreatitis and peptic ulcer [7]. Although peptic ulcer is often reported in PTH [14], our patient was free of it.

The bone signs reflect an imbalance in bone remodeling in favor of osteoclastic resorption [15]. Our patient presented with Von Recklinghausen's osteitis fibrosa cystica characterized by sharp bone pain and pathological fractures with diffuse demineralization and specific subperiosteal erosions [8]. The discovery of PHPT already complicated by osteitis fibrosa cystica is currently rare worldwide due to the widespread use of blood calcium levels since the 1970s [16]. Only less than 2% of patients in the United States suffered from it [17]. In our case, it is a sign of the delay in diagnosis.

Other manifestations of PHPT including nephrolithiasis, nephrocalcinosis and neuropsychiatric manifestations were not observed in our patient [8]. Arterial hypertension would probably be unrelated to PTH due to its long history and family history.

Classically, hypophosphatemia is reported in PHPT due to increased phosphorus clearance related to PTH hypersecretion

[18]. However, it is far from being constant. Normal phosphorus levels are mainly found in postmenopausal women, since oestrogenic deficiency increases serum phosphorus levels [19]. The serum alkaline phosphatase level may be elevated, reflecting increased bone resorption and compensatory osteoformation, but most often remains in the normal range [18] as in our observation.

A tendency to 25 OH vitamin D deficiency was also found in our patient as in the literature [8]. One explanation would be that excess PTH stimulates renal 1α--hydroxylase and promotes the transformation of 25 OH vitamin D into 1,25-$(OH)_2$ vitamin D [16].

The severe hypercalcemia of 3.14 mmol/l and the symptomatic character, especially the presence of bone damage, indicated a surgical removal of the hyperfunctioning parathyroids [20], preceded by pre-operative localization [21]. Cervical ultrasonography can localize parathyroid disease and evaluate thyroid pathologies as a hypoechogenic image plastered against the thyroid gland [8]. However, the paraesophageal location of our patient's tumors could have made them inaccessible to ultrasound. 99mTc-sestamibi scintigraphy has become the most efficient imaging technique with a relative ease of use [22]. It can accurately localize 80% to 90% of single adenomas, which represent 75 to 85% of cases [16]. However, it may not reveal small glands (uptake is related to gland size and serum PTH level) and its sensitivity is decreased for diffuse parathyroid hyperplasia and double adenomas [23]. The combination of ultrasound with scintigraphy is the most used by several teams because of its high sensitivity [24, 25]. In any case, scintigraphy is not operational in our country. This has led to the use of conventional CT scan. Multiphasic CT scan (4D-CT) is an examination preferentially indicated to localize ectopic parathyroid adenomas. It can also detect and localize eutopic parathyroid adenomas and differentiate them from lymph nodes [26]. The adenoma appears more hypodense than the thyroid on examination without injection and then its density increases progressively with the presence of a fatty hilum allowing it to be differentiated from lymph nodes [27]. We do not yet benefit from this revolutionary technology but we have nevertheless been able to localize pathological parathyroids.

The age of our patient, the absence of syndromic manifestations of Multiple Endocrine Neoplasia Type 1 (MEN-1) (PHPT, pancreatic endocrine tumor, duodenal tumor, pituitary adenoma) or MEN-2 (PHPT, medullary thyroid carcinoma, pheochromocytoma), and the absence of a similar family history were rather in favor of sporadic and isolated PHPT than of a PHPT of genetic origin [28]. In terms of therapy, there is currently no specific drug treatment for PHPT. Calcimimetics and biphosphonates are only symptomatically effective in acute hypercalcemia and are only indicated when surgery is not possible [29]. Curative treatment is exclusively surgical, based on bilateral neck exploration parathyroidectomy or minimally invasive parathyroidectomy or endoscopic parathyroidectomy [30, 31]. All this implies a precise topographic diagnosis and an adapted surgical technical platform before the operation in order to limit the extent of the dissection and the post-surgical iatrogenic complications. The effectiveness of the surgical procedure is then assessed by a decrease in the serum concentration of PTH measured during the operation, which would limit the extent of the surgical intervention due to the rapidity of the result [32]. This rapid determination is still not possible in our country. However, the decrease in blood calcium levels indicates the eradication of PHPT. In order to prevent osteoporosis and to limit postoperative hypocalcemia due to the phenomenon of "hungry bone syndrome", our patient was supplemented with vitamin D as recommended in the literature [33]. Follow-up should be at least 6 months and normocalcemia over at least this period is considered a cure [21].

4. Conclusion

Hypercalcemia in subjects with active cancer or cancer in remission is not always related to metastasis but may be related to PHPT. Our observation was such a case. Hence the importance of always measuring the serum PTH level before any hypercalcemia. A symptomatic PHPT like ours requires surgery, the success of which depends largely on the accuracy of tumor localization by imaging. Although not indicated in the first instance, cervico-thoracic CT scans, performed by trained operators, can help localize the tumor and guide the surgeon. Conventional surgery by bilateral neck exploration seemed more prudent than minimally invasive parathyroidectomy given the insufficiency of our technical platform. However, in the future, less invasive surgical techniques such as minimally invasive parathyroidectomy should be developed to facilitate patient management in our country.

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