Hypercalcemia crisis due to complex parathyroid tumour: a diagnostic and surgical dilemma

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Summary
The clinical manifestation of primary hyperparathyroidism (PHPT) as a hypercalcemic crisis should give rise to the consideration of a differential diagnosis between various different clinical processes for variable prognosis and the consideration of an underlying thyroid pathology.
Cystic parathyroid adenoma is one of its most infrequent causes in the group of glandular cystic neoplasms in the cervix.
The diagnosis of its functional character, supported by the determination of calcemia, blood and intracystic immunoreactive parathormone (PTHi), and the interpretation correlated with imaging studies, may contribute to its suspected diagnosis.
Its treatment of choice is surgery by means of selective parathyroidectomy with complete cystic inclusion, and extended to the thyroid depending on their degree of involvement, although this technique may experience modifications depending on the level of confidence in preoperative diagnosis.

Key words: hypercalcemia, parathyroid neoplasia, cyst, hyperparathyroidism.
**Introduction**

Hypercalcemia may be the first manifestation of primary hyperparathyroidism (PHPT), but its expression as a parathyroid crisis is a metabolic emergency which occurs infrequently. Effective medical action is vital to reduce the high risk of mortality associated with it.

A solitary adenoma is usually the most common cause of PHPT, but its presentation in the form of a hypercalcemic crisis requires the consideration of other diagnostic possibilities of disparate prognostic severity, especially if carcinoma is considered.

The concomitance of thyroid pathology with operational repercussions should motivate the carrying out of a preoperative study which clarifies the surgical indication, since the information provided by the imaging tests may distort the importance of this pathology in the absence of specific semiology.

We present a patient with acute PHPT secondary to a cystic parathyroid adenoma concomitant with hyperparathyroidism due to Graves-Basedow disease and a difficult diagnostic interpretation. We report a practical review of the clinical picture which may contribute to its diagnosis and surgical resolution.

**Clinical case**

A woman of 57 years of age with a history of hysterectomy due to myoma and in treatment for depression with paroxetine which was evaluated due to a clinical picture of nausea, vomiting, asthenia, loss of 5 kg of weight, polyuria and polydipsia over a number of weeks; detected in the examination were dry mouth and a painless nodule in the lower right cervix, which became mobile on swallowing, without palpable cervical adenopathy or other semiological findings of interest.

The analytical study showed calcemia of 14.6 mg/dl (N=8.4-10.2) with corrected calcium of 15.9 mg/dl (N=8.4-10.2), phosphatemia of 2.6 mg/dl (N=2.4-4.7), total proteins of 5.7 g/dl (N=6.4-8.3), albuminemia of 2.6 g/dl (=3.5-5), TSH< µUI/ml (N=2.4-4.7), total proteins of 5.7 g/dl (N=6.4-8.3), with corrected calcium of 15.9 mg/dl (N=8.4-10.2).

The patient was initially admitted with a diagnosis of serious hypercalcemia, primary hyperparathyroidism and suspicion of a right thyroid nodule having calcuaria of 912 mg (N=100-300) and phosphaturia of 704 mg (N=600-950) for a diuresis of 4,000 ml in 24 hours. Clinical and analytical stability was achieved by means of saline rehydration, ipso-position and metimazol. The study was completed in outpatients with PTHi of 1,205.8 pg/ml (N=5-65), thyroid negative anti-peroxidase and anti-TSI receptor antibodies of 1.5 U/L (N=0-0.7).

A thyroid ultrasound showed only one cystic nodule of 3 centimetres in the right inferior pole with PAAF of a clear yellowish liquid containing few inflammatory and no epithelial cells, which was reported to be compatible with the contents of a simple cyst.

A gammagraphy with $^{99m}$Tc-sestamibi (Figure 1A) showed a concentration of pathological captation re localised in the upper mediastinum, lateral to the lower pole of the right thyroid, suggestive of ectopic parathyroid adenoma.

With a view to planning for surgery a computerised tomography (CT) was made of the cervix with contrast (Figure 1B) which showed a nodule of 3.6 cm, with mural tumour of a probable parathyroid nature which slightly rectified the lateral right contour of the trachea; and the presence of small jugulodigastric hypocaptive adenopathies.

An en bloc surgical resection was carried out on the patient, which included the right hemithyroidectomy, parathyroidectomy, partial thymectomy with the inclusion of the right paratracheal tissue and lymphadenectomy of the central compartment. The intraoperativePTHi blood determinations were 762.3 pg/ml, 129.4 pg/ml, 110.8 pg/ml and 87.9 pg/ml respectively.

There were no postoperative complications, and the histopathological study was reported as cystic parathyroid adenoma (Figure 2), with no evidence of malignancy in the thymic tissue or in the various isolated adenopathies, and nodular hypoplasia on the right hemithyroid.

During the subsequent follow up the patient took metimazol in reducing doses and had good phospho-calcium metabolism control.

**Discussion**

The most common etiology of PHPT is the single adenoma, whose usual form of presentation is hypercalcemia in a postmenopausal patient of between 50 and 60 years of age, and which exceptionally reaches the clinical range of a parathyroid crisis.

Cystic parathyroid tumours represent 0.6% of thyroid and parathyroid lesions. Their relationship with cystic cervical tumour is lower than 5%+, and the fact that less than 10% of parathyroid cysts present with hyperparathyroidism make their clinical affiliation difficult.

However, a cystic tumour associated with a hyperparathyroid crisis should point towards a differential diagnosis centred on the different processes which may affect these types of glands. Clinically, various criteria have been proposed to suggest malignancy, such as the presence of a palpable tumour greater than 3 cm, calcemia above 14 mg/dl or semiology of serious hyperparathyroidism.

In addition, there is a close association of around 40% between PHPT and some types of essentially benign concomitant thyroid pathology, with surgical implications which mean that they ought to be considered preoperatively with the aim of planning the surgery strategy. In our patient the formation of the cyst was interpreted as being related to the thyroid, since there was concomitant primary hyperthyroidism independently of suspicious adenoma tissue in the parathyroid.

The parathyroid glands show a great variability in terms of number, size, shape and location, but the diagnosis by imaging of a cystic lesion in the
vicinity of a structure radio-
logically compatible with
parathyroid tissue in the
caudal region of the neck,
and concomitant with acute
PHPT, means that its rela-
tionship with these glands
should be discounted,
although the possibility of
cystic formations or func-
tional alterations in the thyroid
may be contemplated. Our
patient it a manifest exam-
ple of this semiological inte-
rrrelationship.

We should also consider
that the parathyroid
microcysts are frequently
found in healthy glands due
to the infiltration of fat over
time, but that macrocycts
are exceptional, and most
frequently affect the lower
parathyroid, although their
clinical repercussions differ
according to whether the
cyst is functional or non-
functional8,9.

The former essentially affect men, with hypercal-
cemia above 13 mg/dl as an indicator of PHPT, and
without precise anatomical location, which explains a
variable expression: from the absence of sympotms
to dyspnoea, dysphonia or dysphagia, according to
the structure compromised by its growth10. The pre-
ence of intracystic haemorrhage could influence an
erroneous diagnosis of malignancy.

On the other hand, the non-functional
macrocysts predominantly found in women, com-
prise 90% of the total and lack metabolic activity.

This classification emphasises the importance
of our contribution dealing as it does with a
woman with lower glandular affectation of a func-
tional character.

Its genesis was not clear10, although it was
thought that it could be derived from the growth
and secretion of colloid from primordial cells per-
sisting in the third and fourth branchial cleft, or in
the fusion of microcysts in healthy glands. In both
theories the cystic tumours would probably not be
functional, and their clinical translation would be
anecdotal, since this happens with a rise in
intracystic PTH without hypercalcemia.

On the other hand, if the cystic tumour derives
from the degeneration of an existing parathyroid
adenoma, as is possible in this case, the presence
of hypercalcemia will define its functional charac-
ter by the raised levels of blood and intracystic
PTH. The presence of haemorrhagic intracystic

Figure 1. Composition of radiological sequences showing evidence of parathyroid lesion: gammadigraphy with
99mTc-sestamibi showing a single pathological hypercapture focus suggestive of ectopic adenoma in upper
mediastinum (A). Axial CT section with well-delineated hypodense nodule in the right lobe of the thyroid
which contains a hypercapture nodule in its lateral wall and results in slight trancheal compression (B)

Figure 2. Histological section of a cystic formation of a fibrous capsule covered with parietal cells, in whose wall can be identified parathyroid tissue with adenomal characteristics and doubtful images of capsular pseu-
doinvasion. Stained with H-E. 4 x
foci may also support its adenomatous origin. Some authors associate cystic haemorrhage with the appearance of hypercalcemic crisis. These characteristics should serve to support the clinical diagnosis due to the current limitations in imaging studies which do not usually provide practical details beyond their cystic nature if there is no well-founded clinical suspicion, resulting frequently in their erroneous association with the thyroid gland, as was the case with our patient. In these cases what may be of great help is a fine needle puncture, to obtain a clear liquid with a high concentration of PTH.

This test could have avoided the carrying out of two image tests which facilitate neither diagnosis nor surgical planning, since while they point towards a thyroid pathology, they do not clarify the origin of the cystic tumour, nor discount the possibility of malignancy. Hence, we consider that any patient with hypercalcemia and high blood PTH in whom ultrasound of the thyroid shows a cystic lesion should be subject to a PAAF of the lesion in order to determine PTH, and a gammagraphy $^{99m}$Tc-MIBI due to the high sensitivity and specificity of this test for a solitary parathyroid adenoma compared with other imaging techniques, with the aim of evaluating a selective cervical approach, although some authors emphasise the value of ultrasound in the hands of expert radiologists for those suspicious cases of cystic adenoma, because of the scarcity of parathyroid tissue in the periphery and a rapid sweep of the scanner may contribute to false negatives in these cases.

In our patient the gammagraphy was capable of identifying the adenoma, but could not relate it to the adjacent cystic formation which was considered to be dependent on the thyroid gland. The other imaging studies should be limited to very specific cases, due to their limited contribution.

Proper preoperative information could contribute to reducing the aggressiveness of surgery, based on the possibility of a hypercalcemic crisis of a malign nature. In our patient, a more reliable diagnosis of benignity would have limited the resection of the parathyroid cyst and the adjacent thyroid tissue, the cyst being partially included in it.

The diagnostic complexity of this pathology would justify a meticulous surgical examination of the other glands in order to discount a multiglandular disease in the form of individualised coexistences of cysts and adenoma, of polyglandular cystic affection or of concomitant hyperplastic disease, although the determination of intraoperative PTH could point us towards the persistence or resolution of the process with greater reliability once the suspicious tissue has been extirpated, reducing surgery time and the risk of morbidity associated with unnecessary explorations.

In conclusion, the scarcity of cases documented in the literature may make difficult the suspected preoperative diagnosis of a benign functional cystic parathyroid tumour, whose confirmation requires compliance with clinical and biochemical criteria of hyperparathyroidism, identification of parathyroid tissue in the cystic wall in the absence of histological signs of malignancy, morphological or functional demonstration of the normal character of the remaining glands, and the regularization of postoperative levels of calcemia.

Declaration of interest: The authors declare the absence of any conflict of interest in this publication.

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