Primary Hyperparathyroidism with Monoclonal Gammopathy: A Mere Association?

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Abstract

It is described the clinical case of a 66 years old patient, male, Caucasian, admitted in the Medicine II Service at HUC, due to hypercalcemia on the 26th July 1991.

He was discharged with a definite diagnosis of primary hyperparathyroidism and monoclonal gammopathy.

The reference to the association to monoclonal gammopathy (of undetermined significance, or multiple myeloma), with primary hyperparathyroidism it is not recent.

In spite of that, there are not many papers reporting such association. At present, most authors think that is a mere coincidence of two frequent conditions.

The condition raises important diagnosis problems, with subsequent therapeutic consequences.

The patient whose clinical condition is described showed also a thyroid papillary carcinoma, association to be approached in a subsequent communication and regarding a clinical case.

Introduction

Hypercalcemia is one of the most common metabolic changes, being life threatening when reaching certain values. Before a patient showing a high calcium level it is necessary to confirm this value with new laboratorial dosages and, to establish the due relation with the albumin values, particularly when the total calcium is just moderately high.

After confirmed the hypercalcemia, the subsequent action is to ascertain its etiology. A range of diseases, rather wide, might be underlying this electrolytic change (Table 1).

In the clinical practice, the conditions most often following hypercalcemia are the primary hyperthyroidism (PHP) and certain neoplasm, making both entities around 90% of cases.[4]

PHP incidence has increased amazingly since serial calcium dosage became a routine procedure, being ever more frequent not very expressive or even asymptomatic cases.[9,17,19]

This way, and according to a Hunter Heath study, in Rochester, Minnesota residents, PHP incidence rose from 7.8 per 100.000, from the 1st January 65 to the 31st June 1974, for 51.1% per 100.000, after the systematic dosage of serial calcium.[9]

The underlying mechanism to the calcium increase in PHP lies mainly in the parathormone acting on the kidney and bones.[1,12,20,21]

A hypercalcemia, in an anorectic patient, a marked weight loss and anemia, leads to a thorough search of neoplasm. Worthy noticing however that high calcium content usually shows up in a known tumor, but seldom is a part of its initial manifestation.[4,16.]

In Table 2 are presented the main neoplasm most often associated to hypercalcemia, and such appearance is predictive of a bad prognosis.[4]

The mechanisms through which neoplasm limit an increase of calcium values change with the different tumors. This way, in breast cancer, hypercalcemia almost always follows a bone involvement, with widespread metastization; it is admitted that an increase in the serum calcium is mainly due to a direct action of the tumor cells, promoting a bone reabsorption.[16] In other tumoral types, as hypernephroma, the squamous cell lung carcinoma, oropharynx, hypopharynx and tongue and also in the pancreas adenocarcinoma, hypercalcemia occurs often without bone metastization[16]. In these cases, most authors advocates the involvement of tumoral mediators which will promote the reabsorption at the skeleton level.[16] Some of these mediators, called as a whole by osteoclast activating factor (OAF) are already identified: it is the case of interleukin-1, the tumoral necrosis fac-

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TABLE I

Hypercalcemia Differential Diagnosis[2]

With high parathormone	Primary Hyperparathyroidism
	Tertiary Hyperparathyroidism
	Non-hematology neoplasm
Without high parathormone	Drugs (tiazides, furosemide, vit. D, calcium, vit.A, lithium)
	Granulomatous diseases (sarcoidosis, tuberculosis, beriliosis)
	Family hypercalcemia hypocalciuric
	Non-hematology neoplasm
	Hematology neoplasm
	Endocrinopathies (Addison disease, hyper and hypothyroidism)

tor and the growing modifier alpha-factor.[16] In the multiple myeloma, one of the neoplasm conditions more often followed by hypercalcemia, is thought to be also involved one or several OAF(s).[16] Another responsible for the increase in serum calcium, in neoplasm, is the PTH-like factor, an immune protein distinct from PTH, but with a similar biologic activity, promoting bone demineralization. This peptide will be particularly responsible, or co-responsible, by hypercalcemia in the hypernephroma and carcinoma in the squamous lung cells carcinoma.[16] Recently and for some authors, this protein related with parathormone, PTH-like, will be increased in most neoplasm following hypercalcemia, being very probably the main responsible for this metabolic change.[5,6] Another cause of hypercalcemia, in neoplasm, is the association of a primary hyperparathyroidism that for some authors will be verified in around 4% of cases.[4]

To make the distinction between the two main pathologic entities, responsible by the calcium high values, neoplasm and HPP, has particular interest the dosage of serum parathormone that, in general, is suppressed in the former and increased in the latter situation.[3,14,15,27,29.] On Table 3, there other laboratorial characteristics contributing for the differential diagnosis; we would like only to emphasize how useless it is the dosage of nephrogenic cyclic AMP, as this is also raised in PHP and in many neoplasm.[6,25]

Monoclonal gammopathy (MG) is an entity relatively common, particularly in individuals over 70 years

TABLE II

Neoplasm most often associated with hypercalcemia[16]

Breast carcinoma = 30 to 40%
Bronchial neoplasm (squamous cells and adenocarcinoma) = 12 to 30%
Squamous cells carcinoma of the head and neck = 3 to 25%
Kidney cells carcinoma = 3 to 17%
Multiple myeloma = 20 to 40%
Lymphoma of T cells in adults > 50%

TABLE III[4]

Hyperparathyroidism	Low phosphorous
	Hyperchloremia
	Increased 1,25 dihydroxi vit. D
Neoplasm	Normal or increased phosphorous
	Metabolic alkalosis
	Low 1,25 dihydroxi vit. D

TABLE IV

Differential diagnosis of monoclonal gammopathy[8]

A – Malignant
1 – Multiple myeloma
2 – Bone Plasmocytoma
3 – Extramedular Plasmocytoma
4 – Primary amyloidosis
5 – Waldenstrom Macroglobulinemia
6 – Heavy chain disease
7 – Associated with non-Hodgkin lymphoma and chronic lymphocyte leukemia
B - Non Malignant
1 – Monoclonal gammopathy of undetermined significance
2 – Reactional
3 – Transitory

old.[8] In its differential diagnosis we must consider several entities (Table 4). Within the MG reactions are included those following infectious, inflammatory

and neoplasm conditions.[8]

The association between PHP and a monoclonal gammopathy (MG) is a rare finding in the literature we searched, to find associations described between byparathyroidism and undetermined gammopathy or multiple myeloma (MM).[7,10,24,26] Some authors advance several etiology hypotheses for the PHP/MG association. Therefore some advocate the hypothesis of MG to be a body reaction to the parathyroid adenomatous tissue or hyperplasy,[7] while others admit that immunoglobuline will stimulate the proliferation of these glands.[7] Another hypothesis points towards the existence of an endogenous or exogenous factor, responsible for the simultaneous appearance of both anomalies.[26] A forth possibility is an anomalous protein which may have an exaggerated want for calcium, reducing the free fraction of this ion and it is therefore a stimulus for the parathyroids.[26] However it seems that most researchers do accept that the association between the referred entities results of a simple coincidence, in the same individual, of more or less frequent pathologies from the age of 50.[7,24]

Clinical Case

J.G. G., 66 years old, male, admitted in the Medicine II Services, on the 26th July 1991 due to epigastralgy, asthenia, anorexia and weight loss.

The patient mentioned the appearance, two months ago, of abdominal pain mainly in the epigastrium getting worst with food intake, and getting better with dorsal decubitus. This painful condition was followed by nausea and foaming vomits, marked anorexia and asthenia, having lost around 4 kg in the fortnight previous to admission.

At the time of admission and evolving for five days, he mentioned a febrile syndrome and frontal headache.

From the personal history is to be highlighted a tuberculosis pleurisies at 18 years of age, chronic bronchitis for the last 30 years, silicosis diagnosed 6 years ago (he used to work at Panasqueira Mining) and high blood pressure. He denied smoking or drinking alcohol habits.

In what refers to the family history there was no relevant fact.

The patient had no fever and showed a similar age to his real one, he was oriented both in time and space. There was no edema, adenopathies or anomalous skin coloration or mucosa. The thyroid was not palpable and cardiopulmonary auscultation was normal. Rhythmic radial pulse, 90 beats/min and a blood pressure of 130/80 mmHg. The abdomen was rounded, depressible, not painful to deep palpation and did not show organomegaly or ascytis.

The laboratorial balance performed was as follows:

Normal Hemogram. Hypercalcemia – 14,2 mg/dL (N 8,1-10,4) for an albumin of 4.3 g/dL (N3,2 – 5,5); Hypophosphoremia – 1,5 mg/dL (N 2,7 – 4, 5); Hyperchloremia – 117 mmol/L (N 90 – 110), Hypertriglyceridemia – 267 mg/dL (N 60-165); alkaline phosphatase of 158/IU/L being the normal value within the range of 15 – 69 UI/L. Renal function and liver enzyme within normal values. Electrophoresis proteinogram was normal and serial protein immunoelectrophoresis detected a monoclonal gammopathy IgA K, being normal the other immunoglobulines. The medulogram performed showed 8% of the cellular population made up by plasmocytes. The summary analysis of urine was normal. Calcium, in 24 hours urine, was slightly increased – 344 mg (N 100 – 250) and urinary phosphorous in the same period of time, was of 0,432 g (N 0,9 – 1,3). The thyroid tests and SACE were normal.

The osteocalcine showed slightly increased values -51ng/mL (N 1,9 – 11,1), being the calcitonine slightly increased – 11 pg/ml (N<10). Parathormone value was 396 pg/mL (N 10-65).

Upper gastroenteroscopy, performed to clarify epigastralgy showed an "acute erosive gastritis"; several erosions in the antrum, the body and fundum with an inflammatory halo and a few small clots".

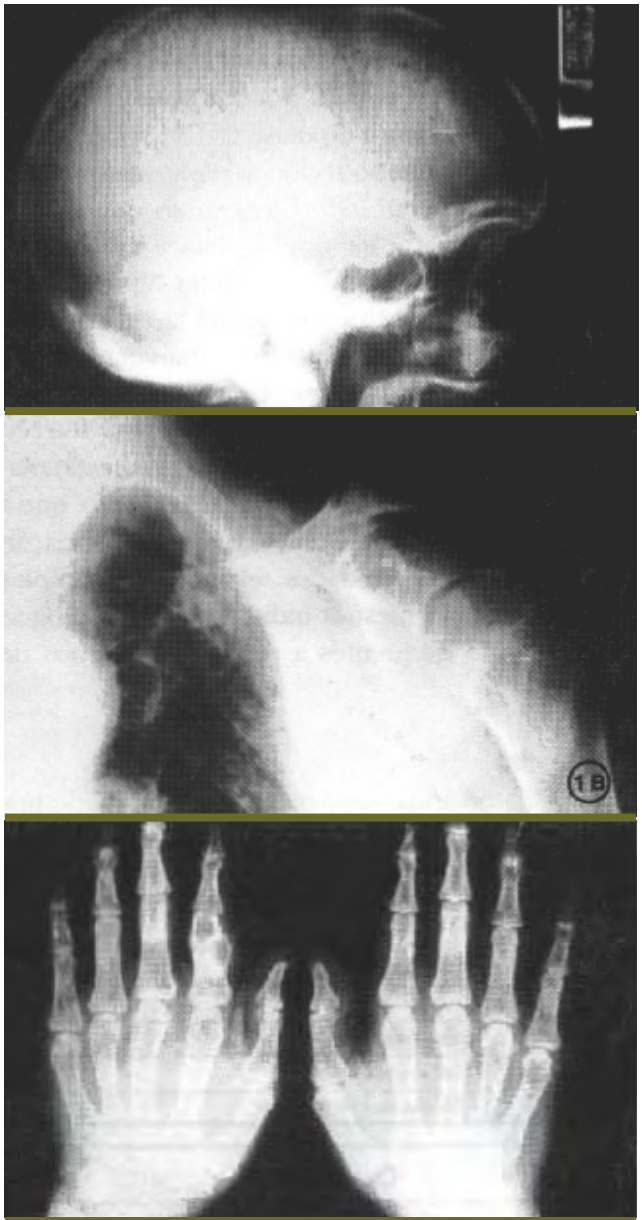
The abdominal echotomography has detected: "…renal and vesicular lytiasis, without any other changes".

The transrectal prostate echotomography has showed: "a prostate of slightly increased size, heterogenous texture with nodular formations, the higher of which with 1.5 cm of higher diameter in the left lobe, with some calcification and preservation of the capsule".

The skeleton radiology study, has shown the following changes (*Fig 1*).

It was also made a Intravenous urography that showed a nephrocalcinosis on the right.

A cervico-mediastinic CAT scan showed an " heteregenous nodular mass with hypodense zones corresponding to the thyroid right lobe. It is suggested a scintigraphy study to a better clarification".



Skeleton radiology changes. A – Image in "salt and pepper" of the skull bones. B – Reabsorbing the clavicle distal third and scapula osteolysis. C – Osteolytic phalanges images.

FIG. 1

The thyroid scintigraphy has shown a "thyroid gland of increased dimensions due to its right lobe that in its lower half is displaced at the top by something compressing its lower part".

Nuclear Magnetic Resonance Imaging referred to "... nodular formation in continuity with the lower third of the thyroid right lobe, measuring in its biggest diameters 2,8 x 3,4 cm, with well defined borders; it is not possible to establish if it is related with a thyroid adenoma or eventually of the parathyroid in lower location than the usual. It also observed the osteolytic image in the left shoulder of a metaphysis location that added to the reminder of the radiology exams suggest to correspond to a brown tumor".

The Electromyography on its turn, has detected "a slight entrapment of the right cubital nerve by the elbow or cubital tunnel. Very slight changes in the morphology of all potential of the motor unit, not fulfilling entirely the myopathic potential criteria.

Before the clinical condition and the diagnosis supplementary exams, namely the increased PTH value, a surgical cervical exploration was made. This has shown a "parathyroid node on the left and a lesion suspect of corresponding to a thyroid right carcinoma, having been a resection in block of the parathyroid node, sub-total thorax lobotomy on the right and thyme resection via cervical".

The Anatomic-pathological study of the surgical piece has shown to be thyroid papillary carcinoma and parathyroid adenoma.

Comments

1 – The primary hyperparathyroidism diagnosis was not hard to make, in the current case, due to the existence of hypercalcemia, hypophosphoremia, hyperchloremia, and parathormone frankly increased.
The radiology study made to the skeleton and abdomen was equally rather suggestive, showing, respectively, a subperiostic reabsorption characterized and images of nephrocalcinosis.
2 – Although the gastroduodenal pathology more often described in association with PHP is a peptic ulcer[2,25] we think it can have a causal relationship between the parathyroid dysfunction and the erosive gastritis present in our patient.
3 - It is curious and not very often, the association verified in the current case between PHP and monoclonal gammopathy (MG). We think to be a gammopathy of undetermined significance (MGUS), due to a normal hemogram, medulogram and renal function.[8] However, it was necessary a regular follow up, performing at regular intervals serial proteinograms and urinary, acknowledged it is a transformation of some of these MGUS in multiple myeloma.[8]
4 – We admit to have had an exaggeration of supplementary diagnosis exam to a pre-surgical location, namely the performance of a CAT scan and NMR. As

a matter of fact it is current opinion that an experienced surgeon in this kind of pathology, is capable of identifying in 95% of cases an abnormal parathyroid, reserving for the cases that undergo a first surgical probe inefficient or recurring , the use of invasive and non-invasive means already described.[13,18]

5 – We decided by the parathyroid surgery, based on the experience of most authors and particularly, in the "Consensus Development Conference Statement" on the diagnosis and handling of PHP, performed in 191, that anticipate the surgical treatment of hyperparathyroidism whenever it is symptomatic.[11,18,22,28] For some authors, when it is verified the association between MG, MM and PHP, even if asymptomatic, must precede the parathyroidectomy, not only to clear any doubt on the hypercalcemia etiology but also, as it can improve the co-existing MM prognosis.[24] ■

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