

Acute Pancreatite Revealor of Primary Hypercalcemic Yperparathyroidia

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Abstract: Primary hypercalcemic hyperparathyroid may be complicated by pancreatitis. This may be, exceptionally, the revealing mode of this endocrinopathy as reported in this observation. The relationship between primary hypercalcemic hyperparathyroid and pancreatitis is controversial to date, although most publications and experimental data support the causal direct or indirect role of hypercalcemia. It may even be a triggering factor in individuals predisposed to pancreatitis by genetic mutations.

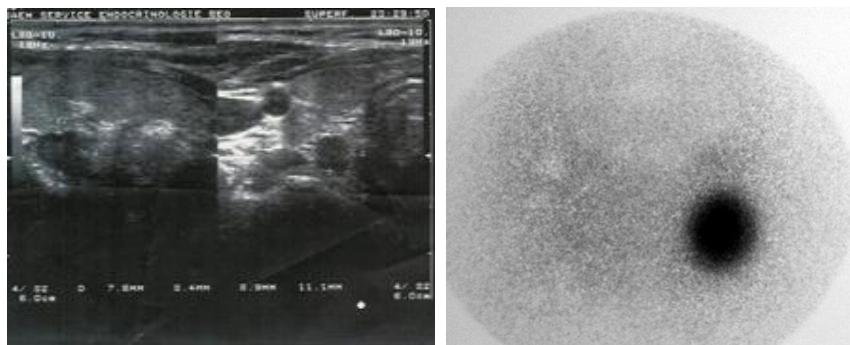
Keyword: hyperparathyroidism, hypercalcaemia, pancreatitis

I. Observation

Patient aged 69 admitted to emergency for acute digestive table made of abdominal pain and vomiting. In these antecedents we note the notion of bilateral colic nephritic episodes spontaneously resolving, of arterial hypertension under bi-therapy (calcium antagonist and angiotensin II receptor antagonist), type IV dyslipidemia under fibrate.

Clinical examination and radiological exploration led to the diagnosis of pancreatitis. The rate of lipase was 261 (N <67). Pancreatitis was classified as stage C of Balthazar with abdominal CT. She was alithiasic in cholangio-MRI. The classic causes of pancreatitis were eliminated and the triglyceride level was normal. Etiologic research revealed a disturbed phosphocalcic balance with a typical profile of primary hyperparathyroidism: PTH 402 pg / ml (15-65), hypercalcemia 147 mg / l (85-105), hypophosphatemia 16, 05 mg / l (20-45). The cervical ultrasound shows a parathyroid nodule of 20x15 mm at the left cervico-mediastinal extending upper the clavicle. There was no effect of hypercalcemia on ECG and renal ultrasound. Dental care was programmed for bisphosphonate perfusion. There was no effect of hypercalcemia on ECG and renal ultrasound.

The treatment included resting for the digestive tract, hydration, Lasilix 40 mg daily, 3 injections of calcitonin subcutaneously at 100 U. The patient will be addressed to surgery.



Left basilobar parathyroid adenoma



Fibrocystic osteitis

II. Discussion

Primary hyperparathyroidism is a frequent endocrinopathy. The clinical presentation has changed and the frequency has increased in recent years since the development of automated measurement of serum calcium. It results from an autonomous, inappropriate, excessive and chronic secretion of PTH. Primary hyperparathyroidism is usually sporadic in 90-95%. It can be genetic in 5 to 10% integrated into one of the following syndromes: multiple endocrine neoplasia NEM1 and NEM 2A, NEM4, familial hyperparathyroidism syndrome, jawtumor syndrome, isolated familial hyperparathyroidism, familial hypercalcemia hypocalciuric, having all in common a dominant autosomal transmission. Sporadic primary hyperparathyroidism is a predominantly female condition. It affects 2 to 3 times more the women from the 5th decade and would be more frequent in postmenopausal women. Our patient was aged 69 years. Primary hyperparathyroidism is related to a single parathyroid adenoma, benign in 75 to 85% as the case of our patient, several adenomas in 2 to 12%, cell hyperplasia in 15 to 25%. Parathyroid cancer is rare in less than 1% of cases.

The pathophysiology of primary hyperparathyroidism is based on the loss of negative retro control of serum calcium on PTH secretion. It will result a sustained inappropriate secretion of PTH that will act on the target organs:

In bones it will stimulate osteoclasts and increase the release of calcium to the plasma. In kidney, where it will have a double action: decrease urinary excretion of calcium; produce the active form of vitamin D calcitriol which will increase intestinal absorption of calcium. All of these actions will result in plasma a hypercalcemia.

From This, Three Clinical Forms Emerge:

Symptomatic bone forms and renal forms becomes exceptional and historical (osteitis fibrocystic), less than 5% and renal form in 20%.

Low or asymptomatic normo-calcemic forms are the most frequent and account for 80%. However, it should be noted that even if calcium is normal, ionized calcium is always high. The first manifestations in our patient were renal by episodes of renal colic spontaneously resolving a year before his hospitalization.

The diagnosis of primary hyperparathyroidism is biological. It is based on bringing out the excessive inappropriate PTH secretion for an elevated or a normal serum calcium levels. The topographic diagnosis involves conventional imaging: cervical ultrasound, CT and cervical MRI; and functional MIBI scintigraphy for ectopic and multiple sites. Our patient had a typical hypercalcemic hypophosphatemic HPTP profile in relation to a 20 x 15 mm parathyroid adenoma.

The treatment of hypercalcemic primary hyperparathyroidism is radical and surgery is not disputed. It's a cervicotomy oriented by morphological and / or functional tracing, where the surgical success rate is better or an exploratory cervicotomy when the adenoma has not been detected preoperatively. For normocalcemic and asymptomatic forms, they are based on the consensus established by evaluating the level of elevation of calcemia and evaluating renal, bone, and age impact as they are criteria for operability. Major hypercalcemic forms of primary hyperparathyroidism should be medically prepared for surgery. Calcium must be lowered and reduced to acceptable levels for anesthesia to control dehydration and cardiovascular risks. Rehydration is of 3 to 6 liters depending on the patient's profile. The medicines used are: Lasilix at a rate of 40 mg per day depending on the blood pressure profile. Corticosteroid therapy is indicated if secondary hypercalcemia in myeloma. Calcitonin is prescribed at 2 to 5 U / kg / day, half-life being short, 3 times subcutaneous.

The bisphosphates by their antiresorptive action have considerably improved the prognosis of these major hypercalcaemias. Administered as perfusion, they allow to normalize the serum calcium rapidly in a few days with a prolonged effect over a month, but this will increase the risk of hypocalcemia in postoperative. The buccal sphere must first be examined to minimize the risk of osteonecrosis of the maxilla, which remains their most serious complication. Our patient received dental care, calcitonin injections before the perfusion of bisphosphonate.

Apart from bone and renal forms, primary hyperparathyroidism can be revealed by atypical forms such as isolated brown tumors or pancreatitis as was the case for our patient, raising the question about the relationship between primary hyperparathyroidism and pancreatitis.

Acute pancreatitis is an inflammation of the pancreas due to activation of pancreatic proenzymes leading a self-digestion of the gland, with release of enzymes in the pancreatic loge the abdomen and the blood and lymphatic circulation. In the benign form, the inflammatory process is limited to edema. In the severe form, the course is towards pancreatic or peri-pancreatic necrosis. His diagnosis must be early. It is based on clinical arguments: a form of abdominal pain syndrome associated with general signs related to the diffusion of enzymes in the circulation. Biologically we note the elevation of enzymes, amylasemia but especially lipasemia which is more specific: greater than 3-4 times the normal. Radiologically by the use of ultrasound and CT which represents the reference examination to draw up a pancreatic and extra-pancreatic lesional balance, follow the evolution, and to establish a classification with prognostic value including the classification of Balthazar. The

two main etiologies of acute pancreatitis are biliary lithiasis 50-60% and alcohol 30-40% cases. The other etiologies of non-biliary and non-alcoholic pancreatitis are rare, represented by: infectious, autoimmune, traumatic, tumoral, medicinal, genetic, metabolic and idiopathic causes. Metabolic pancreatitis is due to hypertriglyceridemia in 1.3 to 5.3% and hypercalcemia. Less than 1% of acute pancreatitis is due to hypercalcemia. The implication of hyperparathyroidism in acute pancreatitis has been reported little in the literature. Since its first description, the association of these two pathologies is still subject to debate about the nature of the relationship and the mechanisms of involvement.

Primary Hyperparathyroidism And Pancreatitis:

The coexistence of these two pathological situations raises the question of the existence of a cause-and-effect relationship. Indeed, the association of primary hyperparathyroidism and acute or chronic pancreatitis is controversial in the literature. The first reported case of the hypercalcemic due to primary hyperparathyroidism associated to pancreatitis dates back to 1940 (1) and already in 1962 Mixter (2) examined 62 cases of pancreatitis reported in literature in patients with primary hyperparathyroidism. Since and despite the publication of series and cases there remains a question between the existences of a real association between these two pathologies. In 2012, an analysis of 10 retrospective studies (3) published until there, showed that 8 studies suggest an association between primary hyperparathyroidism and pancreatitis while two refute this relationship. Studies that support this relationship report a prevalence of pancreatitis in primary hyperparathyroidism of 1 to 15%, with higher serum calcium levels in primary hyperparathyroidism patients with pancreatitis than in patients without pancreatitis, which may assume a threshold level of Calcium predisposing to the occurrence of pancreatitis during primary hyperparathyroidism.

The reports against the existence of such an association come from the Mayo Clinic in Rochester. They argue that it's difficult to establish a relationship between these two pathologies in hospitalized patients due to the biased measurement of serum calcium (4). Although it was not part of the routine admission record, serum calcium was systematically measured in all patients with pancreatitis, so they are preferentially screened for primary hyperparathyroidism compared to those who do not have pancreatitis. In addition, 40 to 65% of the cases of pancreatitis associated with PHPT have had at least one concomitant etiology for pancreatitis, such as gallstones, alcohol abuse or elevated triglycerides. Indeed even our patient had well-controlled hypertriglyceridaemia under treatment. If this argument reinforces the absence of a relationship between these two disorders, it may well suggest that the occurrence of hypercalcemic pancreatitis will require other factors other than hypercalcemia, predisposing or promoting, and makes it understandable that all the patients with primary hyperparathyroidism do not develop pancreatitis and that this is exceptionally reported in normocalcic primary hyperparathyroidism.

It seems more logical now to conceive a link between primary hyperparathyroidism and the occurrence of pancreatitis in which calcemia seems to be a determining modulator or mediator. In a retrospective study (5) comparing two groups of patients with primary hyperparathyroidism, the first one of 19 patients with acute pancreatitis, the second of 65 patients without pancreatitis. Age, PTH, and anatomopathology (number of adenomas) were similar in both groups. Only calcemia appeared to be a prognostic factor for the onset of pancreatitis, it was higher in the first group (3.16 mmol / l) than in the second group (2.82 mmol / l). The implication of hypercalcaemia in the occurrence of pancreatitis is reinforced by observations of pancreatitis in situations of extra parathyroid hypercalcemia such as parenteral nutrition, calcium perfusion during cardiac surgery, myeloma. The pathophysiology of hypercalcaemia in pancreatitis stills a subject to several hypotheses. Some assume that the calcium responsive CaSR receptor expressed in pancreatic acinar cells may play a pathological role. But although some studies (6-7-8) have identified mutations of this receptor in some patients with pancreatitis, these mutations were not increased in patients with primary hyperparathyroidism and pancreatitis compared with those with only primary hyperparathyroidism. Other hypotheses suggest a direct role of plasma hypercalcemia independently of CaSR.

In this case, extracellular hypercalcemia leads to an increase in the calcium of the pancreatic juice and leads to an elevation of cytosolic calcium signals. The result is a local DIC causing lesions of necrosis or haemorrhage, or a pathological activation of the pancreatic proteases in particular trypsin from inactive trypsinogen which leads to the self-regulation of the pancreas. More recently, Felderbauer et al (9) mentioned a genetic risk factor, it's the mutation of the serine protease inhibitor Kasal type 1 (SPINK 1) and CFTR gene. SPINK 1 is a natural inhibitor of trypsinogen and mutations in this gene have been reported in some pancreatitis. The mild mutations in the CFTR gene are responsible for attenuated forms of cystic fibrosis with pancreatitis. The management of these two pathologies must join the treatment reserved for each of the two. The combination of primary hyperparathyroidism doesn't alter the therapeutic management of acute pancreatitis which rests on resting of the digestive tract. Threatening hypercalcemia (> 3 mmol / l) should be given pre-operative medical treatment as was the case for our patient. Parathyroid surgery should be considered as soon as

the acute episode of pancreatitis is resolved after morphological topography by cervical or functional ultrasound by MIBI scintigraphy.

III. Conclusion

Our observation agrees with the literature that the association between primary hyperparathyroidism and pancreatitis is more than fortuitous and that there is a causal link between these two pathologies. Although the pathophysiology of the involvement of HPTP hypercalcemia is not fully elucidated, experimental data argue for the direct or indirect role of hypercalcemia via the activation of pancreatic proteases. Hypercalcemia may act as a permissive mediator or a modulator of genetic or environmental factors. Acute pancreatitis may be indicative of HPTP. HPTP is a curable cause of pancreatitis. It is therefore necessary to systematically search for HPTP by the simple determination of serum calcium in the presence of alithiasic pancreatitis.

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