Hypercalcemia induced pancreatitis as a rare presentation of primary hyperparathyroidism

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Abstract

Acute pancreatitis (AP) is an inflammatory process of the pancreas. It is a relatively common cause of acute upper abdominal pain and is potentially associated with high morbidity and mortality. Underlying hypercalcemia as a cause of AP is very rare. We present a case of a hypercalcemia-induced acute pancreatitis with an underlying parathyroid adenoma in an 81-year-old woman with no previous symptoms of hypercalcemia. The parathyroid adenoma was semi-urgently surgically resected with normalization of calcium-levels. This case report summarizes the causes of acute pancreatitis and hypercalcemia and its management. (Acta gastroenterol. belg., **2021**, 84, **367-370**).

Keywords : Pancreatitis, hypercalcemia, hyperparathyroidism, parathyroidectomy, parathyroid adenoma.

Introduction

We present a case of an 81-year old woman who was diagnosed with acute pancreatitis as a first presentation of hypercalcemia. Gallstones and long standing alcohol use are the most frequent causes of pancreatitis. However, in patients without these risk factors several rare causes, such as auto-immunity, drugs, hypertriglyceridemia or hypercalcemia, should be considered (1,2). Hypercalcemia with an elevation of parathyroid hormone (PTH) is a signature of primary hyperparathyroidism (PHPT) (3).

Case history

An 81-year-old patient presented to the emergency room with acute abdominal pain and vomiting for three days. The pain did not irradiate to the back and was continuous. Fever, diarrhoea, cough or expectoration were absent. There was arterial hypertension, hypercholesterolemia and chronic kidney insufficiency in the patient's history. She was a never-smoker and never-drinker. Her actual therapy consisted of a beta-blocker, thiazide diuretic, ace inhibitor and a statin on a daily basis.

The patient was hemodynamically stable and afebrile upon admission. Physical examination showed an upper abdominal tenderness with rebound tenderness.

Blood analysis revealed leucocytosis of $24.3x10^E9/L$ ($4.20\text{-}9.80x10^E9/L$) with neutrophilia ($21.70x10^E9/L$; 89.5%) and an elevated C-reactive protein (CRP) of 82.0 mg/L (0.0-5.0 mg/L). Lipase was elevated to 606 U/L (13-60 U/L) with liver transaminases, alkaline phosphatase and gamma-glutamyltransferase within normal ranges. Lactate dehydrogenase was normal. The ionogram showed a hypophosphatemia (0.63 mmol/L with reference range 0.81-1.45 mmol/L) and remarkable hypercalcemia of 3.36 mmol/L (2.20-2.55 mmol/L) with albumin within normal range. There was a known and stable impairment of renal function (creatinine 1.30 mmol/L with reference range 0.42-1.14 mmol/L).

A computed tomography (CT) scan of the abdomen with intravenous contrast after intravenous hydration showed an infiltration of the peripancreatic fat without necrosis (Balthazar score 2), indicating mild pancreatitis. Kidneys, adrenal glands, liver and gallbladder occurred normal.

The possibility of hypercalcemia associated acute pancreatitis was presumed. Venous blood gas confirmed an elevated ionized calcium of 1,65 mmol/L (1,15-1,33 mmol/L). Parathormone (PTH) was elevated to 261.0 ng/L (15.9-60.9 ng/L) and 25-OH-vitamine D was low (22.1 µg/L with reference range >30.0 µg/L). A normal 24-hour urinary calcium excretion excluded familial hypocalciuric hypercalcemia.

Ultrasound of the thyroid and parathyroid showed a supplemental hypo-echogenic mass in the right tracheoesophageal groove (figure 1). 99m Tc-sestamibi SPECT-CT showed a focus posterior of the right thyroid lobe, suspicious for parathyroid adenoma (figure 2). Thus, the diagnosis of primary hyperparathyroidism due to a parathyroid adenoma was made. Metanephrines and catecholamines in a 24-hours urinary collection were within normal range and serum calcitonine resulted normal.

Early fluid resuscitation was started in absence of antibiotics with a favourable clinical and biochemical evolution concerning the pancreatitis. Calcium decreased to 2.81 mmol/L after start of cinacalcet, a calcimimetic, and interrupting the use of the thiazide diuretic.

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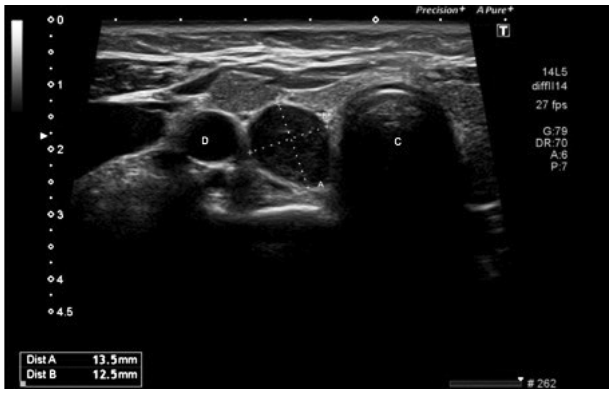

Figure 1 — Ultrasound of the thyroid and parathyroid with a hypo-echogenic mass of 13,5 mm (A) 12,5 mm (B) in the right tracheoesophageal groove, in between the trachea (C) and carotid artery (D).

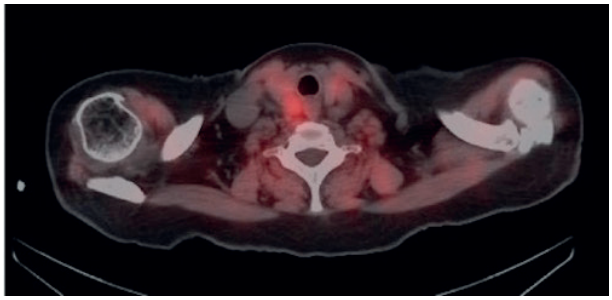

Figure 2 — 99mTc-MIBI thyroid image showing a nodule posterior of the right thyroid lobe with accumulation of the tracer, compatible with parathyroid adenoma.

Semi-urgent parathyroidectomy was performed. The patient was intubated with neuromonitoring endotracheal tube for recurrent laryngeal nerve monitoring. A minimally invasive approach was chosen because of congruous preoperative imaging. Through a 4cm horizontal midline skin incision, the thyroid bed was exposed lateral to the strap muscles. After gentle retraction of the thyroid lobe medially, the parathyroid adenoma was identified inferiorly and was carefully resected with bipolar forceps and cotton peanuts. The vagus nerve was successfully stimulated at the beginning and end of the procedure in the carotid sheath.

Intraoperative PTH-monitoring confirmed successful adenoma resection with a drop from 300ng/L to 98ng/L after 10 minutes, further down to 10,7ng/L (15,9-60,9ng/L) at postoperative day (POD) 1. Calcemia normalised at POD 2 and the patient was discharged at POD 3.

Discussion

Acute pancreatitis

Acute pancreatitis is an inflammatory disease of the pancreas with substantial morbidity and mortality (1). Incidence of acute pancreatitis is rising worldwide.

Table 1. — **Causes of acute pancreatitis** (1,2)

Gallstones / obstructive pancreatitis
Alcohol
Idiopathic
Inherited - genetic
Drug-induced
Iatrogenic (post-ERCP, post-abdominal or cardiac surgery, liver biopsy)
Infectious (parasitic, viral, bacterial, fungal
Hypertriglyceridemia and hypercalcemia
Autoimmune
Other – trauma, pregnancy, ischemia

A nationwide cohort in the Netherlands showed an incidence of 14,7 per 100 000 persons per year (4).

Gallstones (40%) and chronic alcohol consumption (30%) are responsible for most of the cases of acute pancreatitis. Other less frequent causes of acute pancreatitis are listed in Table 1 (1,2).

Acute pancreatitis due to PHPT-induced hypercalcemia is rare. In patients with PHPT, acute pancreatitis is reported in 3%-15% of patients (5,6). Nonetheless, hypercalcemia due to other causes can also induce acute pancreatitis (7). The true association between pancreatitis and PHPT is debatable. Several studies report against a causal relationship because other risk factors were present (5). In our case, the use of a thiazide diuretic was an additional risk factor.

Hypercalcemia induced acute pancreatitis is believed to be caused by inducing increased intrapancreatic conversion from trypsinogen to trypsin leading to damage of the pancreas (2). Also deposition of calcium in the pancreatic duct followed by pancreatic duct obstruction or underlying genetic variants are suggested as pathophysiological mechanisms of acute pancreatitis in PHPT (8).

Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a relatively frequent endocrine disorder. It is characterized by hypercalcemia and (inappropriately) elevated serum levels of PTH. Other causes of hypercalcemia are listed in Table *2*.

The introduction of routinely measurement of serum calcium levels in the 70's has led to identification of a lot of asymptomatic patients. The prevalence is now

Table 2. — **Causes of hypercalcemia** (3)

Primary hyperparathyroidism
Malignancy
Granulomatous disorders (sarcoidosis)
Thyrotoxicosis
Drugs (thiazides, lithium,…)
Milk alkali syndrome (excessive ingestion of calcium carbonate)
Vitamin D toxicity
Familial hypocalciuric hypercalcemia

estimated around 3 per 1000 in the general population of Europe. Elderly women are typically affected with a prevalence around 21/1000 in women between 55 and 75 years old (9).

In 90% of the cases, PHPT is caused by the presence of an adenoma or rarely by multiple adenomas. Hyperplasia of the four parathyroids is another cause of PHPT (10%). Underlying parathyroid carcinoma is an extremely rare finding in patients with PHPT (<1%).

Although the majority of PHPT is sporadic, it is essential to be aware of positive familial history. The physician should be alert to signs of associated endocrinopathies such as pheochromocytoma or medullar thyroid carcinoma, as seen in multiple endocrine neoplasia (MEN) syndrome (10).

As noted above, most cases are detected by elevated serum calcium levels on routine biochemistry. Symptomatic patients can typically present with 'moans, bones, stones and groans' referring to a depressed mood, musculoskeletal symptoms, renal stones and abdominal pain. Polyuria and polydipsia can develop secondary to a hypercalcemia induced nephrogenic diabetes insipidus. Hypercalcemia induced pancreatitis is a very rare presentation of PHPT. Moreover, increasing calcium levels can lead to severe complications varying from coma to shortened QT interval and ventricular fibrillation (3).

The diagnosis of PHPT is based on the finding of a hypercalcemia in combination with augmented or inappropriately normal levels (>20 ng/l) of PTH. Imaging studies, such as ultrasound and 99m Tc-sestamibi SPECT-CT, are used in the further work-up of PHPT, especially in preoperative setting to locate the adenoma as the introduction of perioperative PTH monitoring has made minimal invasive surgery possible.

Parathyroid ultrasound is a safe technique and does not involve radiation. It can detect a parathyroid adenoma as a well-circumscribed mass which is hypo-echogenic to the surrounding thyroid gland with peripheral vascularity. Sensitivity from ultrasound ranges from 70.4 to 81.4% (11). 99m Tc-sestamibi scan is a nuclear imaging technique which is based on different washout rates of sestamibi from the thyroid in comparison to slower washout in hyperactive parathyroid tissue. Adding SPECT-CT results in an increased diagnostic accuracy as it can detect ectopic parathyroid tissue. Sensitivity ranges from 64 to 90.6% (11,12,13).

A 24-hour urine collection is done in patients with suspicion of PHPT to confirm hypercalciuria and high fractional excretion of calcium. Hereby it is possible in majority of cases to differentiate from familial hypocalciuric hypercalcemia (FHH). Diuretics should be withheld before starting the collection (12). In this case 24-hour urinary calcium level resulted normal. This could be explained by the start of cinacalcet before completion of the urinary collection because of symptomatic high serum calcium levels. Moreover, the patient was under active treatment with a thiazide diuretic on admission.

Treatment

Acute pancreatitis

In case of mild pancreatitis, the vast majority of patients recovers with conservative measures. A nothing by mouth policy is recommended for at least 24 hours and fluid resuscitation with intravenous fluids remains the corner stone of treatment in order to preserve adequate intravascular volume as third spacing leads to fluid losses. In case of acute pancreatitis due to hypercalcemia, fluid resuscitation with lactated Ringer's solution is contraindicated because it contains calcium. Secondary, adequate pain control is essential as uncontrolled pain can contribute to hemodynamic instability. The underlying etiology, for example choledocholithiasis, needs to be corrected whenever possible (1,2).

Hypercalcemia

In case of severe hypercalcemia (calcium >3.5 mmol/l corrected for albumin concentration) rehydration with isotonic saline at rate of at least 200 ml/hour is initiated. (12) Loop diuretics are not favoured as they can precipitate intravascular volume decline and worsen hypercalcemia. Calcitonin inhibits bone resorption and is effective in reducing serum calcium concentration but in the acute setting IV bisphosphonates are preferred to treat the cause of hypercalcemia.

Surgery is the therapy of choice in symptomatic patients with PHPT, but is also recommended in patients with very high concentrations of serum calcium (>3 mmol/l), age less than 50 years, osteoporosis (T-score ≤ -2.5) or fragility fracture and declined kidney function (GFR <60 ml/min). If the patient is unable to undergo surgery because of comorbidity, contraindications or failed previous exploration medical therapy is indicated. If bone density is normal, cinacalcet is preferable to bisphosphonates as studies could not establish changes in serum biochemistry in patients treated with bisphosphonates (12).

Thiazide diuretics and hypercalcemia

Thiazide diuretics are frequently prescribed antihypertensive agents. Thiazide-induced hypercalcemia is a very well-known side effect. Several mechanisms of action have been proposed, but reduction of calciuria by increased renal tubular reabsorption of calcium seems to be most likely (14). A retrospective study of 221 patients with thiazide-associated hypercalcemia showed persistent hypercalcemia in 71% of the patients despite discontinuation of the thiazide. So Giebeler *et al*. suggested that an underlying state of PHPT was unmasked in these patients (15). Otherwise, thiazide diuretics may be used in patients with PHPT at risk for nephrolithiasis as thiazides reduce the excretion of urinary calcium and thereby the formation of calcium stones (11).

In conclusion, we report a case of acute pancreatitis as a first presentation of hypercalcemia due to primary hyperparathyroidism, which is rare. Consequently, this case report highlights the importance of exclusion and further investigation of hypercalcemia in acute pancreatitis, even in geriatric patients. Surgery is the first choice of treatment in symptomatic patients with PHPT.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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