1130-0108/2009/101/1/65-69
REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS

REV ESP ENFERM DIG (Madrid)
Vol. 101. N.° 1, pp. 65-69, 2009

CLINICAL NOTE

Acute pancreatitis associated with hypercalcemia. A report of two cases

J. Egea Valenzuela, E. Belchí Segura, A. Sánchez Torres and F. Carballo Álvarez

Service of Digestive Diseases. University Hospital Virgen de la Arrixaca. Murcia, Spain

ABSTRACT

Hypercalcemia due to hyperparathyroidism is a rare etiology for acute pancreatitis, oscillating between 1.5 and 7% in the different series. Although the cause-effect relationship and the pathophysiology of the condition are not clear, it seems that the association among them is not incidental, and serum calcium could be a major risk factor, so that pancreatitis would come to occur during severe hypercalcemia attacks. Mutations in different genes have been proposed as well to justify why only some patients with primary hyperparathyroidism and hypercalcemia develop acute pancreatitis.

References to cases like these ones are rare in the literature. We report two patients with acute pancreatitis associated with hyperparathyroidism and hypercalcemia, one of them with a fatal outcome.

Key words: Acute pancreatitis. Hypercalcemia. Hyperparathyroidism.

Egea Valenzuela J, Belchí Segura E, Sánchez Torres A, Carballo Álvarez F. Acute pancreatitis associated with hypercalcemia. A report of two cases. Rev Esp Enferm Dig 2009; 101: 65-69.

INTRODUCTION

Acute pancreatitis may have a great variety of etiologies. It is accepted that alcohol consumption and biliary lithiasis are responsible for almost 80-90% of all cases. Other, much more infrequent causes include toxics or drugs, neoplastic obstruction of the bile tract or the sphincter of Oddi, metabolic disorders such as hypertriglyceridemia or hypercalcemia, trauma, ischemia, infection, autoimmune diseases, etc. Up to 10% of cases are described as idiopathic pancreatitis because no main cause of the disease could be established.

Patients with hyperparathyroidism and hypercalcemia present with an increased risk of suffering acute pancreatitis, about 10 times above that of the general population. Nevertheless, pancreatic disease is a rare complication in these patients (approximately 2%). Elevated serum calcium levels associated with different mutations in several genes could be responsible for this predisposition in some patients with hyperparathyroidism. In this respect some studies have been already carried out with the SPINK1 (serine protease inhibitor Kazal type 1), CFTR (cystic fibrosis transmembrane conductance regulator), and CASR (calcium-sensing receptor) genes.

Although an association between these entities has been widely described and several theories about their pathogenetic mechanisms have been proposed, references in the medical literature to cases of acute pancreatitis associated with hyperparathyroidism and hypercalcemia are few. Acute pancreatitis episodes are commonly seen in patients already diagnosed with hyperparathyroidism, or immediately after parathyroidectomy, but it is exceptional as a first manifestation of hyperparathyroidism. We herein report two cases that, with no other intercurrent conditions, had acute pancreatitis with no other relevant changes except for elevated serum calcium levels secondary to previously unknown primary hyperparathyroidism.

CASE REPORT 1

A 54-year-old man presented with abdominal pain. He had undergone tonsillectomy during childhood, and some years ago he was admitted to hospital because of community-acquired pneumonia. He was a smoker of

Received: 30-09-08.
Accepted: 13-10-08.

Correspondence: J. Egea Valenzuela. Service of Digestive Diseases. University Hospital Virgen de la Arrixaca. Ctra. Madrid-Cartagena, s/n. 30120 El Palmar. Murcia, Spain

about 10 cigarettes per day with no other toxic use, and was not on chronic treatment.

He had also been admitted to hospital three times for abdominal pain with high serum amylase, whereupon he was diagnosed with idiopathic pancreatitis. A study was carried out by his gastroenterologist, which only intermittently found serum calcium levels near to upper limits of normality (normal range: 8.4-10.4 mg/dl). It is also remarkable that serum calcium levels were always normal during previous acute pancreatitis events.

He is admitted again to our hospital for continuous abdominal pain in the epigastrium accompanied by nausea and vomiting. In the first study we found:

—Hemoglobin: 13.8 g/dl; hematocrit: 40%.

—White blood count: 13,400 (81% neutrophils).

—Glucose: 99 mg/dl; urea: 33 mg/dl; creatinine: 1.03 mg/dl.

—Serum amylase: 1980 U/L; lipase: 630 U/L.

—Cholesterol: 210 mg/dl; triglycerides: 98 mg/dl.

—Total protein: 7.1 g/dl; albumin: 4.5 g/dl.

—Serum calcium: 11.7 mg/dl.

He was diagnosed with acute pancreatitis, and abdominal ultrasounds and endoscopic ultrasonography scans were carried out. These were both normal, with no lithiasis, microlithiasis, or other biliary alterations. An abdominal CT scan showed an edematous, unstructured pancreas with no other findings.

As all these explorations were negative, elevated serum calcium levels were proposed as a potential etiology for this disease. New serum calcium and intact parathyroid hormone (iPTH) measurements were obtained: serum calcium: 11.9 mg/dl; iPTH: 451 pg/ml (normal < 9 pg/ml). Hypercalcemia due to hyperparathyroidism was thus confirmed.

The patient improved in the following days, with amylase and lipase levels back to normal, correct oral feeding, and no abdominal pain. When the disease had disappeared completely a 99mTc-Sestamibi scintigram was performed, which found lower uptake consistent with a right-side parathyroid adenoma. Some days later the patient underwent surgery for the excision of this tumor. During the procedure, immediately after parathyroidectomy, a significant decrease in iPTH levels was confirmed. Afterwards, a histological study of the surgical piece confirmed that the mass was a parathyroid adenoma.

After surgery serum calcium went back to normal, and the patient had no more episodes of abdominal pain during follow-up.

CASE REPORT 2

This was a 73-year-old diabetic male with hypertension who was on no drugs. He reported no toxic or drug usage. Two years ago he had been admitted to hospital because of toxic hepatitis from amoxicillin-clavulanate. Since then, he was being followed up by a gastroenterologist, and had shown elevated serum calcium in several blood tests. No etiology for hypercalcemia was ever confirmed.

This time he was admitted to our hospital because of idiopathic acute pancreatitis with epigastric pain, nausea and vomiting, and significantly elevated amylase and lipase levels, with no other lab or imaging findings. His clinical course was favorable during the first few days -- abdominal pain and vomiting subsided, and oral feeding was restored. Nevertheless, his clinical status suddenly worsened, with abdominal pain and progressive consciousness deterioration. A progressive increase in serum calcium, which reached 15.5 mg/dl (normal: 8.4-10.4 mg/dl), and iPTH levels at 311.2 pg/ml (normal: < 9 pg/ml) were also seen. A cervical sonogram was carried out, and a cystic tumor adjacent to the left thyroid lobe was found.

The patient was admitted to the ICU and did poorly the following days. Serum calcium could not be taken back to normal levels in spite of intensive medical treatment. iPTH reached 1900 pg/ml. He was operated on for the excision of a node located in upper left parathyroid gland. Immediately after surgery iPTH decreased to 324.7 pg/ml, and returned to normal in the following hours, as did serum calcium. Despite these changes and the medical procedures performed, the patient developed severe metabolic acidosis and a refractory shock, and died from asystolia with no response to cardiopulmonary resuscitation.

DISCUSSION

Unknown hyperparathyroidism and hypercalcemia is a rare cause of acute pancreatitis that represents around 1.5-7% of all pancreatitis cases. There is no clear pathophysiological basis, but the relationship between acute pancreatitis and primary hyperparathyroidism seems not casual, and high serum calcium levels may be the main risk factor for developing acute pancreatitis in this context. So, there seems to be a direct effect of calcium levels on the severity of pancreatic disease. Hypercalcemia would be responsible for an activation of pancreatic enzymes through acid lysosomal hydrolases, which play a decisive role in this process.

It is very important that hypercalcemia be treated extensively in these patients, and its origin should be found early. Management must be carried out in intensive care units because of the severity of this disease, and it is desirable that gastroenterologists and endocrinologists also participate. Definitive treatment consists of surgically excising the responsible parathyroid adenoma.

Although patients with hypercalcemia due to primary hyperparathyroidism are more at risk of acute pancreatitis than the general population (about ten times more),

this association is relatively infrequent. There are several theories involving genes such as SPINK1 (serine protease inhibitor Kazal type 1) or CFTR (cystic fibrosis transmembrane conductance regulator). Some authors support the possibility that mutations on these genes may facilitate the development of this disease in situations of intense hypercalcemia. Studies are ongoing on other genes such as CASR (calcium-sensing receptor), but their role in this process is not clear yet.

CONCLUSION

In acute pancreatitis associated with hypercalcemia primary hyperparathyroidism should be suspected. Complementary explorations such as serum calcium and intact parathyroid hormone levels, and imaging techniques such as cervical ultrasounds, computed tomography and scintigraphy using 99mTc-Sestamibi, should be ordered, which will lead to confirm clinical suspicion and definitive surgical treatment.

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Pancreatitis aguda asociada a hipercalcemia. Presentación de dos casos

J. Egea Valenzuela, E. Belchí Segura, A. Sánchez Torres y F. Carballo Álvarez

Servicio de Aparato Digestivo. Hospital Universitario Virgen de la Arrixaca. Murcia

RESUMEN

La hipercalcemia secundaria a hiperparatiroidismo es una causa rara de pancreatitis aguda, variando entre el 1,5-7% según las series consultadas. Aunque la relación causal y la fisiopatología del proceso no están totalmente aclaradas, parece claro que la asociación no es incidental y que los niveles de calcio sérico serían un factor de riesgo mayor, desencadenándose los cuadros de pancreatitis durante las crisis de hipercalcemia. También se han descrito alteraciones en diversos genes que podrían estar implicados, justificando por qué sólo unos pocos pacientes con hiperparatiroidismo primario e hipercalcemia sufren pancreatitis aguda.

Existen muy pocas referencias en la literatura a casos como los que nos ocupan. Presentamos a continuación dos pacientes con cuadros de pancreatitis aguda asociados a hiperparatiroidismo e hipercalcemia, uno de ellos con desenlace fatal.

Palabras clave: Pancreatitis aguda. Hipercalcemia. Hiperparatiroidismo primario.

INTRODUCCIÓN

La pancreatitis aguda es un cuadro que puede presentar gran variedad de etiologías. Se acepta que el alcohol y la patología litiásica de la vía biliar están detrás de entre el 80-90% de los casos. Otras causas más raras pero posibles son tóxicos o drogas, obstrucciones neoplásicas de la vía biliar o del esfínter de Oddi, alteraciones metabólicas