CASE REPORT

UDC: 616.37-002.1-02:616.447
DOI: 10.2298/VSP150210121T

Hyperparathyroidism as a cause of recurrent acute pancreatitis – A case report

Hiperparatireoidizam kao uzrok recidivantnog akutnog pankreatitisa

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Abstract

Introduction. One of the more uncommon etiological factors responsible for the development of acute pancreatitis (AP) is hypercalcemia. Hyperparathyroidism (HPT), as a cause of hypercalcemia, is responsible for 1.5–13% of AP according to a number of studies. A mechanism of the development of AP in hyperparathyroidism is still unclear. **Case report.** We presented a 47-year-old female patient, who had five episodes of AP in total before the etiological factors were finally determined. The patient had certain comorbidities which were considered to be potential causes of AP. She had chronic renal insufficiency (she was on a regular hemodialysis program), systemic lupus erythematosus and mioma uteri. She used to regularly take an antiepileptic drug (combination of sodium valproate and valproic acid). During the fifth episode of AP, the serum calcium level was for the first time elevated to twice the normal value. Level of parathyroid hormone was several times higher. A static scintigraphy found hyperplasia or hyperfunctional adenoma of the right inferior and superior parathyroid glands. Abdominal multislice computed tomography (MSCT) scan verified the enlargement of the entire pancreas, as well as the presence of heterogeneous structures with diffuse amorphous calcifications. The lytic lesions in the pelvic bones could be seen in both sides. Parathyroidectomy was being postponed by an endocrine surgeon because of the poor overall condition of the patient. In the next period the patient had five more episodes of AP. The condition was significantly contributed by increasingly more frequent and longer episodes of metrorrhagia. Despite all therapeutic measures that were taken, systemic inflammatory response syndrome (SIRS) developed, and fatal outcome occurred. **Conclusion.** In case of recurrent pancreatitis, hyperparathyroidism is to be considered even if a significant elevation of serum calcium is not present. This is especially the case for patients with chronic renal insufficiency or impaired vitamin D metabolism, who have a higher risk of secondary hyperthyroidism.

Key words:
pancreatitis; hyperparathyroidism; comorbidity; diagnosis, differential; kidney failure, chronic.

Apstrakt

Uvod. Jedan od ređih etioloških faktora odgovornih za razvoj akutnog pankreatitisa (AP) jeste hiperkalcemija. Hiperparatireoidizam (HPT), kao uzrok hiperkalcemije, odgovoran je za 1,5–13% AP prema različitim studijama. Mehanizam nastanka AP kod hiperparatireoidizma još je uvek nedovoljno jasan. **Prikaz bolesnika.** Predstavili smo 47-godišnju bolesnicu, koja je imala pet epizoda akutnog pankreatitisa, pre nego što je konačno utvrđen etiološki faktor. Bolesnica je imala i određene komorbiditete koji su razmatrani kao potencijalni uzročnici AP. Imala je hroničnu bubrežnu insuficijenciju (bila je na hroničnom programu hemodijalize), sistemski eritemski lupus i miom materice. Redovno je uzimala antiepileptik (kombinacija natrijum valproata i volproinske kiseline). Tokom pete epizode AP vrednosti kalcijuma u serumu prvi put su bile dvostruko veće od normalnih vrednosti. Nivo paratirodnog hormona bio je višestruko povećan. Statičkom scintigrafijom nađena je hiperplazija ili hiperfunkcionalni adenom gornje i donje desne paratireoidne žlezde. Na ponovljenoj multislajsnoj kompjuterskoj tomografiji (MSCT) trbuha verifikovan je u celini uvećan pankreas heterogene strukture sa difuznim amorfnim kalcifikatima. Takođe, pri ovom pregledu uočene su li-

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tične lezije u karličnim kostima obostrano. Paratireoidektomija je odložena na predlog endokrinog hirurga zbog lošeg opšteg stanja bolesnice. U narednom periodu bolesnica je imala još pet epizoda AP. Stanje je značajno pogoršano sve češćim i dužim epizodama metroragije. Uprkos svim terapijskim merama, došlo je do razvoja sindroma sistemskog inflamatornog odgovora (SIRS) i fatalnog ishoda. **Zaključak.** Kod recidivantnog AP treba razmišljati o hiperparatireoidizmu i onda kada nema značajnog porasta serumskog kalcijuma. Ovo se naročito odnosi na bolesnike sa hroničnom bubrežnom insuficijencijom ili poremećenim metabolizmom vitamina D, što uvećava rizik od razvoja sekundarnog hiperparatireoidizma.

Ključne reči:
pankreatitis; hiperparatireoidizam; komorbiditet; dijagnoza, diferencijalna; bubreg, hronična isuficijencija.

Introduction

Timely detection of the etiological factor responsible for the development of acute pancreatitis (AP) is important for designing an optimal therapeutic treatment plan and prevention of AP. Numerous etiological factors are responsible for the development of AP. AP of alcoholic or biliary origin is most commonly seen in practice. Idiopathic AP (10% of the diseased) comes in the third place by frequency [1]. Such a significant percentage of idiopathic AP is probably a consequence of limited diagnostic possibilities or nonspecificity of manifestation of certain etiological forms of pancreatitis.

One of the more uncommon etiological factors responsible for the development of AP is hypercalcemia. Hyperparathyroidism (HPT), as a cause of hypercalcemia, is responsible, according to a number of studies, for 1.5–13% of AP [2, 3]. A mechanism of the development of AP in hyperparathyroidism is still unclear [3–5]. Although the correlation between AP and HPT is controversial, HPT is recognized as an etiological factor responsible for the development of AP [5–7].

We presented a patient with recurrent AP which used to be defined as idiopathic until the fifth episode. The patient had certain comorbidities which were considered to be potential causes of AP.

Case report

A 47-years-old woman had the first episode of AP in January, 2012, when she was clinically examined and treated at the Clinic for Gastroenterology and Hepatology in Niš, Serbia. In the medical history, the patient had a record of several surgical procedures in her childhood because of benign brain tumors and she used to regularly take an antiepileptic drug (combination sodium valproate and valproic acid). In 2006 the patient was diagnosed with systemic lupus (SLE) and chronic renal insufficiency (she refused a kidney biopsy). From 2010 the patient was on the regular hemodialysis program, three times *per* week, for four hours each time, and dialysis had a good depuration effect. The phosphorus-calcium ratio was maintained regardless of regular intake of phosphate binders. From 2011 the patient had leiomyoma of uterus, and since then frequently suffered from metrorrhagia.

During the first episode of AP, biochemical analyses showed elevated levels of serum amylase (1,604 U/L), lipase (1,676 U/L) and C-reactive protein (CRP) (18.3 mg/L); the levels of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), cholesterol and triglycerides were within reference values. The level of Ca in the serum was at the upper reference limit (2.65 mmol/L). An abdominal ultrasound of liver, bile ducts, gallbladder and pancreas showed normal findings. Spleen had an interpolar diameter of approximately 140 mm and a homogenous structure. The kidneys were reduced in size and had an altered structure. After consulting a neurologist, on antiepileptic drug (combination sodium valproate and valproic acid), as a possible cause of AP, was replaced with a different antiepileptic drug. The patient was released home in a satisfactory overall condition. Pancreatic enzyme supplements were recommended.

Three months later, a new episode of AP occurred with similar clinical, laboratory and ultrasound findings. After consultations with rheumatologists, the possibility of active SLE was ruled out. As a part of immunological analyses, IgG4 antibodies were also tested and since they turned out to be negative, the possibility of autoimmune AP was excluded. The patient was released home in satisfactory overall condition. The continuation of pancreatic enzymes supplementation was recommended.

Three months later, a new AP episode occurred. Biochemical analyses showed elevated values of amylase, lipase, ALT, GGT, and Ca (slightly over the upper reference limit value). An abdominal ultrasound showed edematous pancreas and the presence of peripancreatic fluid collections in smaller amount. Multislice computed tomography (MSCT) finding was not significantly different from the ultrasound finding. Magnetic resonance cholangiopancreatography (MRCP) scan results came with the conclusion that the findings are normal. Because of the still unclear etiology of AP, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy was performed. Color Doppler of abdominal arteries and veins was within normal limits. During hospitalization, the patient developed metrorrhagia, because of which she was examined by a gynecologist on several occasions.

By the end of 2012, the patient had three more episodes of AP with a milder clinical picture and several episodes of metrorrhagia. During her last hospitalization in December 2012 pain in muscles of all extremities was present. Laboratory analyses showed serum calcium elevated to twice the normal value. Parathyroid hormone was several times

higher (1,165.0 pmol/L) than normal (1.6–6.9 pmol/L). A static scintigraphy with a radiopharmaceutical, technetium (^{99m}Tc) 2-metoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) was performed. The finding corresponded to scintigraphic presentation of hyperplasia or hyperfunctional adenoma of the right inferior and superior parathyroid glands (Figure 1).

During the following period, until the end of 2013, the patient had five more episodes of AP. The endocrine surgeon postponed parathyroidectomy because of the poor overall condition of the patient. The condition was significantly contributed by increasingly more frequent and longer episodes of metrorrhagia, because of which the patient was examined

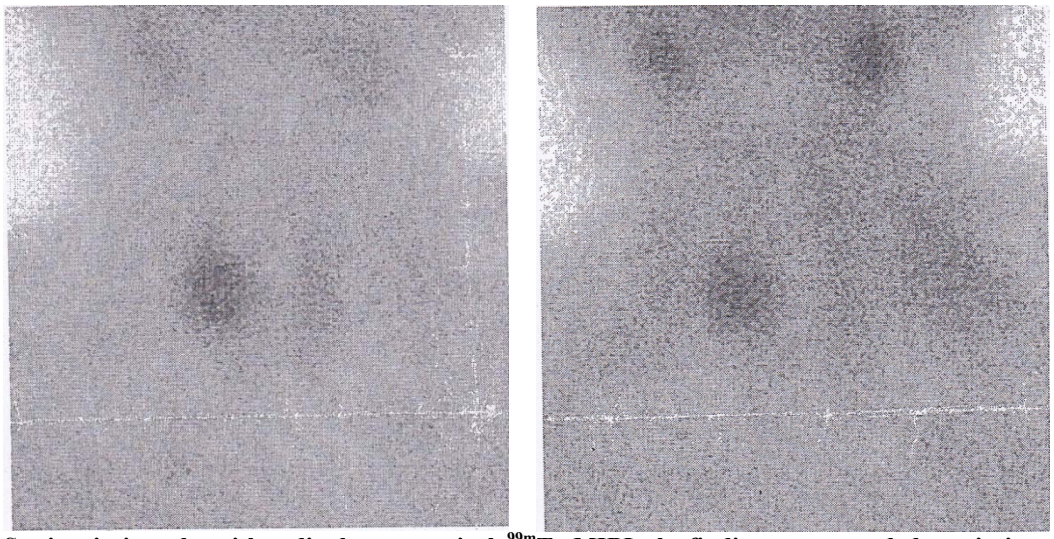

Fig. 1 – Static scintigraphy with radiopharmaceutical, ^{99m}Tc-MIBI: the finding corresponded to scintigraphic presentation of hyperplasia or hyperfunctional adenoma of the right inferior and superior parathyroid glands. ^{99m}Tc-MIBI – ^{99m}Tc 2-metoxy-isobutyl-isonitrile.

Parathyroidectomy was indicated. However, soon after the ongoing AP episode was taken care of, a new AP episode occurred during the preparations for the parathyroid surgery. A repeated abdominal MSCT scan verified the enlargement of the entire pancreas, as well as the presence of heterogeneous structures with diffuse amorphous calcifications. The pancreatic duct was dilated in the tail of pancreas. There was a smaller amount of peripancreatic free fluid collections. Enlarged lymph nodes could be seen in retroperitoneum, some up to 10 mm. Also, during this examination, lytic lesions in the pelvic bones could be seen on both sides (Figure 2).

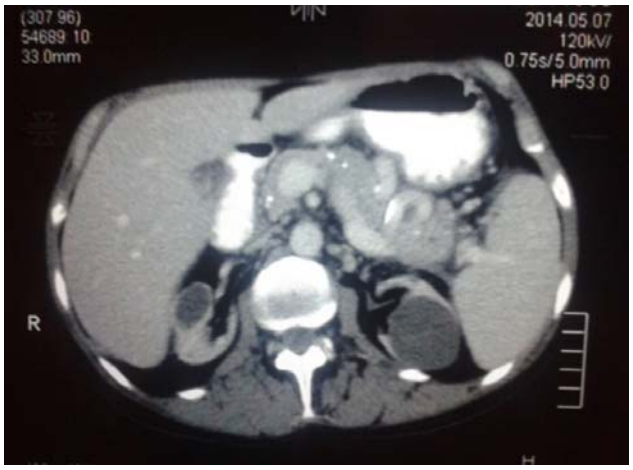

Fig. 2 – Abdominal multislice computed tomography (MSCT) scan verified the enlargement of the entire pancreas, as well as the presence of heterogeneous structures with diffuse amorphous calcifications.

and treated at the Gynecology and Obstetrics Clinic, where palliative interventions were performed in order to stop the bleeding. Shortly, a significant deterioration of a subjective and objective condition occurred along with the development of systemic inflammatory response syndrome (SIRS) without AP. Despite all therapeutic measures that were taken, a fatal outcome occurred three weeks later.

Discussion

Hypercalcemia as a cause of AP is strongly connected with the presence of hyperparathyroidism. Pathophysiological mechanism of the development of AP in patients with hyperparathyroidism has not been precisely determined. It is believed that in cases of hypercalcemia, calcium stimulates exocrine secretion of pancreas, induces activation of trypsinogen with consequential autodigestion and it accumulates in pancreatic ducts, causing their obstruction [8–10]. Data from studies indicate that a mutation of certain genes (SPINK1 – serine protease inhibitor Kazal-type 1 and CFTR – cystic fibrosis transmembrane conductance regulator) can increase the risk of AP development in patients with HPT [11]. Also, a mutation of CaSR (calcium-sensing receptor) is mentioned which occurs in hypercalcemic conditions. Functional significance of the mutations of these genes in the context of pancreatitis needs further studies [12, 13].

The concentration of serum calcium greater than three times the reference value is a predisposition for the development of AP [10]. In the presented patient, the values of serum calcium were at the upper limit until the moment of establishing the diagnosis, when the value was doubled.

The risk of developing AP is thirty times greater in patients with primary hyperparathyroidism than in the general population [10]. The prevalence of AP in primary HPT is different. In a study conducted in India, authors diagnosed AP in 6.8% of patients with primary HPT; AP was the initial clinical manifestation of HPT in 5 of 6 patients, which was the case with the presented patient, as well. All patients with AP had two or more episodes before diagnosing with hyperparathyroidism. In some cases, there was a delay in the diagnosis up to 12 months [12]. Our patient had had five episodes of AP in total before the etiological factors were finally determined, 15 months after the first episode. Since the values of serum calcium were at the upper reference limit during the AP episodes, HPT was not suspected until the values of serum calcium doubled. Besides, imaging methods (ultrasound and MSCT) of the abdomen did not verify calcifications earlier. Acute pancreatitis is usually correlated with the decrease in serum calcium values. According to Ranson's criteria, lower values of calcium in serum have prognostic significance [14, 15]. Therefore, the detection of hypercalcemia in patients with severe AP should always draw attention of doctors to potential hyperparathyroidism or malignancy [16, 17]. Values of parathyroid hormones are to be determined and examination of parathyroid glands performed. Taught by our own experience, but not by the experience of other authors, in patients with recurrent AP, when other common factors are excluded, values of parathyroid hormones are to be tested even if the values of serum calcium are normal [3, 4, 11, 18]. Since the presented patient was on the regular hemodialysis program, there was a significant possibility that this was a case of tertiary hyperparathyroidism, which develops from the secondary after a long period of its duration, when parathyroid glands lose their ability to produce a regulatory response for a concentration of calcium that causes continuously increased secretion of parathyroid hormone. The consequence is an impaired phosphate and calcium metabolism, characterized by hyperphosphatemia and hypercalcemia (in people with previously lower or normal level of calcium in serum). Measuring PTH by C-fragments is unreliable, because of the accumulation of C-fragments in the organism and because of reduced clearance in renal insufficiency [19]. Parathyroid adenomas in HPT are larger in patients who during the evolution of HPT suffer from AP, as well [1].

Conclusion

In case of recurrent pancreatitis, hyperparathyroidism is to be considered even if a significant elevation of serum calcium is not present. This is especially the case in patients with chronic renal insufficiency or impaired vitamin D metabolism, who have a higher risk of secondary hyperthyroidism.

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Received on February 10, 2015.
Accepted on August 12, 2015.
Online First May, 2016.