Govaresh/ Vol. 22, No.2, Summer 2017;126-130.

Case Report

Parathyroid Adenoma and Hypercalcemic Crisis; a Rare Cause of Acute Pancreatitis

Farid Poursadegh[1], Parvin Layegh[2], Peyman Shalchian[3], Neda Bagherzadeh[4], Ladan Goshayeshi[5,6,*]

[1] Internal Medicine Resident, Faculty of Medicine, Mashhad University of medical sciences, Mashhad, Iran.
[2] Endocrinology Department, Faculty of Medicine, Mashhad University of medical sciences, Mashhad, Iran.
[3] Internal Medicine Department, Emamkhomeini hospital, Fariman, Iran.
[4] Pathology Resident, Faculty of Medicine, Mashhad University of medical sciences, Mashhad, Iran.
[5] Department of Gastroenterology and Hepatology, School of Medicine Mashhad University of Medical Sciences, Mashhad, Iran.
[6] Gastroenterology and Hepatology research center ,Faculty of Medicine, Mashhad University of MedicalSciences, Mashhad, Iran.

ABSTRACT

The relationship between primary hyperparathyroidism and pancreatitis has yet to be established firmly. We present a patient with acute pancreatitis and a hypercalcemic crisis induced by a parathyroid adenoma.

A 72-year-old woman presented with lethargy and a constant pain in the epigastric region. She had a medical history of diabetes mellitus, hypertension, nephrolithiasis, and ischemic heart disease. Blood examination revealed leukocytosis and high serum amylase and lipase levels. Ultrasound exam confirmed the diagnosis of acute pancreatitis with a normal biliary tract and no gallstones. On further evaluation severe hypercalcemia (24 mg/dL) was detected, which was treated with 0.9% sodium chloride solution and calcitonin. The acute pancreatitis and its symptoms resolved after 3 days. Ultrasound exam and technetium 99 m sestamibi scan showed a parathyroid lesion. Ultimately the patient underwent right thyroid lobectomy because of refractory hypercalcemia. The pathology report was indicative of a parathyroid adenoma. Subsequently, the parathyroid gland was resected with normalization of calcium, parathyroid hormone, and amylase levels and the patient was discharged in good condition 7 days after surgery.

Apart from the acute supportive management, common to all cases of acute pancreatitis, definite management must be tailored to the specific cause. Hypercalcemia during the course of pancreatitis must prompt an investigation for primary hyperparathyroidism with early surgical intervention if a parathyroid source is detected.

Keywords: Hypercalcemia, Parathyroid adenoma, Pancreatitis, Parathyroid hormone.

please cite this paper as:
Poursadegh F, Layegh P, Shalchian P, Bagherzadeh N, Goshayeshi L. Parathyroid Adenoma and Hypercalcemic Crisis; a Rare Cause of Acute Pancreatitis. *Govaresh* 2017;22:126-130.

Corresponding author:
Ladan Goshayeshi, MD
Assistant Professor, Department of Gastroenterology and Hepatology, Mashhad University of Medical Sciences, Mashhad, Iran.
Tel: + 98 51 38598818
Fax: + 98 51 38932481
Email: goshayeshil@mums.ac.ir

Received: 10 Mar. 2017
Edited: 10 May 2017
Accepted: 11 May 2017

INTRODUCTION

Primary hyperparathyroidism (PHPT) affects approximately 1-2% of the population, most of whom are women(1,2). The disease usually presents non-specifically with lethargy, weakness, mild depression, generalized pain, and anorexia. Affected patients may also have urolithiasis, bone pain, and pathological fractures(3,4).

Hypercalcemia, most commonly caused by PHPT, is usually asymptomatic. Occasionally, however, hypercalcemic crisis may occur, presenting as serum calcium levels above 15 mg/dL and central nervous system, cardiac, gastrointestinal, and/or renal dysfunction. Undoubtedly, the mortality rate reaches

Table 1: patient laboratory tests during admission

Variable		Patient value (Reference value)
Leukocyte (Neutrophil) count (µL)		22.9 (4-11) µ L
Hemoglobin (g/dL)		15 (12-14) g/dL
Platelet count		247000 (150000-400000)
ESR (mm/hr)		40 (<10) mm/hr
CRP (mg/dL)		106 (<10) mg/dL
Ca (mg/dL)	admission	24 (8.5-10.5) mg/dL
	Pre-op	11 (8.5-10.5) mg/dL
	Post-op	8.7 (8.5-10.5) mg/dL
P	Pre-op	2.5 (2.5-5) mg/dL
	Post-op	2.3 (2.5-5) mg/dL
PTH (mg/dL)	Pre-op	411 (10-65) mg/dL
	Post-op	33 (10-65) mg/dL
K (mE/l)		4 (3.5-5.5) mE/l
25OHVITD (ng/ml)		11.5 (20-40) ng/ml
TG (mg/dl)		100 (<150) mg/dl
Na (mEq/L)		138 (135-145) mEq/L
Albumin (mcg/mg)		4.1 (3.5-5.5) mcg/mg
Urea (mg/dL)		91 (7-20) mg/dL
Creatinine (mg/dL)		1.8 (<1) mg/dL
AST (IU/L)		28 (<40) IU/L
ALT (IU/L)		14 (<40) IU/L
ALP (IU/L)		621 (<350) IU/L
Total bilirubin (mg/dl)		0.8 (1) (mg/dl)
Direct bilirubin (mg/dl)		0.4 (0.1-0.3) (mg/dl)
TSH (mU/L)		0.7 (0.4-4) mU/L
T4 (pmol/L)		10 (4.6-12) pmol/L
Amylase (U/L)		795 (<80) u/l
Lipase (U/L)		746 (<60)u/l

100% if treatment is delayed(5-7).

Hyperparathyroidism may rarely be complicated by acute pancreatitis, in which hypercalcemia plays a significant role. However, since PHPT is seen in less than 1% of acute pancreatitis cases and less than 4% of patients with hyperparathyroidism develop acute pancreatitis, the association between the two disorders is disputed(8-10).

In this case, a state of hypercalcemic crisis resulting from PHPT is reported in a patient presenting with acute pancreatitis. In the present case, the resolution of acute pancreatitis after urgent medical and surgical treatments, is suggestive of a significant causative role for hypercalcemia in acute pancreatitis.

CASE REPORT

A 72-year-old woman presented with 4 days of upper abdominal pain. The pain was constant in nature with radiation to the back. It was associated with nausea, vomiting, weakness, and minor confusion. There was a positive history for diabetes mellitus, hypertension, renal stones, and ischemic heart disease with coronary artery bypass surgery. The patient had no history of gallstones or of any alcohol or drug abuses.

On physical examination, the patient was lethargic and had a pulse rate of 110 bpm and a blood pressure of 160/100 mmHg. She had a normal respiratory rate and body temperature. The mucosa was dry with no jaundice. Bowel sounds were reduced and epigastric and right upper quadrant tenderness was present without any rebound tenderness or abdominal guarding; Murphy's sign was negative.

On laboratory testing, the white blood cell count was 22900 cells/mmc with 87% neutrophil dominance. Prerenal azotemia was detected with a blood urea nitrogen of 91 mg/dL and a creatinine level of 1.8 mg/dL. Serum amylase and lipase levels were high (795 IU/L and 746 IU/L, respectively). Also serum calcium level was very high (24 mg/dL). Serum potassium, triglyceride, cholesterol, blood sugar, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were unremarkable. Subsequent evaluation showed a serum phosphorus level of 2.5 mg/dL, a parathyroid hormone (PTH) level of 411 pg/mL, serum vitamin D (25[OH]D) was 11.5 ng/mL, and serum albumin level was 4.1 g/dL.(table 1)

Abdominal ultrasonography revealed enhanced heterogenous parenchymal echo in the head and body of the pancreas, confirming the initial diagnosis of pancreatitis. There was no ultrasonographic evidence of cholecystitis, cholelithiasis, or bile duct dilation.

Immediate treatment for hypercalcemia with 0.9% sodium chloride (200 mL/h intravenous [IV] infusion), furosemide (20 mg IV twice a day), and calcitonin (4 IU/kg subcutaneously, twice a day) reduced the levels to 14 mg/dL and 11 mg/dL in 24 h and 48 h respectively. The symptom of abdominal pain resolved after 3 days of treatment when enteral feeding was initiated.

Based on the hypercalcemia and elevated PTH levels, ultrasound evaluation of the neck was done, which revealed a cystic lesion (13×15 mm) posterior

Fig.1: Sestamibi scan with Technetium 99m (99mTc) of a parathyroid adenoma in the right thyroid lobe.

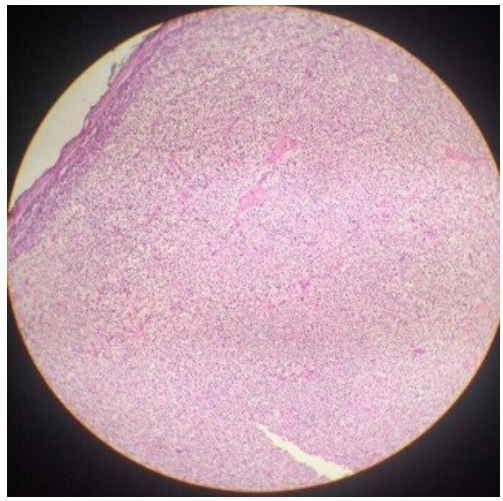

Fig.2: Parathyroid capsule without neoplastic invasion

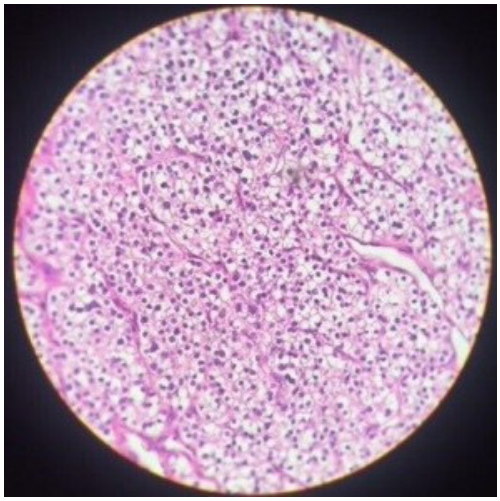

Fig.3: Infiltration of monomorphic cells with round nuclei and acidophilic to clear cytoplasm in a vascular stroma without vascular invasion

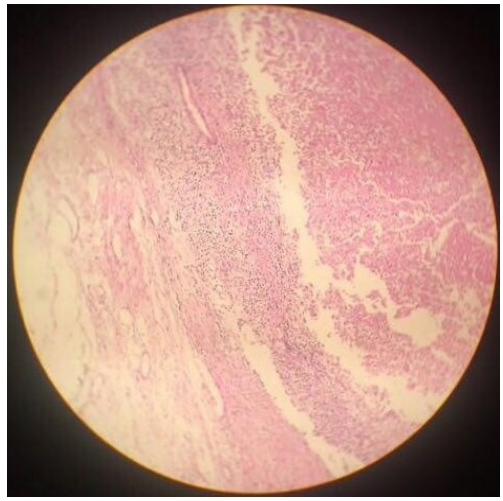

Fig.4: Coagulative necrosis and histiocytic reaction

to the right thyroid lobe, most likely from a parathyroid origin. Subsequently, sestamibi scan with technetium 99m (99 mTc) was indicative of a parathyroid adenoma in the right thyroid lobe.(figure 1) Based on the clinical, laboratory, and imaging revelations, and probable parathyroid carcinoma, the right thyroid lobe was resected 7 days after admission.

Pathological evaluation of the excised specimen showed thyroid follicles of different sizes with foci of interfollicular papillary hyperplasia, confined to the gland capsule and made up of monomorphic cells with a round nucleus and bright acidophilic cytoplasm in a vascular stroma with foci of coagulative necrosis and no vascular or capsular invasion. Findings were indicative of a parathyroid adenoma.(figures 2, 3, 4)

Following surgery, serum calcium and phosphorus levels steadily declined within 4 days, reaching to 8.7 mg/dL and 2.3 mg/dL, respectively. Similarly, PTH levels normalized to 33 pg/mL. Because of hungry bone syndrome, oral calcium and rocatrol were administered. The patient was discharged from the hospital in stable condition 7 days after operation.

DISCUSSION

Hypercalcemic crisis is an uncommon medical emergency with a good prognosis provided to early detection and appropriate treatment. However, if treatment is delayed the mortality rate is high. In a review by Payne and Fitchet, serum calcium levels above 15 mg/dL and disturbances of the gastrointestinal, cardiovascular, and central nervous systems and acute kidney injury were considered as states of crisis resulting from hypercalcemia and/or hyperparathyroidism. Yet, it remains to be seen if acute pancreatitis can occur as a complication of a critical hypercalcemic state induced by PHPT(7,11,12).

Pancreatitis is most commonly caused by gallstones and alcohol. The prevalence of PHPT amongst patients with acute pancreatitis is 3.6% (1.5% to 15.3%), an association that has rarely been reported(8,9,13). However, overall hospital admission rates indicate that the likelihood of acute pancreatitis occurring in patients with PHPT is 30 times higher than that of the general population of patients admitted to hospital(10). Despite the ill-defined relationship between PHPT and acute pancreatitis, hypercalcemia plays a significant role in the pathogenesis of the latter(14). Serum calcium levels have been shown to be higher amongst patients with both pancreatitis and PHPT than those with PHPT alone(15).

The premature activation of protease enzymes as a result of abnormally sustained exposure of pancreatic acinar cells to calcium may be one mechanism behind the development of acute pancreatitis in hypercalcemia(9). Although a direct toxic effect of PTH on the pancreas has been suggested, acute pancreatitis is not common in patients on dialysis with elevated PTH levels. Furthermore, patients with pancreatitis during the course of PHPT have not always been found to have elevated PTH levels. Genetic predisposition has been shown to contribute(16).

There have been few reports of the association between PHPT and acute pancreatitis. The first, to the best of our knowledge, was by Smith and Cook in 1940(17). In 1972, Daum and colleagues described a 12-year-old girl with acute pancreatitis and severe hypercalcemia resulting from an adenoma of the parathyroid gland(18). A review, by Mixter, of 62 patients with PHPT and acute pancreatitis was conducted in 1962. Many similar cases can be found in the literature; however, the association between the two disease entities is a topic of much debate.

Based on a cumulative review of the available large case series and cohorts about PHPT and pancreatitis over the last 30 years, the latter is seen more frequently in hospital inpatients with PHPT than those without PHPT(9). Jacob and colleagues studied 101 subjects with PHPT, out of whom 13 had at least one episode of pancreatitis, and concluded that roughly half of the latter patients had experienced recurrent bouts of the disease(10).

Melek Uyar and co-workers described a 27-year-old man with acute pancreatitis and PHPT-induced hypercalcemic crisis who responded remarkably to medical treatment and excision of the parathyroid tumor(19).

From a retrospective study of all patients with pancreatitis who admitted to the intensive care unit and gastroenterology ward over a 4-year period, Dialleo and others found five cases of PHPT and concluded that pancreatitis was a rare event in the former. However, they noted that normal or raised calcium levels during acute or chronic pancreatitis should raise concern as to a possible underlying PHPT(13).

The early management of an episode of acute pancreatitis, which requires great effort in supportive care, is not altered by the presence of PHPT. Calcitonin is safe and effective in severe hypercalcemia and may be given with IV bisphosphonates(11,20,21). After the resolution of the attack, parathyroidectomy is performed as definite treatment(9).

Finally, definite treatment of acute pancreatitis should be individualized and based on the underlying etiology. Serum calcium should be checked in patients with pancreatitis and elevated levels should always prompt an investigation for an endocrine or malignant source. Conversely, patients with PHPT who present with abdominal symptoms should be evaluated for pancreatitis. Once PHPT is diagnosed, early surgical intervention as well as proper medical treatment is required in order to prevent mortality and reduce complications.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

REFERENCES

1. Melton GB, Somervell H, Friedman KP, Zeiger MA, Cahid Civelek A. Interpretation of 99mTc sestamibi parathyroid SPECT scan is improved when read by the surgeon and nuclear medicine physician together. *Nucl Med Commun* 2005;26:633-8.
2. Ravipati NB, McLemore EC, Schlinkert RT, Argueta R. Anterior mediastinotomy for parathyroidectomy. *Am J Surg* 2008;195:799-802.
3. Koksal H, Kurukahvecioglu O, Yazicioglu MO, Taneri F. Primary hyperparathyroidism due to parathyroid adenoma. *Saudi Med J* 2006;27:1034-7.
4. Padmanabhan H. Outpatient management of primary hyperparathyroidism. *Am J Med* 2011;124:911-4.
5. Bilezikian JP, Silverberg SJ. Asymptomatic primary hyperparathyroidism. *N Engl J Med* 2004;350:1746-51.
6. Al-Azem H, Khan A. Primary hyperparathyroidism. *CMAJ* 2011;183:E685-9.
7. Kelly TR, Zarconi J. Primary hyperparathyroidism: hyperparathyroid crisis. *Am J Surg* 1981;142:539-42.
8. Janka-Zires M, Hernández-Calleros J, Gómez-Pérez FJ, Uscanga-Domínguez LF, Pelaez-Luna MC, Almeda-Valdés P. Decrease in the Prevalence of Pancreatitis Associated with Primary Hyperparathyroidism: Experience at a Tertiary Referral Center. *Rev Invest Clin* 2015;67:177-81.
9. Bai HX, Giefer M, Patel M, Orabi AI, Husain SZ. The association of primary hyperparathyroidism with pancreatitis. *J Clin Gastroenterol* 2012;46:656-61.
10. Jacob JJ, John M, Thomas N, Chacko A, Cherian R, Selvan B, et al. Does hyperparathyroidism cause pancreatitis? A south indian experience and a review of published work. *ANZ J Surg* 2006;76:740-4.
11. Ahmad S, Kuraganti G, Steenkamp D. Hypercalcemic crisis: a clinical review. *Am J Med* 2015;128:239-45.
12. Payne Jr RL, Fitchett CW. Hyperparathyroid Crisis Survey of the Literature and a Report of Two Additional Cases. *Ann Surg* 1965;161:737-47.
13. Diallo I, Fall CA, Ndiaye B, Mbaye M, Diedhiou I, Ndiaye AR, et al. Primary Hyperparathyroidism and Pancreatitis: A Rare Association with Multiple Facets. *Int Sch Res Notices* 2016; 2016: 7294274.
14. Cope O, Culver PJ, Mixter Jr CG, Nardi GL. Pancreatitis, a diagnostic clue to hyperparathyroidism. *Ann Surg* 1957;145:857-63.
15. Carnaille B, Oudar C, Pattou F, Combemale F, Rocha J, Proye C. Pancreatitis and primary hyperparathyroidism: forty cases. *Aust N Z J Surg* 1998;68:117-9.
16. Stepanchick A, McKenna J, McGovern O, Huang Y, Breitwieser GE. Calcium sensing receptor mutations implicated in pancreatitis and idiopathic epilepsy syndrome disrupt an arginine-rich retention motif. *Cell Physiol Biochem* 2010;26:363-74.
17. Mixter CG, Keynes WM, Cope O. Further experience with pancreatitis as a diagnostic clue to hyperparathyroidism. *N Engl J Med* 1962;266:265-72.
18. Daum F, Rosen JF, Boley SJ. Parathyroid adenoma, parathyroid crisis, and acute pancreatitis in an adolescent. *J Pediatr* 1973;83:275-7.
19. Uyar M, Özkul MH, Bayram Ö, Dikmen B, Özer SP. Acute pancreatitis as a precursor sign of parathyroid adenoma. *KBB Uygulamaları* 2015;3:47-50.
20. Thiebaud D, Jacquet A, Burckhardt P. Fast and effective treatment of malignant hypercalcemia: combination of suppositories of calcitonin and a single infusion of 3-amino 1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990;150:2125-8.
21. Ralston SH, Alzaid AA, Gardner MD, Boyle IT. Treatment of cancer associated hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin. *Br Med J (Clin Res Ed)* 1986;292:1549-50.