

Pancreatitis—Primary Hyperparathyroidism Association: Case Report and Literature Review

Muhammad Abdullah, FRCS (England), FRCS (Glasgow)

Department of Surgery, University of Malaya, Kuala Lumpur, Malaysia

The relationship of cause and effect between acute pancreatitis and primary hyperparathyroidism (pHPT) continues to be debated. Critics see any association of pancreatitis with pHPT as only incidental or even a *result of* parathyroid surgery. Counter arguments claim that pancreatitis is actually a manifestation of pHPT and definitive management of such pancreatitis should be directed towards dealing with the hyperparathyroidism. Our paper aims to review the debate in the published medical literature starting from the first reporting of such association in 1947. In this controversy we add our own case of a 49-year old non-alcoholic man presenting with recurrent attacks of acute pancreatitis. Investigated with ultrasound, CT scan, ERCP and biochemical profiles, it was not until his 3rd admission that his raised serum calcium was acted upon. High intact parathyroid levels were confirmed. Open neck exploration found a solitary parathyroid adenoma. After surgery the serum calcium returned to normal and abdominal symptoms have not recurred in the subsequent three years. This supports our belief that acute pancreatitis is one of the symptoms of pHPT, often caused by a parathyroid adenoma and curable by its excision. Calcium and parathyroid profiles should be scrutinized in all fresh cases of acute pancreatitis. (**Korean J Endocrine Surg 2002;2:55-57**)

Key Words: Primary hyperparathyroidism, Pancreatitis, Parathyroid adenoma

INTRODUCTION

Pancreatitis is known to be associated with primary hyperparathyroidism (pHPT). However the relationship of cause and effect between the two diseases continues to be debated in the medical literature in determining whether one leads to the other.

CASE REPORT

We report a 49 years old Malay man who presented in July 1997 to the University of Malaya Medical Center, Kuala Lumpur. He had one-day history of severe upper abdominal pain and vomiting. The vital observations were normal but there was tenderness in the upper abdomen. Past history revealed occasional episodes of loin pains and passing stones per urethra. He admitted to be a smoker but had never consumed alcohol.

Investigations revealed serum amylase of 2,285 IU/L (n=25~150), mild hyperglycemia and crystalluria. Serum calcium level was 2.65 mmol/L (n=2.20~2.60). Ultrasound examination showed a normal gallbladder without any stones. A calculus was noted in the right kidney. CT scan showed inflammation of pancreatic tail and a suspected stricture of pancreatic duct. Somehow on this occasion the hypercalcemia was not pursued. At the suggestion of the gastroenterologists, an ERCP was done which showed normal common bile and pancreatic ducts. The symptoms soon settled on conservative management and he was discharged home.

His next review was in a urology clinic where he presented with features of acute right epididymo-orchitis which was investigated and successfully treated with antibiotics. In November 1997 and in February 1998 he had two further admissions with clinical features of acute pancreatitis with serum amylase levels of 1,410 and 1,147 IU/L respectively. On both occasions he quickly settled spontaneously and requested for discharge. Once again, routine calcium of 2.80 mmol/L did not raise any alarm.

It wasn't until May 1998, nearly ten months after his first presentation and after a third admission with acute pancreatitis (serum amylase: 1,354 IU/L) that the hypercalcemia was noted and acted upon. On this admission the serum calcium was 2.89 mmol/L and serum phosphate, 0.94 mmol/L (n=0.9~1.5). He was also hyperglycemic, his blood glucose being 13.6 mmol/L. Repeat checks confirmed persistent hypercalcemia (calcium=3.09 mmol/L), hypophosphatemia (phosphate=0.7 mmol/L), a normal albumin (43 g/L) and a urinary calcium of 5.5 mmol/L (n=2.2~7.5).

Correspondence: Muhammad Abdullah, Department of Surgery, University Hospital, Kuala Lumpur 59100, Malaysia, Tel: 60-3-7950, 2440, E-mail: mabdullah@ummc.edu.my

Accepted: June 5, 2002

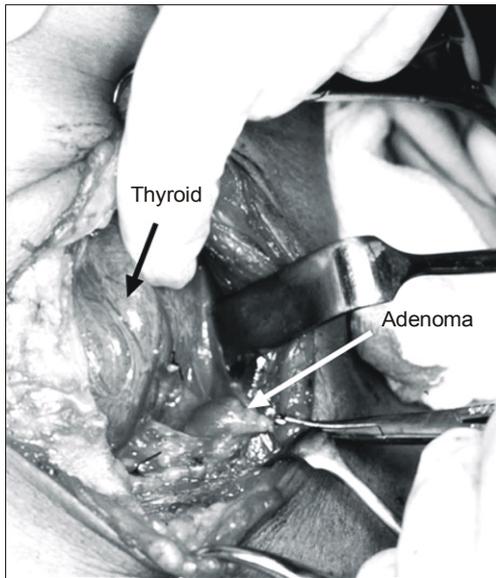


Fig. 1.

Screening for Bence-Jones proteins and serum electrophoresis was normal as was the blood urea, electrolytes, creatinine and fasting lipid levels and the thyroid hormonal assay. The intact parathyroid hormone level (iPTH) level was 99.8 pg/ml ($n=11.0 \sim 54.0$), which confirmed the suspicion of primary hyperparathyroidism. Follow up investigations were done to ascertain the nature and extent of the hyperparathyroidism (HPT). The hand and skull X-ray did not reveal any obvious features of bone disease. An isotope scan (Tc-99M Tetrofosmin 131-Iodine subtraction parathyroid scintigraphy) reported "no hyper-functioning parathyroid adenomas in neck or mediastinum". CT scan of the neck reported left parathyroid gland enlargement with a low attenuation lesion within the upper pole of left thyroid lobe. He then underwent a bilateral neck exploration, which showed a 1 cm left inferior parathyroid adenoma, confirmed on frozen section (Fig. 1). The three other parathyroid glands were normal; confirmation been done by a frozen section of the right inferior parathyroid. The thyroid gland was also normal. The calcium came down to 2.16 mmol/L before the patient was discharged home.

Two months after his parathyroid surgery he had one further episode of documented acute pancreatitis with serum amylase of 4727 IU/L, calcium of 2.39 mmol/L and albumin of 49 g/L ($n=35 \sim 50$). He settled spontaneously within a couple of days. After this he did not have any further attack of pancreatitis and has been symptoms free till his last review in January 2002. The blood work up done one year after his parathyroid surgery records a calcium level of 2.32 mmol/L and phosphate of 1.3

mmol/L. Currently he is under follow up for his diabetes under the physicians.

DISCUSSION

Pancreatitis related to hyperparathyroidism (HPT) was first reported in 1947 by Martin and Canseco (1) although it was 10 years later that pancreatitis as a feature of primary HPT became well known through the writing of Cope. (2) Since then, individual cases and series have been reported periodically in the belief that pancreatitis is just one of the manifestations of pHPT and that recurrent pancreatitis can be cured by treating the cause of pHPT.

However not everyone accepts this. Some suggest that the association of pancreatitis with pHPT is incidental or in fact pancreatitis may be *the result* of parathyroid surgery for some other reason. The main challenge has come from Bess (3) and colleagues from Mayo clinic in 1980. Reviewing 1,153 patients with proven pHPT they found only 17 patients with pancreatitis. They suggested that the association of HPT and pancreatitis was due to bias in patient selection or just chance alone since the incidence of pancreatitis in their series is too low.

These objections by Bess and his colleagues have consistently been challenged with counter arguments. Even before the Mayo clinic report, Kelly (4) in 1968 published an experimental study, demonstrating that persistent hypercalcemia increases the calcium content of the pancreatic juice. This lead to accelerated intrapancreatic conversion of trypsinogen to trypsin, the latter causing pancreatic damage.

Sitges-Sera (5) and co-authors in 1988, have also stressed the point that hypercalcemia *per se* is behind the causation of pancreatitis. They highlighted the association of pancreatitis with non-hyperparathyroid causes of hypercalcemia. Hypercalcemic conditions like parenteral nutrition, calcium infusion, myeloma, disseminated breast cancer or severe hyperthyroidism are all associated with pancreatitis. Presenting their own 10 cases in support they have suggested that pancreatitis is more likely to develop in patients who exhibit moderate to severe hypercalcemia. According to Sitges-Sera those patients with asymptomatic hyperparathyroidism and/or with mild hypercalcemia are less prone to develop pancreatitis.

Carnille (6) and colleagues have made an interesting narration on the issue from France in 1998. They reviewed 1,435 consecutive patients who were operated on for hyperparathyroidism. Of these, 1,224 patients had a biochemically proven pHPT, the remaining 211 had renal hyperparathyroidism (RHPT). They found that a total of 40 patients (3.2%) with pHPT had pancreatitis. Out

of these, 18 had acute pancreatitis; the remaining having sub-acute or chronic inflammation. This rate of pancreatitis was higher than in their random hospital population. Surgical cure of pHPT was followed by the spontaneous healing of 17 out of 18 patients with acute pancreatitis. A single diseased gland was found in 27 (out of 40 patients with pancreatitis), which is in favour of primary parathyroid disease being responsible for, and not a consequence of pancreatitis. In 78% of cases, pancreatitis preceded the diagnosis of pHPT and that no pancreatitis was recorded either in the RHPT group or after parathyroidectomy. Their laboratory data suggest that pancreatitis is an effect of hypercalcaemia and not of high intact parathyroid hormone levels (iPTH) levels *per se*. Their conclusion was that (i) the Pancreatitis-pHPT association is not incidental; (ii) pancreatitis is the consequence and not the cause of pHPT; (iii) hypercalcaemia seems to be a major factor in the development of pancreatitis in pHPT patients; and (iv) cure of pHPT leads to the healing of acute pancreatitis.

A controversial aspect of the Pancreatitis-HPT association is the suggestion that pancreatitis may be caused by parathyroid surgery or at least should be accepted as an uncommon complication of it. Supporters of this theory, Reeve and Delbridge, (7) had postulated in 1982 that the mechanism was the release of parathyroid hormone and an acute rise in serum calcium consequent on operative manipulation of a parathyroid tumour. In their experience, this complication was much more common when thyroid lobectomy or bilateral subtotal thyroidectomy was performed in addition to parathyroidectomy.

This has been contested by Robertson (8) and associates from the Leicester Royal Infirmary. They reported a study in 1995 to test the hypothesis that up to 35% of patients may experience hyperamylasaemia after parathyroidectomy indicating subclinical inflammation of the pancreas. A series of 26 patients undergoing parathyroidectomy were studied by preoperative and post operative biochemical analysis and CT scan of the pancreas after operation. However postoperatively, there was no evidence in any patient of acute pancreatic inflammation or hyperamylasaemia. They postulated that any amylase elevation in other reports might

reflect an increase in salivary isoamylase as a result of extensive neck dissection rather than reflecting a subclinical pancreatitis.

Finally, Shepard (9) from Tasmania in 1996 has also disagreed with the theory of post-parathyroidectomy pancreatitis. Reviewing the literature on the subject, Shepard's suggests that it is the surgical stress rather than manipulation of the parathyroid gland, which is responsible for excessive parathyroid hormone release in patients after parathyroidectomy.

In conclusion, acute pancreatitis is one of the symptoms of primary hyperparathyroidism, often caused by a parathyroid adenoma and curable by its excision. Calcium and parathyroid profiles should be scrutinized in all fresh cases of acute pancreatitis even though primary hyperparathyroidism is a rare cause.

REFERENCES

- 1) Martin L, Canseco JD. Pancreatic calculosis. JAMA 1947;135: 1055.
- 2) Cope O, Culver P, Mixter C, Nardi G. Pancreatitis, a diagnostic clue to hyperparathyroidism. Ann Surg 1957;145:857-863.
- 3) Bess MA, Edis AJ, von Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association? JAMA 1980;243: 246-247.
- 4) Kelly TR. Relationship of hyperparathyroidism to pancreatitis. Arch Surg 1968;108:267-274.
- 5) Sitges-Serra A, Alonso M, de Lecea C, Gores PF, Sutherland DE. Pancreatitis and hyperparathyroidism. Br J Surg 1988; 75(2):158-160.
- 6) 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(2):117-119.
- 7) Reeve ST, Delbridge LW. Pancreatitis following parathyroid surgery. Ann Surg 1982;195:158-162.
- 8) Robertson GS, Gibson PJ, London NJ, Johnson PR, Iqbal SJ, Bell PR. Does subclinical pancreatic inflammation occur after parathyroidectomy? Ann R Coll Surg Engl 1995;77(2):102-106.
- 9) Shepherd JJ. Hyperparathyroidism presenting as pancreatitis or complicated by postoperative pancreatitis. Aust N Z J Surg 1996; 66(2):85-87.