CASE REPORT

Pancreatitis in Primary Hyperparathyroidism

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Summary

The cause and effect relationship between acute pancreatitis and primary hyperparathyroidism (pHPT) still evokes controversy. Our paper reviews the debate in the medical literature. In this controversy we add a case of a 49-year old non-alcoholic man presenting with recurrent attacks of acute pancreatitis. His raised serum calcium was realized rather late. Eventually, high intact parathyroid hormone levels led to open neck exploration and finding of a solitary parathyroid adenoma. Post-surgery, serum calcium returned to normal and abdominal symptoms disappeared.

The case report and the accompanying literature review support our belief, that acute pancreatitis is one of the symptoms of pHPT often caused by a parathyroid adenoma and curable by its excision.

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. Besides, other causes of acute pancreatitis like gallstone disease and alcoholism in Malaysia are far more common. For this reason the appearance of a raised serum calcium level, in the "routine" biochemical profiles of a patient first presenting with acute pancreatitis, does not raise much alarm. To our embarrassment, it took the following case report to learn a lesson.

Case Report

We report a 49 years old Malay man who presented to the University of Malaya Medical Centre, Kuala Lumpur with one-day history of severe upper abdominal pain and vomiting. Past history, revealed occasional episodes of loin pains. He had never consumed alcohol in his life. Investigations revealed serum amylase of 2285 IU/L (n=25-150), mild hyperglycemia and crystalluria. Serum calcium level was 2.65 mmol/L (n=2.20- 2.60). Ultrasound examination and CT scans showed a normal gallbladder and inflammation of pancreatic tail. The hypercalcemia was ignored on this occasion and the patient discharged home when the symptoms settled.

In the next six months he had two further admissions with clinical and biochemical features of acute pancreatitis. On both occasions he settled spontaneously and requested for discharge. Once again,"routine calcium" of 2.80 mmol/L did not raise any alarm.

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It wasn't until nearly ten months after his first presentation on his third admission with acute pancreatitis (serum amylase: 1354 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, (Glucose = 13.6 mmol/L). Repeat checks confirmed persistent hypercalcemia (3.09mmol/L), hypophosphatemia (0.7 mmol/L), a normal albumin (43 g/L) and a urinary calcium of 5.5 mmol/L (n=2.2-7.5). The initial suspicion of primary hyperparathyroidism was confirmed when his intact parathyroid hormone level (iPTH) level was found to be 99.8 pg/ml (n=11.0- 54.0).

The patient then underwent an open bilateral neck exploration, which showed a 1cm left inferior parathyroid adenoma (Fig. 1). Frozen section showed that the other three parathyroid glands were normal. Postoperatively 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=35-50). He settled spontaneously. After this he did not have any further attack of pancreatitis and has been symptom-free till his last review 18 months post-surgery. On this occasion, the serum calcium was 2.32 mmol/L and phosphate, 1.3 mmol/L.

Discussion

Pancreatitis related to hyperparathyroidism (HPT) was first reported in 1947 by Martin and Canseco in the *Journal of American Medical Association.* But it was 10 years later that pancreatitis as a feature of primary HPT became well known through the writing of Cope in the *Annals of Surgery* in 1957. Since then, individual cases and series have been reported periodically in the belief that pancreatitis is just one of the manifestations of

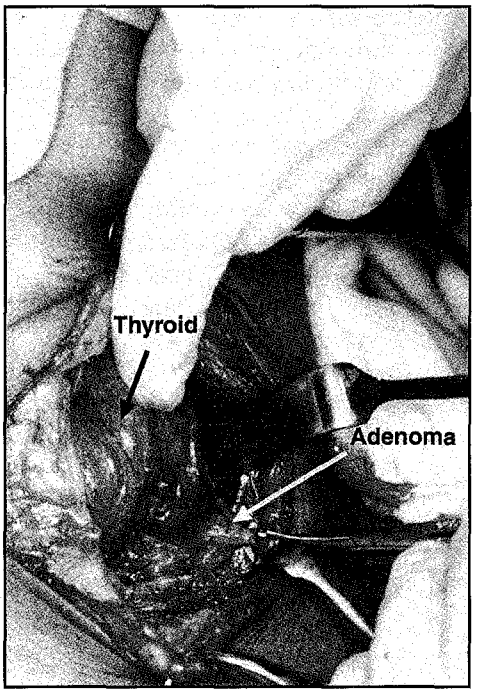

Fig 1: The operative

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[1] and colleagues from Mayo clinic in 1980. Reviewing 1153 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 was too low.

These objections by Bess and his colleagues have been challenged with counter arguments. Even before the Mayo clinic report, Kelly in 1968 published an experimental study in the *Archives of Surgery,* demonstrating that persistent hypercalcemia increases the calcium content of the

pancreatic juice leading to accelerated intrapancreatic conversion of trypsinogen to trypsin, the latter causing pancreatic damage.

Sitges-Sera[2] 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 like parenteral nutrition, calcium infusion, myeloma, disseminated breast cancer or severe hyperthyroidism. They have also criticized the report by Bess and co-workers, pointing out that the apparently low incidence of pancreatitis in the Mayo clinic series of pHPT patients is not true. In is only apparent because in that institution many patients with asymptomatic hyperparathyroidism and/or slight hyper-calcaemia are submitted to parathyroid surgery (before they have a chance to develop pancreatitis). Presenting their own 10 cases in support they have stressed that pancreatitis is more likely to develop in patients who exhibit moderate to severe hypercalcemia while patients with asymptomatic hyperparathyroidism and/or with mild hypercalcemia are less prone to develop pancreatitis.

Carnille[3] and colleagues reported from France in 1998 after reviewing 1435 consecutive patients operated for hyperparathyroidism. Of these, 1224 patients had biochemically proven pHPT, the remaining 211 had renal hyperparathyroidism (RHPT). They found that a total of 40 patients (3.2%) with pHPT had pancreatitis, 18 having an acute attack. This rate of pancreatitis was higher than in their random hospital population. Spontaneous healing of 17 out of 18 patients with acute pancreatitis followed surgical cure of pHPT. 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.

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, 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 and associates in the *Annals of the Royal College of Surgeons of England.* 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

Shepard[5] from Tasmania in 1996 has also disagreed with the theory of post-parathyroidectomy pancreatitis. Reviewing the literature on the subject, Shepard 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. Any oversight will result in diagnostic delays like the one that we had in our case.

Acknowledgement

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References

1. Bess MA, Edis AJ, von Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association? JAMA 1980; 243: 246-7.
2. Sitges-Serra A, Alonso M, de Lecea C, Gores PF, Sutherland DE. Pancreatitis and hyperparathyroidism. Br J Surg 1988 Feb; 75 (2): 158-60.
3. Carnaille, B.; Oudar, C.; Pattou, F.; Combemale, F. Rocha, J.; Proye, C. Pancreatitis and primary hyperparathyroidism forty cases. Aust N Z J Surg 1998 Feb; 68 (2): 117-19.
4. Reeve ST, Delbridge LW. Pancreatitis following parathyroid surgery. Ann. Surg. 1982; 195: 158-62
5. Shepherd, J.J. Hyperparathyroidism presenting as pancreatitis or complicated by postoperative pancreatitis. Aust N Z J Surg 1996 Feb; 66 (2): 85-7