Case report

# Recurrent pancreatitis associated with normocalcemia, parathyroid hyperplasia, and increased serum parathormone

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In recent years, normocalcemic primary hyperparathyroidism has been recognized more frequently. Usually, these patients have recurrent renal calculi and normal serum calcium values.[1, 2] The association of pancreatitis with hyperparathyroidism has been recognized since 1940.[3] Reviews by Mixter et al[4] and by Turchi et al,[5] in 1962, stressed the importance of pancreatitis as a clue in the diagnosis of hyperparathyroidism. A nearly normal serum calcium value and a decreased serum phosphorus level in cases of acute pancreatitis should arouse suspicion of hyperfunctioning parathyroid glands. Ballon et al[6] reported a case of recurrent pancreatitis associated with a parathyroid adenoma in a normocalcemic patient.

This case of severe relapsing pancreatitis was associated with a normal serum calcium level, parathyroid hyperplasia, and elevation of serum parathormone level to three times the normal range for the patient's age. The aim of this report is to alert clinicians to the relationship of pancreatitis with normocalcemia and to speculate on the role of parathormone in the etiology of the pancreatitis.

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## Case report

A 14-year-old white girl was referred for evaluation of recurrent epigastric pain. The patient had a history of six episodes of epigastric pain requiring six hospitalizations. The pain was severe, nonradiating, and was associated with severe nausea, vomiting, and a low grade fever. There was no jaundice or diarrhea. Each episode of pain persisted 5 to 6 days. During her first hospitalization an appendectomy was performed, and there were no pathological findings. In the intervals between attacks, the patient was asymptomatic. There was no family history of gallbladder disease and pancreatic disease. Examination was normal except for mild epigastric tenderness. The following laboratory tests disclosed normal values: hemogram, serum electrolytes, serum amylase, serum lipase, serum triglycerides, serum carotene, urine porphyrin, urinalysis, urine culture, and stool culture. Stool analysis was normal twice except for one 2+ guaiac reaction. The serum calcium value was 10.9 mg/100 ml and the serum phosphorus level was 5.5 mg/100 ml. Roentgenographic examination of the stomach and of the small bowel showed no abnormality. The diagnosis was functional bowel disease and the patient was discharged.

Five months later the patient had similar epigastric pain. She was afebrile, and the abdomen was soft, with tenderness in the hypochondrium and periumbilical regions. There was no rebound tenderness or organomegaly, and the bowel sounds were normal. One examiner heard a bruit in the epigastric region. The white cell count was 12,700/cu mm with a normal differential count. The serum electrolytes were normal, but on admission the serum amylase was 537 Somogyi units. Urinary amylase was 248 Somogyi units/hr. The serum lipase was 1.7 Cherry-Crandall units. The next day the serum amylase was 381 Somogyi units and the serum calcium value was 10.3 mg/100 ml. The serum amylase returned to normal on the fourth hospital day. A sweat test was performed and interpreted as normal. A D-xylose test could not be interpreted correctly because of an inadequate urinary volume (44 ml). A 3-hour glucose tolerance test was within normal limits. A stool guaiac reaction was 4+. A cholecystogram was normal. An electroencephalogram was interpreted as normal. The patient had no history of frothy, foul smelling bowel bowel movements or diarrhea. The diagnosis was recurrent pancreatitis, and it was decided to perform celiac angiography and a diagnostic laparotomy if another admission was necessary.

The patient was readmitted 5 days later with a 2-day history of vomiting and acute epigastric pain which radiated along the costal margins. Abdominal examination revealed epigastric tenderness, no organomegaly, no rebound tenderness, and no bruit was heard. The serum amylase was 434 Somogyi units and urine amylase was 868 Somogyi units in a random specimen. The serum lipase was 2.4 Cherry-Crandall units. The hemogram was within normal limits. The serum amylase on succeeding days was 482 and 503 Somogyi units. Chromatography of urinary aminoacids revealed no lysine or cystine in the urine. An angiogram of the celiac and superior mesenteric arteries was interpreted as normal. An exploratory laparotomy was performed in an attempt to explain the recurrent pancreatitis. The tail of the pancreas was found to be involved in an acute inflammatory process, and a small inflammatory cyst was found. The head of the pancreas was hard and irregular, but not thickened. An operative cholecystocholangiogram and pancreaticogram were normal. The tail of the pancreas was resected. Pathologic diagnosis of the resected pancreatic specimen was severe chronic pancreatitis. The patient had an uneventful recovery and was sent home with the diagnosis of recurrent pancreatitis of unknown etiology.

Three months later the patient was admitted with a 36-hour history of colicky

epigastric pain, nausea, and vomiting. The patient had been well for the past 3 months and had gained 4.5 kg. Results of physical examination were unremarkable, with abdominal examination showing epigastric tenderness, hypoactive bowel sounds, and no rebound tenderness. Laboratory studies disclosed the following values: white cell count 14,000/cu mm, normal serum electrolytes, serum amylase 407 Somogyi units, and serum lipase 1.1 Cherry-Crandall units. Serum calcium was 10.0 mg/100 ml on admission. The serum parathormone level was 150 μlEq/ml (normal 0 to 44), total serum calcium 9.5 mg/100 ml (normal 9.75 ± 0.54), and serum phosphorus 2.19 mg/100 ml (normal 4.78 ± 1.52). The symptoms gradually abated in 4 days.

The patient was admitted for selective neck exploration 1 month later because of the elevated parathormone levels. She had no abdominal pain, and had no history of steatorrhea. Results of examination were normal. The serum amylase was normal and serial serum calcium values were 11.2 mg/100 ml, 10.8 mg/100 ml, and 10.3 mg/100 ml. At the same time serum phosphorus determinations were 5.8 mg/100 ml, 5.7 mg/100 ml, and 5.9 mg/100 ml. A urinary calcium was 154.8 mg/24 hr in 1,090 ml of urine. The patient underwent parathyroid exploration with excision of the right lower and left upper glands, biopsy of the other two glands, the thymus, and the thyroid. The pathologic diagnosis of the excised glands was hypercellular parathyroid segments with fibrous stroma, compatible with parathyroid hyperplasia. The thymus and thyroid sections were normal. Postoperatively, the serum calcium and phosphorus values were within normal limits, and the patient had an uneventful recovery.

Since the operation, the patient has had another attack of abdominal pain. Serum parathormone assay was 150 μlEq/100 ml, serum calcium 10.2 mg/100 ml, and serum phosphorus 4.45 mg/100 ml on one occasion, and parathormone assay 110 μlEq/100 ml, serum calcium 10.0 mg/100 ml, and serum phosphorus 6.25 mg/100 ml on another.

## Discussion

The incidence of pancreatitis associated with hypercalcemic hyperparathyroidism varies. Purnell et al[7] reported a 2% incidence, Mixter et al[4] reported a 7% incidence, and he stated that Kyle had found a 12% incidence. There is no known incidence of pancreatitis with normocalcemic hyperparathyroidism; in fact, the case reported by Ballon et al[6] is the first in the recent medical literature.

The previous reports have stressed the significance of pancreatic calcifications in association with hyperparathyroidism. Hyperparathyroidism is a strong diagnostic possibility when a patient is seen initially with pancreatitis and pancreatic calcifications. In Mixter's series, 81% had pancreatic calcifications. In both Ballon's and our case, there were no pancreatic calcifications.

The nearly normal serum calcium and depressed serum phosphorus levels during an episode of acute pancreatitis have been clues to the diagnosis of hyperparathyroidism. The severity of the pancreatitis may be misjudged by the serum calcium, for usually the decrease in serum calcium parallels the severity of the pancreatitis. After the acute episode, the serum calcium returns to the hypercalcemic levels. In normocalcemic hyperparathyroidism related to pancreatitis, the serum calcium value is normal during the acute episode and the symptom-free intervals. Our patient was normocalcemic in both situations. The pancreatitis she had was of the recurrent variety, the most common type of pancreatitis

associated with hypercalcemic hyperparathyroidism. Thus a normal serum calcium level in a patient with pancreatitis does not rule out the possibility of hyperparathyroidism.

Secondary hyperparathyroidism may be seen in association with pancreatitis.[8, 9] There is usually evidence of pancreatic insufficiency with steatorrhea and resulting osteomalacia. In our patient, there was no evidence of pancreatic insufficiency or osteomalacia. Even with hyperparathyroid-related pancreatitis, the exclusion of biliary tract disease, alcoholism, peptic ulcer disease, hereditary metabolic disorders, congenital developmental defects, hyperlipidemia, viral illness, and trauma as possible etiologies of the pancreatitis is mandatory. None of these were applicable in this case.

The pathogenesis of pancreatitis related to hyperparathyroidism has been attributed to the following possible mechanisms: (1) Hypercalcemia predisposes to calcium salt precipitation in an alkaline medium such as found in the kidneys, prostate, and pancreas. The resultant intraductal calcifications in the pancreas may lead to obstruction and pancreatitis. (2) The activation of trypsinogen to trypsin is dependent upon calcium ions.[10] Hypercalcemia may lead to excess calcium ions and resultant acceleration of the conversion to trypsin with resultant pancreatitis.[11] (3) Thromboarteritis and focal pancreatic tissue necrosis have resulted after the administration of parathormone to laboratory animals.[12, 13] The possible direct role of parathormone in the etiology of pancreatitis must be considered.

In a normocalcemic individual, the absence of increased serum calcium values makes the mechanisms of trypsinogen activation and intraductal calcifications unacceptable as etiologies of the pancreatitis. The possible direct effect of parathormone on pancreatic tissue, as a mechanism in the development of the pancreatitis, may be given support by the elevation of the patient's serum parathormone and the correlation with the patient's symptoms, before and after surgery. To our knowledge the parathormone level in either hypercalcemic or normocalcemic hyperparathyroid-related pancreatitis has not been reported previously in the recent medical literature.

At present, research is underway to investigate the relationship of normocalcemic hyperparathyroidism with pancreatitis and the possible direct etiologic role of the serum parathormone in its pathogenesis.

## References

1. Nichols G Jr, Flanagan B: Normocalcemic hyperparathyroidism. Trans Assoc Am Physicians **80:** 314–322, 1967.
2. Wills MR, Pak CYC, Hammond WG: Normocalcemic primary hyperparathyroidism. Am J Med **47:** 384–391, 1969.
3. Smith FB, Cooke RT: Acute fatal hyperparathyroidism. Lancet **2:** 650–651, 1940.
4. Mixter GG Jr, Keynes WM, Cope O: Further experience with pancreatitis as a diagnostic clue to hyperparathyroidism. N Engl J Med **266:** 265–272, 1962.
5. Turchi JJ, Flandreau RH, Forte AL, et al: Hyperparathyroidism and pancreatitis. JAMA **180:** 799–804, 1962.
6. Ballon S, Cohen H, Strasberg Z: Recurrent pancreatitis due to parathyroid adenoma in a normocalcemic patient. Can Med Assoc J **106:** 51–52, 1972.
7. Purnell DC, Smith LH, Scholz DA, et al: Primary hyperparathyroidism; a prospective clinical study. Am J Med **50:** 670–678, 1971.
8. Smith JF: Parathyroid adenomas associ-

ated with the malabsorption syndrome and chronic renal disease. J Clin Pathol **23:** 362–369, 1970.
9. Plough JC, Kyle LH: Pancreatic insufficiency and hyperparathyroidism. Ann Intern Med **47:** 590–598, 1957.
10. Dreiling DA: Pathological physiology of pancreatic inflammation; current status, 1960. JAMA **175:** 183–186, 1961.
11. Haverback BJ, Dyce B, Bundy H, *et al*: Trypsin, trypsinogen and trypsin inhibitor in human pancreatic juice; mechanism for pancreatitis associated with hyperparathyroidism. Am J Med **29:** 424–433, 1960.
12. Hueper WC: Metastatic calcification in organs of dog after injections of parathyroid extract. Arch Path Lab Med **3:** 14–25, 1927.
13. Cantarow A, Stewart HL, Housel EL: Experimental acute hyperparathyroidism. II. Morphologic changes. Endocrinology **22:** 13–27, 1938.