Pancreatitis, A Diagnostic Clue to Hyperparathyroidism *

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THE DIAGNOSIS of hyperparathyroidism generally depends upon the presence of a complication of the primary metabolic disorder. In only a rare instance has the disease been identified in the absence of the classic bone disease, urinary tract calcification or peptic ulceration. The symptoms due to the hypercalcemia itself, such as fatigue, lassitude and dyspepsia, are so uncharacteristic and so common in the population that dependence upon them to call the diagnosis to the attention of the clinician has proved unrewarding. Since hyperparathyroidism certainly exists in the absence of demonstrable bone disease, renal stones and peptic ulcers, any other state which might serve as a diagnostic clue should be significant. Recent experience with two patients who had concomitant pancreatitis and hyperparathyroidism and isolated reports in the literature of the same association indicate that pancreatitis may also be a complication, and, therefore, a diagnostic signpost.

When hyperparathyroidism was established as a disease in 1926, it was considered to be a disease of bone, the classic bone malady of von Recklinghausen.[21] The exact effect of the parathyroid hormone on bone is not yet known, but it has subsequently been determined that hyperparathyroidism exists without x-ray or microscopic evidence of bony abnormality. This was established when a significant number of patients with urinary tract calcification were found to have hyperparathyroidism.[4, 5] The increased excretion of calcium through the kidney was believed to be the precipitating cause of the calcification. Since some of the patients with the classic bone disease do not have renal calcification, and many of the patients with renal calcification have no bone disease,[5] it is obvious that both the bone disease and renal calcification must be complications of the primary disorder.

The description of peptic ulceration as an accompaniment of hyperparathyroidism came much later in the course of the unfolding knowledge of this disease.[27, 28] The relation of the excess of parathyroid hormone to the ulceration is less clear than to the bony and renal changes. It is probable that the ulceration also represents a complication. Only a minority of the patients of proved hyperparathyroidism have any evidence of gastric or duodenal ulceration.

The metabolic disturbance created by an excess of the parathyroid hormone is reflected in the blood serum by a rise in the level of calcium and a fall in that of phosphorus, and in the excretion through the

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kidney of an increase of both calcium and phosphorus. The patient probably is unaware of the changes in phosphorus metabolism. The changes in calcium metabolism, on the other hand, may be associated with symptoms. The more prominent are those related to the elevated blood calcium level. The increase in calcium ions is associated with muscular relaxation which the patient appreciates as lassitude and fatigue.[5, 14, 24] The patients are usually unaware of these symptoms until after operation when they sense of new feeling of well being. The increased excretion of calcium in the urine may produce polyuria and polydipsia. These symptoms are so subtle in the patients with mild degrees of hyperparathyroidism that once again the majority are not conscious of their presence until the metabolic disorder has been corrected. Since the symptoms produced primarily by the hormonal disturbance are so uncharacteristic and fickle, a constant search has been maintained for new diagnostic clues. Recent experience has suggested such a clue.

Two of the patients with hyperparathyroidism treated at the Massachusetts General Hospital have had associated pancreatitis. The first developed acute pancreatitis during a phase of known hyperparathyroidism. In the second, who was under treatment for recurrent pancreatitis, the diagnosis was established fortuitously. These experiences, one the converse of the other, have suggested that pancreatitis is another complication of hyperparathyroidism. If this is true, all patients with pancreatitis should be screened for hyperparathyroidism. Furthermore, it should be borne in mind that patients believed to have hyperparathyroidism may develop pancreatitis.

CASE REPORTS

Case 1. (MGH Hyperparathyroidism Case No. 102.) A 52-year-old housewife was admitted to the hospital in 1949 with symptoms of hyperparathyroidism of at least 8 years' duration. A parathyroid carcinoma was excised from the left side of the neck with relief of the skeletal symptoms. Two further operations, however, were required in 1951 to excise functioning local recurrences.

In 1952 the patient was given Chloromycetin® because of persistent urinary tract infection. On the 20th day of therapy, she developed abdominal pain, nausea and vomiting. These symptoms were interpreted at the time as due to the drug which was then omitted. The symptoms continued, however, and 2 months later she was readmitted to the hospital.

Laboratory examination indicated another recrudescence of hyperparathyroidism and exploration of the neck was again undertaken. No metastases were encountered in the old wound but a benign adenoma was found on the right side. The blood calcium level failed to decline after its removal. On the second postoperative day her abdominal symptoms became much more severe. A diagnosis of hemorrhagic pancreatitis was made. She died on the tenth postoperative day. Autopsy confirmed the presence of pancreatitis and of presumably functioning parathyroid metastases in the liver.*

Comment: In retrospect it seems likely that she had had a low grade pancreatitis for the 2 months prior to the last operation. The surgical procedure was followed by a flareup which proved fatal.

Case 2. (MGH Hyperparathyroidism Case No. 153.) A 62-year-old woman who had suffered from epigastric distress for 3 years was first seen in the hospital suffering from a severe attack of acute pancreatitis which resolved on conservative therapy. Despite a rigorous regimen of diet, medication, cholecystectomy, sphincterotomy and prolonged drainage of the biliary tract, she persisted in having recurrent episodes of pancreatitis of varying intensity (See chart). Readmission to the hospital was required on 3 occasions during the next 10 months. On the third admission, she was comatose and moribund. A serum calcium determination done at this time was unexpectedly high, 14.4 mg. per 100 ml., and in retrospect it was recognized that the level of 8.5 mg. at the time of her first admission was higher than one would have expected for the severity of her disease. For the first time attention was focused on this abnormality, and further findings consistent with hyperparathyroidism were elicited. At the time of discharge plans were made for surgical exploration of the neck in the future. However, another severe attack of pancreatitis precipitated her readmission and it was not until she recovered from this that parathyroid exploration could be undertaken.

* This patient has been previously reported as Case 1 in a report on parathyroid carcinoma.[11]

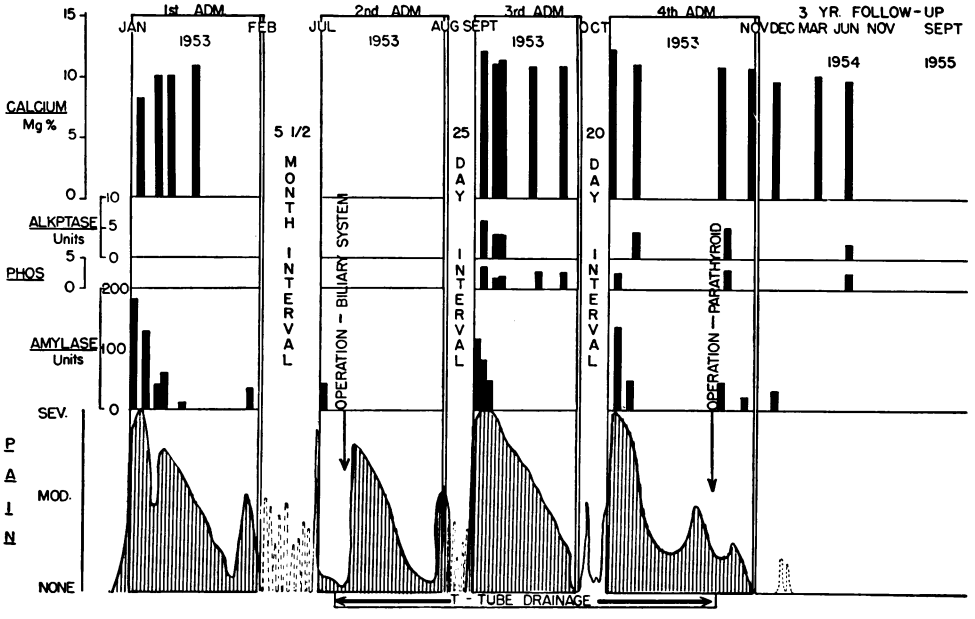

FIG. 1. Correlation of the clinical course and laboratory data in case 2.

A typical adenoma was found in the region of the right lower lobe. After it had been removed and the disordered metabolism had returned to normal, her abdominal symptoms promptly subsided. For the subsequent 3 years, to the present time, she has been remarkably well and entirely free of symptoms suggestive of pancreatitis.

Comment: In retrospect, it is likely that the patient's symptoms during the 3 years prior to her first admission were evidence of chronic pancreatic disease. Throughout the period of observation from January 1953 until December 1953 she had countless abdominal episodes of varying severity despite rigorous therapy. In the six weeks following the parathyroidectomy there were three attacks of abdominal discomfort, each milder than the previous one. From December 1953 to November 1956 (the date when last seen), there have been no further episodes. It is hard to escape the conclusion that the correction of the hyperparathyroidism has been responsible.

LITERATURE

The striking features of these two cases prompted a review of the literature. It was found that the association of pancreatitis, either with or without pancreatic calculi, had already been recorded in isolated case reports.

In 1923 Dawson and Struthers [12] reported the case of a 49-year-old man suffering from generalized osteitis fibrosa cystica who, at autopsy, was found to have a parathyroid adenoma and calcium deposits of varying size in all the parenchymal tissues of the body.

In 1940 Smith and Cooke [30] recorded their findings in a 44-year-old woman who for two years had suffered from rheumatism, pain in the legs and limping because of bowed thighs. She died after an illness of 16 days characterized by severe abdominal pain, distention, nausea and vomiting. On the day of death the blood calcium level was reported to be 23 mg. per cent. At autopsy there were areas of fat necrosis and the pancreas was swollen, the right half being gray and necrotic. Microscopically there was widespread calcinosis in the gland. A parathyroid adenoma was found in the right neck.

In 1947 Rogers, Keating, Morlock and Barker [28] recorded the history and findings of a 68-year-old man with symptoms which in retrospect were probably due to hyperparathyroidism of two to three years' duration. In addition, he complained of increas-

ingly severe epigastric pain, the cause of which was thought to be a long standing duodenal ulcer. This had failed to respond to a good medical regimen and surgical therapy. At autopsy the ulcer was found healed. Also found were hyperplasia of the parathyroidis and evidence of chronic pancreatitis with multiple calculi up to 2 cm. in diameter with ductal obstruction.

In the same year Martin and Canseco,[22] in a review of patients with pancreatic lithiasis, mentioned a 50-year-old colored man who had a serum calcium level of 14.2 mg. per cent. At autopsy a parathyroid adenoma was found and calculi were present in the pancreas, prostate and urinary tract.

Page [25] has recently discussed a 56-year-old man who was first seen with clinical, x-ray and laboratory findings of steatorrhea of pancreatic origin. An unexpected finding was laboratory evidence of hyperparathyroidism. The patient died a short time later from widespread malignant melanoma. Autopsy revealed a parathyroid adenoma and calcium carbonate stones in the pancreas, one of which had occluded the main pancreatic duct.

DISCUSSION

The coexistence of pancreatitis and hyperparathyroidism has now been recorded. The pancreatic disease involves the exocrine aspect of the gland. The hyperparathyroidism is an established endocrine disturbance. The clinical impression suggests that the association of these diseases is more than fortuitous. There are theoretical reasons for suspecting an etiologic relationship between them.[19, 34] It remains to be determined, however, whether the coexistence, and thus the etiologic relationship, is statistically significant.

Consideration of a causal relationship between pancreatitis and hyperparathyroidism hinges on which disease plays the primary rôle. It appears likely that the overactivity of the parathyroid gland initiates the pancreatitis, although the possibility of the reverse is not to be discarded.

As recorded above, the acute and chronic forms of pancreatitis have been observed in the presence of hyperparathyroidism. Some of the patients have exhibited demonstrable calcification in the pancreas. There has been considerable discussion as to the exact mechanism by which such depositions occur. Some believe that local degeneration of the tissue is primary and precedes calcification.[1, 8] Experimentally, areas of focal necrosis have been produced in the pancreas as well as in other organs following overdosage with Parathormone®.[18, 23] It would appear entirely possible, therefore, that this necrosis is one of the initiating factors in the development of acute pancreatitis, and that calcification in these areas follows in those patients who survive. This would explain the calcification occurring interstitially but not the calculi observed in the ductal systems of this and other organs.*

Others believe that the calcification occurs in situations where the medium is alkaline and, therefore, the calcium less soluble.[2, 6, 15, 33] It has been pointed out that calcium is precipitated within those tissues which are locally alkaline as a result of their acid secretory function. Thus, it is commonly seen interstitially in the lungs and fundus of the stomach and in the kidneys when the urine is acid. Conversely, it has been suggested that the calcium is not precipitated in those tissues which are locally acid when producing alkaline secretions, but rather in the ductal systems of such organs. Ureteral calculi and those in the renal pelvis occur primarily in the presence of alkaline urine and less commonly when the urine is acid. The observation has

* The term *metastatic calcification*, used widely in the literature, does not properly describe the calcifications observed in hyperparathyroidism. The deposition in the tissues is not a transfer of one calcium deposit to another area; rather a *de novo* process resulting from the parathyroid overactivity. *Pathologic calcification* is a better term.

also been made that an increase in calcium excretion by the salivary glands occurs in Parathormone® overdosage,[3, 7] and parotid calculi have been observed on two occasions among the series of cases of hyperparathyroidism reported from the Massachusetts General Hospital. Similarly, in this series and elsewhere,[22] calculi have been found in the prostate, an alkaline secreting organ. It would appear likely, therefore, that the mechanism involved when pancreatitis and hyperparathyroidism are associated is the deposition of calcium in the pancreas as a result of the hyperparathyroidism with subsequent blockage of the pancreatic ducts. Of particular interest in this regard is the observation that the stones in the majority of patients with pancreatic lithiasis are composed of calcium carbonate and phosphate, and are located primarily within the ducts rather than interstitially.[1, 22] This was true in four of the cases reviewed above.

The sequence of events are thus visualized as 1) the development of hyperparathyroidism, 2) the formation of pancreatic calculi, either superimposed on tissue trauma or as a primary precipitation of calcium, and 3) ductal obstruction and pancreatitis. The explanation of why reports of the roentgenographic demonstration of pancreatic calculi in hyperparathyroidism are rare may lie in the fact that abdominal x-rays are seldom focused on the pancreas. It is also known that symptoms from pancreatic calculi may precede the demonstration of radio opacities in the organ by many months.[22]

The prompt subsidence of the pancreatitis following parathyroid adenomectomy in case 2 may be explained by the relief of ductal obstruction upon resorption of the calculi following the return of a normal serum calcium level. Calculi in the urinary tract are not infrequently reabsorbed following the correction of hyperparathyroidism.[9]

Though the primary role of hyperparathyroidism appears most likely, cognizance should be taken of the possibility that pancreatitis could be the initiating disease in this complex. Secondary hyperparathyroidism is a well recognized condition arising, it is felt, from the stimulus of a low serum calcium level in a variety of diseases.[16, 26, 29, 31, 32] Reduced calcium levels are also found in pancreatitis. In the acute types in which the serum level falls in inverse proportion to the severity of the disease, this may be accounted for by the dislocation of large amounts of calcium from the blood stream into the areas of fat necrosis.[13] Tetany in the presence of normal serum calcium values is also reported in acute pancreatitis due possibly to the binding of ionic calcium by serum fatty acids which are elevated at such times. The low ionic calcium in this situation is presumably comparable to the low ionic calcium of hypoparathyroidism, and calls for increased parathyroid activity.[17]

In long standing relapsing pancreatitis and pancreatic lithiasis serum calcium levels are also frequently depressed. This is presumably the result of the fatty diarrhea and failure of absorption of fat soluble vitamin D commonly seen in these diseases. Thus, one might postulate that these forms of pancreatitis are also followed by parathyroid overactivity.

The sequence of parathyroid stimulation followed by hyperplasia and neoplasia has been advanced to explain the parathyroid abnormalities found in other conditions which similarly depress serum calcium.[12, 20] Although secondary hyperparathyroidism is believed to stimulate diffuse hyperplasia of the parathyroid glands, the development of an adenoma or carcinoma has not been established. For example, the best understood stimulator of secondary hyperparathyroidism, renal disease, is associated with diffuse hyperplasia, but not neoplasia.[10] Although germinal centers in the parathyroids have been postulated as the possible focal point of an adenoma,[34] no hyperfunctioning neoplasms have been found even

after chronic renal disease of many years' duration. Thus it seems unlikely that the low serum calcium level associated with pancreatitis could have caused the hyperfunctioning carcinoma or adenoma found in the two cases reported in this paper.

Although the exact mechanisms involved in the interrelationship between pancreatitis and hyperparathyroidism are, at the present time, purely hpothetical, the experience with the two cases presented here demonstrates certain practical points regarding the serum calcium levels. The elevated serum calcium of hyperparathyroidism may be reduced to deceivingly normal levels in the presence of complicating pancreatitis and render the diagnosis of hyperparathyroidism difficult. In case 2 it was not until the serum calcium level rose above normal that the possibility of hyperparathyroidism was even considered. Conversely, normal calcium levels in these situations can mask a severe pancreatitis, and lull the physician into a false optimism regarding the gravity of the pancreatic disease. This was particularly true of case 2 on her first admission, at which time the level of 8.5 mg. per 100 cc. appeared to indicate a far less severe degree of pancreatitis than actually existed. Similarly, in case 1, the terminal serum calcium level did not truly reflect the fatal nature of the pancreatitis. Thus, the clinician should be alert to the vagaries of serum calcium levels which are possible when pancreatitis and hyperparathyroidism coexist.

SUMMARY

1. Two patients have been encountered with concomittant pancreatitis and hyperparathyroidism. Isolated cases of this association have been previously recorded in the literature.

2. The serum calcium levels under such circumstances may be wholly unreliable and render the evaluation of both diseases difficult.

3. These cases suggest that pancreatitis is a complication of hyperparathyroidism and should, therefore, serve as a diagnostic signpost to overactivity of the parathyroid glands.

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