Original Article

PHPT with Pancreatitis: Atypical Presentation of PHPT

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Abstract

Background: Primary hyperparathyroidism (PHPT) is rarely associated with the occurrence of acute or chronic pancreatitis, requiring complex perioperative management. This study aimed to assess the prevalence and disease characteristics of pancreatitis in PHPT. **Materials and Methods:** This study is a clinicopathological analysis of the medical records of patients who were diagnosed with PHPT with pancreatitis between 1989 and 2021 in the Endocrine Surgery department, SGPGI, Lucknow. **Results:** Out of 548 PHPT cases, 44 (8.03%) were found to be associated with pancreatitis. The mean age was 33.57 years (15–65 years); 5 were ≤20 years, while 26 were ≤30 years of age. There were 27 males and 17 females. Twenty-one cases were of acute (11 acute, nine recurrent acute, one acute on chronic), whereas 23 were of chronic pancreatitis (six chronic calcific pancreatitis). The major clinical presentation of PHPT with pancreatitis was abdominal pain (65.91%). The mean number of attacks per patient in recurrent acute pancreatitis was two. Mean PTH levels were 68.19 pmol/L. The mean tumor size (in the largest dimension) was 2.79 ± 1.4 cm while the mean tumor weight was 4.91 g. Nephrolithiasis was associated with 25 cases. An association with multiple endocrine neoplasia type 1 syndrome was seen in one case. The final histopathological diagnosis was parathyroid carcinoma in two, hyperplasia in three, and parathyroid adenoma in 39 cases. Normocalcemia was seen in 27.2%, hypercalcemic crisis in 15.9%, and 25% of patients required semi-emergency parathyroidectomy. The outcome was favorable in all, as none had any further attacks of pancreatitis. **Conclusion:** In our study, the prevalence of pancreatitis in PHPT cases was 8.03%. The majority of patients were young. Normocalcemia was seen in 12 patients, so even if calcium levels are normal, PHPT should be suspected in young patients with pancreatitis. Parathyroidectomy resulted in the complete resolution of symptoms of pancreatitis in all 44 patients.

Keywords: Pancreatitis, parathyroidectomy, PHPT (Primary hyperparathyroidism)

Introduction

Primary hyperparathyroidism (PHPT) is caused by excessive, incompletely regulated secretion of parathyroid hormone (PTH) from one or more of the four parathyroid glands. Usually asymptomatic, it is one of the most common causes of hypercalcemia and thus should be considered in anyone with an elevated calcium concentration.[1] The clinical profile of PHPT in western countries has shifted from a symptomatic disorder, toward a more asymptomatic state. However, in developing countries like India, it continues to be mostly a symptomatic disease with skeletal, renal, cardiovascular, neuropsychiatric, and gastrointestinal manifestations.[2-4] Few studies from India have attributed the greater severity of PHPT to delayed diagnosis and widely prevalent vitamin D deficiency.[5]

Pancreatic disease in PHPT can present as acute pancreatitis (AP); recurrent AP (RAP) with no evidence of chronic pancreatitis (CP); CP with no calcification; chronic calcific pancreatitis; or PHPT complicated by AP in the postoperative period[6] Recurrent abdominal pain is the most common manifestation of the life-threatening AP with PHPT. AP is an inflammatory disease affecting the exocrine part of the pancreatic gland. It is associated with high morbidity and mortality. The most frequent causes are gallstones and alcohol abuse, in up to 75% of the cases. Metabolic conditions giving rise to pancreatitis are less common, accounting for 5–10% of cases. The causes include hypertriglyceridemia, hypercalcemia, diabetes mellitus, porphyria, and Wilson's disease.[7]

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Three mechanisms are involved in the development of PHPT-induced AP. One is PHPT-induced high serum calcium level, which can lead to an acceleration of the conversion of trypsinogen to trypsin in the pancreas, resulting in pancreatic auto-digestion and subsequent AP.[8] Secondly, the accumulation of calcium can promote the formation of ductal obstruction, pancreatic calculi, and subsequent attacks of AP.[9] Thirdly, genetic variants in serine protease inhibitor Kazal type 1 and cystic fibrosis transmembrane conductance regulator genes in combination with hypercalcemia markedly increase the risk of developing AP in patients with PHPT.[10]

CP with PHPT is also characterized by recurrent abdominal pain along with exocrine insufficiency and endocrine dysfunction. Hyperparathyroidism is rarely associated with pancreatitis, but when this combination occurs, the pancreatitis is likely to be severe. Despite its rarity, a cause-and-effect relationship is still suggested by the fact that parathyroidectomy seems to prevent the recurrence of pancreatitis.[11-14]

Pancreatitis is uncommon in PHPT, and the coexistence of the two diseases has widely been reported in the literature, but a causal relationship remains debatable. Considering the above-mentioned background, we reviewed the records to study the clinicopathological profile and treatment outcomes of patients with PHPT and pancreatitis.

Patients and Methods

This clinicopathological profile of patients who were diagnosed with PHPT with pancreatitis between 1989 and 2021 in the Endocrine Surgery department, SGPGI, Lucknow, was extracted from medical records and analyzed. Approval from the institutional ethics committee was obtained on January 25, 2023. Diagnosis of acute, recurrent acute, or chronic pancreatitis with PHPT was based on any two of the following three criteria[15]: (1) abdominal pain; (2) serum lipase activity and/or serum amylase levels at least three times greater than the upper limit of normal; (3) characteristic findings of pancreatitis on imaging. For PHPT, hypercalcemia associated with increased PTH levels implied diagnosis. Patients with other causes of acute or CP, including gall stones, alcohol consumption, hypertriglyceridemia, or medications and with another etiology that could explain pancreatitis, were not retained.

Ethical Clearance Statement

The study was approved by SGPGI IEC (Institutional Ethics clearance) with waiver of consent vide letter no. 2022-145-MCh-EXP-50 dated on 25-Jan -2023. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. All the procedures and interventions done hereby follow the guidelines laid down in the Declaration of Helsinki (2013).

Results

Out of 548 PHPT cases, 8.03%, that is, 44 patients were found to be associated with pancreatitis. The patient's ages ranged from 15 to 65 years, and the mean age of presentation was 33.57 ± 13.16 years, with a male-to-female ratio of 1.59:1.

The average duration of symptoms was 44.19 months, with a range of 1–180 months. The major clinical presentation of PHPT with pancreatitis was abdominal pain (65.91%), followed by renal manifestations (56.82%), musculoskeletal symptoms (54.54%), fatigue (31.82%), and neuropsychiatric symptoms (11.36%). Seven (15.9%) patients presented with a hypercalcemic crisis, and palpable neck mass was present in two (4.55%) patients. An association with multiple endocrine neoplasia (MEN) type 1 syndrome was seen in one case. Pancreatitis was the initial presentation in 12 cases.

Out of 44 patients of PHPT with pancreatitis, 11 patients had AP, 9 had RAP, 1 had acute on chronic, and 23 had CP, out of which 6 were of chronic calcific pancreatitis as shown in [Table 1].

Twelve patients had normal or high normal calcium levels, while seven patients presented with a hypercalcaemic crisis. Mean serum calcium levels were 12.05 mg/dL (n = 8.5–10.5 mg/dL), and mean phosphorus and alkaline phosphatase were 2.68 mg/dL (n = 3–5 mg/dL) and 414 u/L (n = 35–150 u/L) respectively. The mean serum creatinine was 1.06 mg/dL. The mean number of attacks per patient in RAP was two attacks per patient. Mean PTH levels were 68.19 pmol/L (1.66.9 pmol/L).

Eleven cases were taken up for semi-emergency parathyroidectomy. The average duration of hospital stay was 13 days. The outcome was favorable in all, as none had any further attacks of pancreatitis and were normocalcemic at the last follow-up.

The mean tumor size in the largest dimension was 2.79 ± 1.4 cm while the mean tumor weight was 4.91 g. Single-gland involvement was seen in 40 cases, three had multiglandular involvement, and one had mediastinal parathyroid adenoma. Histopathological diagnosis was parathyroid adenoma in

Table 1: Types of pancreatitis in PHPT patients

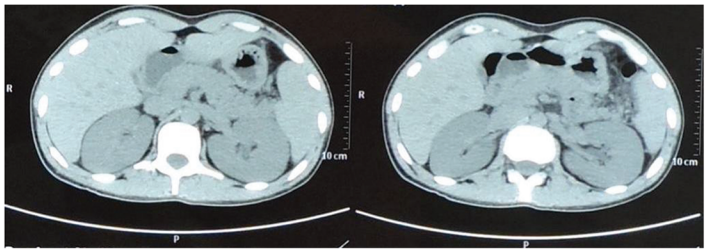
PHPT with pancreatitis	No. of patients
PHPT with Pancreatitis (Total patients)	44
Acute pancreatitis	11
Recurrent acute pancreatitis	9
Acute on chronic pancreatitis	1
Chronic pancreatitis*	23
*Out of 23 patients of chronic pancreatitis, 6 had chronic calcific pancreatitis	

PHPT=Primary hyperparathyroidism

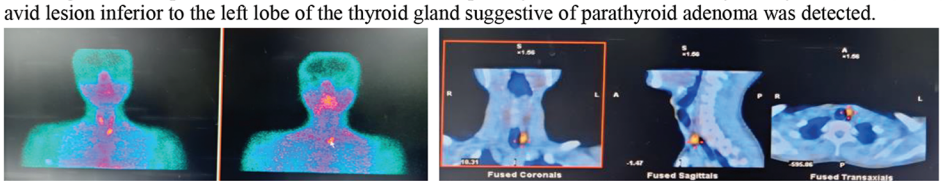
Table 2: Pathological profile of patients

Mean tumor size (cm)	2.79±1.4
Mean tumor weight (g)	4.91
Adenoma	39
Hyperplasia	3
Carcinoma	2

A 22-year-old male presented with multiple episodes of nonbilious, nonprojectile vomiting containing undigested food particles, along with decreased appetite and generalized weakness for the last 25 days, along with pain in the abdomen. The patient was found to have hypercalcemia with serum calcium levels of 14.7 mg/dL and iPTH (intact parathyroid hormone) levels of 76.13 pmol/L with raised amylase and lipase levels.



Contrast-enhanced computed tomography abdomen showing a bulky pancreas with mild peripancreatic fat stranding predominantly involving pancreatic tail. Ultrasonography of the neck revealed a hypervascular, hypoechoic lesion of size 5 × 16 mm seen inferior to the inferior pole of the left lobe of the thyroid, almost reaching into the suprasternal notch – s/o Left inferior parathyroid adenoma. Methoxyisobutyl isonitrile (MIBI) avid lesion inferior to the left lobe of the thyroid gland suggestive of parathyroid adenoma was detected.



The patient underwent focussed left inferior parathyroidectomy with FSB + intraoperative parathyroid hormone (IOPTH) and was relieved of his symptoms and was discharged in stable condition with no recurrence of pancreatitis till the last follow-up.

Figure 1: Case report. MIBI is also known as 99m Tc-methoxy isobutyl isonitrile. CECT: Contrast enhanced computed tomography, FSB: Frozen section biopsy, IOPTH: Intra-operative parathyroid hormone

39 patients, hyperplasia in three patients, and parathyroid carcinoma in two cases [Table 2].

Discussion

PHPT represents a nonphysiological overproduction of PTH. It is most commonly caused by a single adenoma of the parathyroid gland (80–85%), but less common causes include parathyroid hyperplasia, carcinoma, and MEN types 1 and 2A. The causal relationship between PHPT and pancreatitis has been debated for decades.

Eirdheim was the first to report a case of the association of PHPT and AP in 1903 when he noted necrotizing pancreatitis in a patient with parathyroid adenoma.[15] However, it was only in 1957 that Cope and his colleagues wrote an original paper on pancreatitis as a presenting manifestation of PHPT.[9]

Since then, there have been many individual cases and case series reported periodically in the belief that the concomitance of hyperparathyroidism and pancreatitis is more than coincidental and that recurrent pancreatitis can be cured by treating the cause of primary hyperparathyroidism.[9,16] The first largest series was reported by Mixter *et al.*[17]; they reported eleven cases of pancreatitis out of 155 cases of hyperparathyroidism in Massachusetts General Hospital between 1950 and 1962. Mixter estimated that pancreatitis occurred in between 7% and 10% of patients with hyperparathyroidism.

This observation was later challenged by Bess and colleagues from the Mayo Clinic in 1980. They reviewed 1153 patients and showed that the coexistence or history of pancreatitis was found only in 1.5% of patients, similar to the frequency of AP observed in the matched control group. They suggested that the association may be casual rather than causal.[18] Of 1153 patients with PHPT seen at Mayo Clinic between 1950 and 1975, only 17 (1.5%) had pancreatitis, a prevalence similar to that in the random hospital population; in addition, several of these patients had alternative explanations for pancreatitis.[18] The same study concluded that it is generally difficult to draw correlations between the two disorders among hospitalized patients because of measurement bias. As serum calcium was routinely measured in patients presenting with pancreatitis, they may have been preferentially screened for PHPT over non-pancreatitis patients. Khoo *et al.*[19] reported that the estimated rate of development of AP in PHPT was actually lower than a randomly selected group of control subjects without PHPT; it was 114 per 100,000 person-years among patients with PHPT versus 140 per 100,000 person-years among the controls. This study concluded that AP was not increased in community-dwelling patients with PHPT, and therefore, there does not appear to be a causal relationship between PHPT and AP. Another recent study has reported that chronic hypercalcemia in PHPT may not cause exocrine pancreatic dysfunction and CP.[20]

A strong argument against a causal relationship between PHPT and pancreatitis is that many of the patients with PHPT-associated pancreatitis have been reported to

have additional risk factors for pancreatitis. Much later, publications dealing with parathyroid have shown an increased association of pancreatitis from 3.2 to 5.6%.[6,21,22] These publications criticize the report by Bess and co-workers and point out that the reason for the low incidence is that most of these patients present in the asymptomatic stage with slight hypercalcemia and are submitted to parathyroid surgery before they have a chance to develop pancreatitis. Similarly, other studies have reported that half of PHPT patients with pancreatitis had additional risk factors for AP.[11,19] This could suggest that PHPT is a coincidental association. Alternatively, it could signify that multiple pancreatitis-causing factors are often necessary to develop the disease. The latter hypothesis would explain why only a minority of patients with PHPT develop pancreatitis, that is, they need to get an additional one or more hits along with PHPT to manifest the disease. However, in our study, none of the PHPT cases had additional risk factors for pancreatitis.

Among the studies that have reported a positive association, Four from India have reported the highest rates of pancreatitis among patients with PHPT. KG Rashmi *et al.* reported the occurrence of pancreatitis in 12 of 51 (23.5%), Arya *et al.* reported the occurrence of pancreatitis in 35 of 218 (16%), Bhadada *et al*. reported the occurrence of pancreatitis in nine of 59 (15%), while Jacob *et al*. reported it in 13 of 101 (13%) patients with PHPT.[5,6,23] The other positive studies reported lower rates of pancreatitis that ranged from 3.3 to 8.1%.[24]

Nevertheless, pancreatitis seems to be 10 times more frequent in PHPT patients than in a population free of parathyroid disease.[26,27] In our study, the prevalence of pancreatitis in PHPT cases was 44 of 548 (8.03%) patients, which is in accordance with the above studies. Table 3 shows a comparison between various studies.

The mean serum calcium, serum PTH , serum alkaline phosphatase levels, and mean tumor weight were comparable with combined mean levels found in the study by Yadav *et al*.[31]

Our study suggests a strong causal association between PHPT and pancreatitis, as cases having additional risk factors for pancreatitis were excluded. None of the pancreatitis cases in our study had additional risk factors for pancreatitis, such as gallstones, alcohol abuse, or hypertriglyceridemia. PHPT-Pancreatitis presented at a younger age with a male preponderance, in contrast to the female preponderance (27 out of 44). In both studies by Carnaille *et al*.[22] from France and the study by Jacob *et al*.[6] From India, a younger age of presentation with a male preponderance of pancreatitis was reported, which is in agreement with our observation. The exact pathogenesis of this younger age of presentation, male preponderance, and the presence of fewer skeletal/renal manifestations has not been established. A possible explanation could be the earlier detection of disease due to AP at a relatively mild stage with a lesser degree of elevation in intact PTH (iPTH) levels. Additionally, genetic risk factors for the development of AP could have contributed to the younger age of presentation.[27] Normal or High normal calcium levels seen in 12 patients may be due to the reason that AP is well known to lower total serum calcium levels, hypercalcemia of the underlying PHPT may be masked, and the diagnosis missed unless serum calcium is remeasured on follow-up after resolution of pancreatitis.

Our study is spread over a long span of time, so PTH levels have been estimated by various generations of assays over years of use, and the impact on correlation is still not clear, though, according to a study by Smit *et al*.[32] in 2019, for classic PHPT, the type of PTH assay used will not affect diagnosis or management because the precise concentration of PTH is less relevant. The American Association of Endocrine Surgeons guideline for the management of PHPT does not mention differences in PTH assays and does not give

Table 3: Review of literature

Study	Country	No. of PHPT patients	PHPT with pancreatitis	Type of pancreatitis
Bess *et al*.[18]	USA	1153	17 (1.5)	10 AP (0.86%), 7 CP
Sitges-Serra *et al*.[28]	Spain	86	7 (8.1)	3 AP (3.4%), 1 RP, 3 CP
Koppelberg *et al*.[29]	Germany	234	13 (5.6)	9 AP (3.8%), 4 CP
Shepherd *et al*.[30]	Australia	13	7 (5.1)	All AP (5.1%)
Carnaille *et al*.[22]	France	1224	40 (3.3)	18 AP (1.47), 8 RP, 14 CP
Agarwal *et al*.[21]	India	87	6 (6.9)	5 RP, 1
Jacob *et al*.[6]	India	101	13 (12.9)	6 AP (5.94%), 6 RP, 1 CP
Bhadada *et al*.[23]	India	59	9 (15.3)	All CP
Khoo *et al*.[19]	USA	684	10 (1.5)	All AP (1.5%)
Felderbauer *et al*.[10]	Germany	1259	57 (4.52)	16 AP (1.27%), 15 CP, 26 NA
Arya *et al*.[5]	India	218	35 (16)	18 AP (8.25%), 17 CP
Misgar *et al*.[3]	India	242	15 (6.19)	14 AP (5.78%), 1 CP
KG Rashmi *et al*.[27]	India	51	12 (23.5)	5 AP (9.8%), 7 CP
Total		5535	241 (4.35)	116 (2.09%) AP
Our study	India	548	44 (8.03)	11 AP (2.01%), 9 RAP, 1 AOC, 23 CP {AP + RAP + AOC}-21 (3.83%)

AP=Acute pancreatitis, RAP=Recurrent acute pancreatitis, AOC=Acute on chronic pancreatitis, CP=Chronic pancreatitis, PHPT=Primary hyperparathyroidism

recommendations on this issue.[33] In contrast, the international workshop on diagnosing asymptomatic PHPT does consider differences in PTH assay measurements and recommends using assay-specific reference values.[34,35] The workshop states that PTH measurement can be performed with second and third-generation PTH assays because both assay generations have similar diagnostic sensitivity for PHPT. Overestimation of PTH by second-generation assays would be of minor consequence in patients with hypercalcemic PHPT because, in these patients, the distinction between hypercalcemia due to PTH overproduction and PTH-independent causes of hypercalcemia is clear-cut. However, accurate measurement of PTH is important in identifying patients with normocalcemic primary hyperparathyroidism.[36]

Most studies from India report an incidence between 6.8 and 12%.[6,21,37] The possible explanation for the high incidence of pancreatitis in our part of the world could be explained by the fact that most of our patients present with symptomatic disease and they have relatively higher calcium values than in the West. Parathyroidectomy resulted in the complete resolution of symptoms of pancreatitis in all 44 patients. It is being suggested that parathyroid surgery should precede any pancreatic surgery for its beneficial effect on the course of the latter, and acute episodes of pancreatitis should not be a deterrent for early surgery.

The strengths of our study are the inclusion of a larger number of patients, and comprehensive clinical and biochemical evaluation. The limitations include the retrospective nature of the study and the lack of long-term follow-up.

Conclusion

In our study, the prevalence of pancreatitis in PHPT cases was 8.03%. Some firm conclusions can be drawn from our study. Young patients are more likely to present with pancreatitis; if a patient with pancreatitis shows normal calcium values, hyperparathyroidism should be suspected. More males are likely to present with pancreatitis. Parathyroidectomy results in the complete resolution of symptoms of pancreatitis, as seen in all 44 patients. An acute episode of pancreatitis should not be a deterrent for early surgery.

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Conflicts of interest

There are no conflicts of interest.

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