Parathyroid scintigraphy, histopathology correlation in patients with tropical pancreatitis and coexisting primary hyperparathyroidism

Subramanyam Padma, Palaniswamy Shanmuga Sundaram

Department of Nuclear Medicine and PET CT, Amrita Institute of Medical Sciences and Research Centre, Cochin, Kerala, India

ABSTRACT

**Purpose:** Tropical pancreatitis (TP) is a juvenile, non-alcoholic type of chronic pancreatitis and is highly prevalent in Kerala, India. Increasing prevalence of TP and its varied manifestations prompted us to undertake this retrospective analysis. We attempted to study the incidence of TP in patients with primary hyperparathyroidism (PHPT) and correlate with calcium levels, scintigraphy and histopathology findings. **Materials and Methods:** Records of 44 hypercalcemic patients with raised parathormone (PTH) were analyzed. Clinical, biochemical and imaging findings were noted to look for diabetes mellitus and pancreatitis. All patients underwent dual phase 99mTc methoxy isobutyl isonitrile parathyroid scintigraphy in our department between January 2007 and 2010. Gamma probe assisted minimally invasive parathyroidectomy was performed. Histopathological correlation was obtained in all patients. **Results:** Our study shows 18% (8/44 patients) incidence of TP in patients with PHPT (compared to 7% reported in 1970’s) in Kerala. Results show involvement of middle aged, non-alcoholic males. No direct association between severity of diabetes, pancreatitis and PHPT was noted in our series. Parathyroid adenoma was the most common underlying pathology. All TP patients’ clinical outcome improved post parathyroidectomy. TP patients with PHPT demonstrated adenomas, mainly composed of oxyphilic cells. Non pancreatitis group interestingly showed a varied picture of adenoma, hyperplasia with predominance of chief cells histologically. **Conclusion:** There is a 2.6 fold increase in the incidence of TP (18%) in patients with PHPT. Hypercalcemia may be the causative factor leading to TP in PHPT patients in our limited series. The data suggests a causal association between pancreatitis and PHPT. Patients presenting with either one or a combination of hypercalcemia, pancreatic dysfunction or raised PTH need to be thoroughly evaluated as their management is interlinked.

**Keywords:** Diabetes mellitus, parathyroid scintigraphy, single photon emission computed tomography, tropical pancreatitis

INTRODUCTION

Tropical pancreatitis (TP) was first described by Zuidema of Indonesia in 1959. A distinct non-alcoholic type of juvenile chronic pancreatitis presenting with abdominal pain, steatorrhea and diabetes mellitus with uncertain etiology called “TP” is prevalent in Kerala, India. This chronic relapsing form of pancreatitis typically manifests as abdominal pain (80-90% of cases), weight loss, glucose intolerance or frank diabetes mellitus. Patient’s age at disease onset is variable, ranging from infancy to adolescence. Previously TP was related to malnutrition and patients presented with bluish discoloration of lips, bilateral parotid involvement and a pot belly.

Due to its high prevalence in tropics, it is aptly called as TP. It is also commonly referred as “Pancreatic diabetes” characterized by a younger age onset, presence of large intraductal pancreatic calculi, more aggressive pancreatitis and a high incidence of pancreatic malignancy. Apart from protein energy malnutrition, a number of factors are implicated in the etiopathogenesis of TP such as pancreatic ductal anomalies, food toxicities (i.e., chronic cyanide toxicity from cassava) and possible genetic predisposition (serine protease inhibitor, Kazal type 1, N34S mutation and cystic fibrosis transmembrane conductance regulator mutation).
Balakrishnan et al. conducted a demographic study and analyzed a cohort of 220 patients from our institute. They described the differentiating features between TP, alcoholic pancreatitis in Kerala [Table 1] and found variations in patients presenting as TP. They reported an older age at presentation, an early onset of a milder form of diabetes mellitus. Based on this publication we attempted to study (a) the incidence of TP with co-existing primary hyperparathyroidism (PHPT), (b) how many of them reveal an underlying parathyroid pathology and (c) how the histological picture in this subgroup varies from other cases of PHPT unassociated with pancreatitis.

Pancreatitis is rarely linked to hyperparathyroidism, but the pancreatitis is often severe when it is associated with PHPT. Studies have suggested that parathyroidectomy has cured and prevented the recurrence of pancreatitis, but cause and effect relationship still remains controversial. PHPT can be scintigraphically evaluated using one or more radiopharmaceuticals like 201Thallium or 99mTc labeled Sesta methoxy isobutyl isonitrile (MIBI)/tetrofosmin.

Pitchumoni et al. reported the association of PHPT and TP in Kerala to be only 7% with a male preponderance in 1970%. To our knowledge, there are no studies in literature that have used scintigraphy as a tool in evaluation of TP patients with raised serum parathormone (PTH).

Patients with history of thyroid disorders, previous parathyroidectomy, recent intra-abdominal surgeries, gall stones or any previous pancreatic diseases were excluded in an effort to rule out false positive scintigraphy findings.

**Scintigraphic procedure and interpretation**

555-740 MBq of 99mTc Sesta MIBI was injected intravenously; dual phase planar imaging was performed in all patients. Single photon emission computed tomography with CT (SPECT/CT; Infinia Hawkeye; GE Healthcare, Milwaukee, US) imaging of neck and mediastinum were reserved for those patients with ill-defined or suboptimal MIBI uptake at parathyroid location in planar images.

Planar and SPECT/CT images were interpreted by two experienced nuclear medicine physicians. Homogenous normal tracer distribution in thyroid bed with or without a focal increased tracer uptake in any of the parathyroid locations in initial image and demonstrable washout from the normal thyroid tissue with retention in the hyper functioning parathyroid in delayed image is characteristic of adenoma/hyperplasia. We also correlated planar with SPECT/CT images to localize the exact site and position of parathyroid pathology.

**Gamma probe assisted minimally invasive parathyroidectomy procedure**

Gamma probe assisted minimally invasive parathyroidectomy was performed in all patients with scintigraphic confirmation of parathyroid adenoma. On the day of surgery, patients were re-injected with 111-185 MBq of 99mTc Sesta MIBI intravenously and taken up for surgery after an hour to obtain a better background clearance of tracer in neck. Using pre-operative Sesta MIBI scintigraphy images as a guide, patient's skin over the neck was scanned by the surgeon with the gamma probe to determine the accurate site of cutaneous surgical incision. Location of parathyroid adenoma was reconfirmed and the adenoma was removed through a small, 1.5-2.5-cm, skin incision. Radioactivity was measured intraoperatively on the gland (P), thyroid (T) and background (B) (apex of the lung contralateral to adenoma). Radioactivity was also measured in the parathyroid bed (P-bed) after excision of adenoma to check for residual tracer activity and in the

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**Table 1: Differentiating features of tropical pancreatitis from alcoholic pancreatitis in Kerala**

| Feature                        | Tropical pancreatitis TP                                                                 | Alcoholic pancreatitis AP                                      |
|--------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Age                            | Young                                                                                    | Middle aged                                                  |
| Sex                            | Male preponderance (2.7:1)                                                               | Equal                                                        |
| Diet                           | High intake of Cassava                                                                  | No history of cassava intake                                  |
| Nutrition                      | Malnourished                                                                             | Well nourished                                               |
| Geographical region            | Tropical                                                                                 | Temperate                                                    |
| Socio-economic class           | Low                                                                                      | All classes                                                  |
| Alcoholism                     | Present but are dense, large, multiple, and always intraductal                           | Associated with alcoholism                                    |
| Smoking                        | Non-smokers                                                                              | Mainly in smokers                                            |
| Diabetes mellitus              | In 70% to 80% before, with or after onset of abdominal pain                              | In about 50% usually after onset of pain                      |
| Typical features               | Bluish hue of lips, parotid Enlargement, pot belly                                       | None                                                         |
| Pancreatic duct                | Markedly dilated                                                                         | Less dilated                                                 |
| Pancreatic calculi             | Present but are small, scattered in small ducts, parenchymal calcification               | Present but are small, scattered in small ducts, parenchymal calcification |
| Associated malignancy          | Common                                                                                   | Less common                                                  |

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**Patient population**

Medical records of 44 hypercalcemic, raised PTH level patients (Male:Female 28:16, age range: 19-65 years, mean 41 ± 9 years) who underwent 99mTc Sesta MIBI dual phase parathyroid scintigraphy in our department between January 2007 and 2010 were analyzed. History of alcohol consumption and medications were noted. Clinical and biochemical evidence for diabetes mellitus and pancreatitis (serum amylase levels) were checked. Patients with elevated amylase levels were further subjected to abdominal ultrasound/computed tomography (CT) and the imaging findings were noted.
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**RESULTS**

**Clinical and biochemical results**

A total of 44 hypercalcemic patients (Male:Female = 28:16, age range: 19-65 years, mean 41 ± 9 years) with diabetes mellitus and raised serum PTH were retrospectively analyzed.

Clinically, 4 out of 8 patients with elevated amylase levels presented with abdominal pain. Patients also presented with bone pain, loin pain and pathological fractures and duration of symptoms ranged from 45 days to 12 months. 2 out of 44 patients gave a history of alcoholism. None of them exhibited classical findings of parotid swelling or bluish discoloration of lips. Two patients however were malnourished clinically.

Patients with PTH values above 60 pg/ml (normal 11-54 pg/ml) on at least 2 occasions, serum amylase levels above 140 U/L (normal 40-140 U/L) underwent abdominal ultrasound/CT. Mean calcium levels were higher in patients with pancreatitis than those with no associated pancreatitis (14 ± 2 mg/dl vs. 10.8 ± 0.30, normal values range from 8.8 to 10.6 mg/dl).

**Imaging results**

Of the total 44 patients, 42 (95.4%) patients were positive for parathyroid adenoma. Two patients demonstrated parathyroid hyperplasia. [Figures 1-2] [Table 2] 8 out of 44 patients (18%) had association of parathyroid adenoma and features of TP. Pancreatic calculi, mostly intraductal, were present in 5 out of 8 cases (62.5%). Scintigraphically all PHPT patients with coexisting TP (8/44) showed parathyroid adenoma as the underlying pathology. One patient demonstrated bilateral inferior parathyroid adenomas [Figure 3]. However, none of them revealed ectopic parathyroid adenomas [Figure 3]. Histopathological correlation was also obtained post-operatively.

**Table 2: Location of parathyroid adenomas/hyperplasia**

| Number of pts | Location of adenoma/hyperplasia |
|---------------|---------------------------------|
| 27            | Left inferior parathyroid adenoma |
| 4             | Left superior parathyroid adenoma |
| 9             | Right inferior parathyroid adenoma |
| 2             | Right superior parathyroid adenoma |
| 2             | Left superior parathyroid hyperplasia |

**Table 3: MiB uptake ratios and correlation with intraoperative parathormone levels**

|                     | T/B  | P/T  | P/B  | P-bed/B | PTH a | PTH b |
|---------------------|------|------|------|---------|-------|-------|
| Range               | 1.3–1.6 | 1.1–2.9 | 1.5–3.9 | 0.9–1.1 | 78–869 | 7–47  |
| Mean                | 1.5   | 1.5   | 2.5   | 1.0     | 189.2  | 21.3  |
| SD                  | 0.1   | 0.4   | 0.5   | 0.03    | 129.6  | 11.4  |

excised adenoma extro to confirm successful parathyroidectomy. Retention ratio of thyroid to background (T/B), parathyroid to thyroid (P/T), parathyroid to background (P/B) and P-bed/B ratios were calculated. Intraoperative quick PTH was measured by immunofluorimetric assay (normal values 10-54 pg/ml). PTH was measured just before the beginning of surgery (depicted as PTH a) and 10 min after parathyroidectomy (depicted as PTH b in Table 2). Histopathological correlation was also obtained post-operatively.
Surgical results
Patients with parathyroid adenoma were considered for minimally invasive gamma probe guided surgery to reduce operative timing and morbidity in view of coexisting diabetes and pancreatitis. Mean operating time for conventional parathyroidectomy in our institute without gamma probe guidance was 75 ± 7 min, which was significantly reduced to 43 ± 5 min with a probe assisted surgery. The scar size was only 1.5-2.0 cm, thereby ensuring faster post-operative patient mobilization [Figure 4]. A reduction in ioPTH values by at least 50% compared to baseline PTH value was used to confirm complete excision of adenoma. Serum PTH prior and after surgery, shows a significant reduction in post-surgical PTH levels as shown in Table 2.

Histological correlation
Parathyroid specimens were examined to determine the cell type of the adenomas [Figure 5]. The cell type was predominantly oxyphilic in adenomas of TP patients (6/8 patients). Patients with no clinical or biochemical evidence of pancreatitis show a varied picture of adenoma, hyperplasia with predominance of chief cells histologically.

Patients were kept on close follow-up. There was significant improvement in PTH levels and serum amylase levels at 3 and subsequently 6 months follow-up.

DISCUSSION
TP may be defined as a form of idiopathic chronic pancreatitis usually reported from developing countries. It affects children and young non-alcoholic adults and is characterized by recurrent abdominal pain, large pancreatic intraductal calculi, diabetes, steatorrhea and malnutrition. These cases are increasingly susceptible to develop pancreatic malignancy.

Our findings are in agreement with previous observations of a relationship of pancreatitis with PHPT. There is a significant increase in the association of PHPT with TP when compared with previous association of only 7% in 1970’s from our state. This may be due to a referral bias, more inclusive, but less stringent diagnostic criteria, wider availability of biochemical tests, better imaging technology and higher awareness. There is a shift in the disease pattern in our study showing involvement of middle aged males, which is in line with other published data.[3,5,6] Diabetes in patients with TP may have a slow progressive course. It is usually ketosis resistant and is termed as fibro calcific pancreatic diabetes and follows an aggressive course to reach the endpoints of diabetes, pancreatic calculi and exocrine pancreatic dysfunction (steatorrhea) in the majority of cases.[7] Diabetes mellitus in TP is thought to be related to the duration of pain and calcification and not to the presence or absence of exocrine dysfunction. Abdominal pain is usually the first presentation in TP. A severe form of pancreatic injury is provoked by elevated intracellular calcium levels.

Histologically, the main features in TP are progressive fibrosis resulting in shrinkage of the pancreas together with stone formation and dilatation of the pancreatic ducts. There is atrophy of the exocrine pancreas in association with intense fibrosis and loss of pancreatic islets, although some residual islets show hyperplasia and beta cell proliferation.[8]

Tc Sesta MIBI was first used to image parathyroid glands in 1989. Since then many investigators have reported uniformly excellent results for localization of parathyroid adenomas while using several different imaging protocols. However, accuracy of localizing parathyroid hyperplasia has not met with the same success. Diagnostic utility of Sesta MIBI protocols equals or exceeds other non-invasive, non-scintigraphic imaging strategies, including high-resolution ultrasound, CT and magnetic resonance imaging.

ioPTH monitoring is a robust indicator to determine the success of parathyroidectomies. A significant rise in the ioPTH immediately after resection of a single parathyroid is
often perceived to be indicative of the presence of additional hyperfunctioning glands and enables multiglandular disease to be excluded with a high degree of certainty during surgery. It has been shown to predict long-term cure after parathyroidectomy in almost 95-98% of cases. In contrast, the role of post-operative PTH measurements in predicting long-term cure after parathyroidectomy is less well-studied.

In our series, we find an early onset of diabetes mellitus, which may be related to hypercalcemic or hyperparathyroidism status of patients. It is well-known that derangement of glucose metabolism is found frequently in all forms of hyperparathyroidism. This can be explained as follows — when PTH is high it produces elevation in intracellular calcium levels that impairs post receptor binding insulin action, such as the dephosphorylation of glycogen synthase and of insulin regulatable glucose transporter-4. Another possible mechanism is that elevated intracellular calcium enhances calmodulin binding to insulin receptor substrate-1, which interferes with insulin-stimulated tyrosine phosphorylation and phosphatidylinositol 3-kinase activation. Indeed, PTH has been shown to be inversely associated with insulin sensitivity. Clinical outcome improved post-operatively in all patients. Corrected serum calcium was above the normal range for all our patients as reported in other studies. The mean calcium values were significantly higher among patients with PHPT and pancreatitis compared with patients with PHPT and no pancreatic involvement. This makes us believe that the mechanism of development of pancreatitis in PHPT is correlated to the degree of hypercalcemia.

We postulate two possible reasons for this increased association of TP with PHPT. First, TP is highly prevalent in this part of the country and is thought to be closely related to dietary toxins, cassava intake, malnutrition and certain genetic, familial factors. Secondly PHPT in the present study is largely biased as in the other western studies as it is a symptomatic disease. Clinical presentation of PHPT, diabetes, pancreatitis and pancreatic calculi in background of hypercalcemia probably leads to higher rate of diagnosis in our tertiary care center.

In a study of Chiu et al., 1475 patients with acute pancreatitis, hyperparathyroidism accounted for only 5 cases (0.4%). However, in patients with hyperparathyroidism and resulting hypercalcemia, pancreatitis occurs 10-20 times more often than in the general population. The mechanism of hypercalcemia as a cause of pancreatitis is controversial and not clearly understood.

Possible mechanisms implicated in the development of acute pancreatitis in patients with PHPT are mainly related to hyperparathyroidism that directly increases pancreatic enzyme output releasing gastrin and cholecystokinin-pancreozymin. Some believe necrosis of acinar and ductal pancreatic cells is linked to increased pancreatic duct permeability due to hypercalcemia. Another possibility is the de novo activation of trypsinogen to trypsin resulting in autodigestion of the pancreas and subsequent pancreatitis. It is also thought to be precipitated by pancreatic ductal obstruction due to calculi resulting in attacks of acute or chronic pancreatitis. Finally, factors other than calcium, such as genetic risk factors, may predispose patients with PHPT to acute pancreatitis.

Pancreatitis related to hyperparathyroidism was first reported over 6 decades ago. The cause and effect relation between the two pathologies initially led to controversies. The pathophysiological theory that pancreatitis is the cause for hyperparathyroidism is no longer entertained and it appears to be the consequence rather than the cause of hyperparathyroidism. The healing of pancreatitis after parathyroidectomy confirms this hypothesis.

To summarize, we found a 2.6 fold (18%) increase in the association of TP and PHPT since 1970’s. This association is not incidental; pancreatitis is the sequela of parathyroid adenoma as clinically and biochemically patients showed improvement after parathyroidectomy. Hypercalcemia seems to be a major factor in the development of pancreatitis in this setting and there is a definite correlation between hypercalcemia, PHPT and incidence of TP. Surgical excision of parathyroid adenoma or hyperplasia leads to amelioration of symptoms of pancreatitis.

CONCLUSION

There is a 2.6 fold (18%) increase in the incidence if TP in patients with PHPT. Hypercalcemia may be the causative factor leading to PHPT in patients with TP in our limited series. The data suggests a causal association between the pancreatitis and PHPT. Patients presenting with either one or a combination of hypercalcemia, pancreatic dysfunction or raised PTH need to be thoroughly evaluated as their management is interlinked.

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