Clinical Case Report

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Acute pancreatitis as an initial manifestation of parathyroid carcinoma

A case report and literature review

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Abstract

Rationale: Parathyroid carcinoma is a rare endocrine malignancy. Acute pancreatitis as an initial manifestation of parathyroid carcinoma has been rarely reported.

Patient concerns: A 22-year-old woman was admitted to emergency room with a sudden attack of severe epigastric pain.

Diagnoses: Acute pancreatitis was diagnosed as elevated levels of serum amylase. During the work-up for acute pancreatitis, patient's abnormally increased serum calcium and bones destruction revealed by abdominal computed tomography (CT) scan raised the suspicion of hyperparathyroidism or malignancy. Elevated serum parathyroid hormone (PTH) levels, parathyroid ultrasound and scintigraphy gave rise to the diagnosis of primary hyperparathyroidism (PHPT) due to a left parathyroid tumor.

Interventions: The patient was given a complete tumor excision. After the surgery, parathyroid carcinoma with capsular and vascular invasion was confirmed histologically. A second surgery was then performed, including resection of the ipsilateral thyroid lobe and anterior cervical nodes.

Outcomes: Serum calcium and PTH levels returned to normal postoperatively.

Lessons: Acute pancreatitis accompanied with hypercalcemia should always raise the suspicion of PHPT. The spicule sign, which always suggests the infiltrating pattern growth of tumor, was neglected at first and was observed during a second review of the ultrasound images postoperatively. This specific feature may be predictive for the preoperative diagnosis of parathyroid carcinoma or at least suspicion of malignancy.

Abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator, CT = computed tomography, H&E = hematoxylin–eosin, PHPT = primary hyperparathyroidism, PTH = parathyroid hormone, SPINK 1 = serine protease inhibitor Kazal type 1.

Keywords: acute pancreatitis, parathyroid carcinoma, primary hyperparathyroidism

1. Introduction

Alcohol and biliary tract stones are the leading causes of acute pancreatitis.[1] Acute pancreatitis due to primary hyperparathyroidism (PHPT) is an uncommon condition.[2] Parathyroid carcinoma is a rare cause of PHPT, accounting for <1% of all cases of PHPT.[3] Parathyroid carcinoma is generally associated with an indolent and slowly progressive course.[4] Most patients present with signs and symptoms of PHPT and hypercalcemia, including nephrolithiasis, nephrocalcinosis, osteopenia, pathological fractures, gastrointestinal disturbances, fatigue, and depression.[4,5] Acute pancreatitis presenting as the first manifestation of parathyroid carcinoma was rarely described before. Here we report a case of parathyroid carcinoma presenting with acute pancreatitis as an initial manifestation in a young woman. Relevant literature was also reviewed in this paper.

2. Case report

A 22-year-old woman presented to the emergency room with a sudden attack of severe persisting epigastric pain accompanied by nausea and vomiting for 3 days. Abdominal examination revealed diffuse tenderness all over the abdomen, especially in the epigastric area. Laboratory data showed high levels of serum amylase (1200 U/L), lactate dehydrogenase (282 U/L), alkaline phosphatase (732 U/L), impaired renal function (serum urea nitrogen 28.16 mmol/L, creatinine 446.9 μmol/L), and hypercalcemia (2.88 mmol/L, normal range 2.1–2.55 mmol/L). Based on the clinical picture and blood analysis, the patient was diagnosed with acute pancreatitis and renal failure.

The patient was admitted to the ward. Abdominal computed tomography (CT) scan confirmed the diagnosis of exudative pancreatitis. Moreover, it demonstrated bilateral diffuse

Editor: Parag Parekh.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:44(e8420)

Received: 6 February 2017 / Received in final form: 19 April 2017 / Accepted: 4 October 2017

http://dx.doi.org/10.1097/MD.0000000000008420

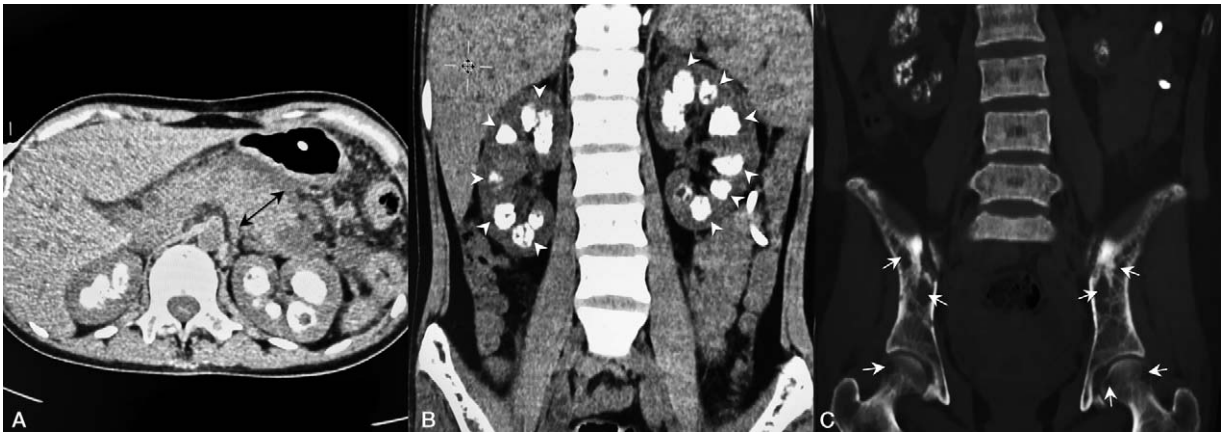

Figure 1. Abdominal computed tomography scan. (A) An axial image at the level of the pancreas showed enlarged pancreas (double-headed arrow) with indistinct boundaries and surrounding exudates. Note medullary calcinosis in both kidneys. (B) Coronal multiplanar reformation (MPR) image showed dense calcifications (arrowheads) throughout both kidneys, which correspond the shape and position of the renal pyramids. (C) Coronal MPR image showed multiple bone destruction (arrows) of bilateral ilium and femoral head.

medullary nephrocalcinosis and destruction of multiple bones (Fig. 1). Subsequently bone scintigraphy showed homogeneously increased metabolism of whole body bones, especially the craniofacial bones. In contrast to what was expected in a case of acute pancreatitis, serum calcium kept rising to a maximal level of 3.36 mmol/L. Persisting hypercalcemia in combination with destruction and increased metabolism of bones raised a suspicion of hyperparathyroidism or malignancy, such as multiple myeloma. Plasma levels of parathyroid hormone (PTH) were then determined and showed a marked increase up to 2677.7 pg/mL (normal range 15.0–68.3 pg/mL). A palpable 2 cm medium–hard mass without adherence to the skin was detected on the left side of the neck. Neck ultrasound scan revealed a round-shaped heterogeneous hypoechoic nodule, sized of 2.3×1.7 cm, posterior to the upper third of the left thyroid lobe. Color Doppler showed a diffusely increased vascularity inside the nodule (Fig. 2). Parathyroid scintigraphy with dual-phase Tc-99m sestamibi revealed an abnormal accumulation of radiopharmaceutical in the left superior parathyroid region (Fig. 3). A left upper parathyroid adenoma was diagnosed by ultrasound and scintigraphy.

The patient was given a parathyroid surgery. During the procedure, a medium–hard mass with well-defined margins was found behind the upper segment of the left thyroid lobe. A $2.5 \times 1.8 \times 1.5$ cm mass was completely removed. Frozen section identified a parathyroid tumor. However, it was unable to determine whether it was benign or malignant. After the surgery, hematoxylin–eosin (H&E) stains revealed a parathyroid carcinoma with capsular and vascular invasion (Fig. 4). Immunohistochemical stains for CD34 also confirmed vascular invasion. Two days later, a second surgery was performed, including resection of the left thyroid lobe and anterior cervical nodes. Histological examination showed that the thyroid lobe and cervical lymph nodes were not involved. Postoperatively, calcium and PTH levels returned to normal (2.08 mmol/L and 19.9 pg/mL, respectively). Neck ultrasound images were carefully reviewed again and at this time, spicule margin of the tumor was observed, which was previously neglected (Fig. 2B).

The laboratory findings are summarized in Table 1.

This study was approved by the Ethics Committee of Tongji Medical college, Huazhong University of Science and Technology. The patient has given informed consent to publish these case details.

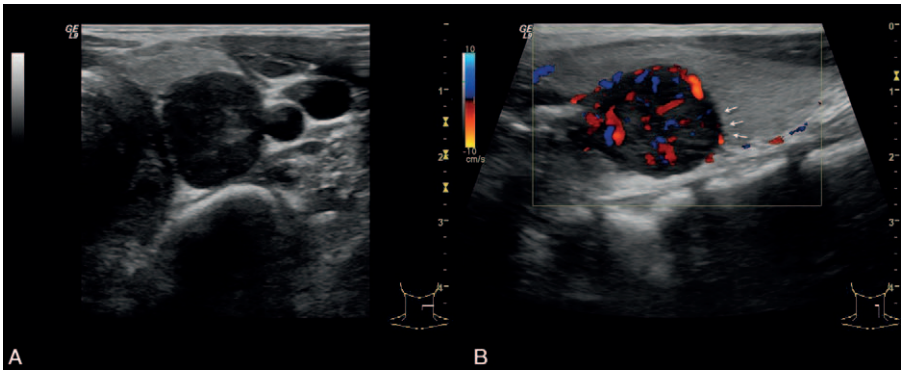

Figure 2. Neck ultrasound imaging. (A) Transversal sonogram showed a 2.3×1.7 cm round hypoechoic nodule posterior to the left thyroid lobe. (B) Color Doppler sonogram showed increased vascularity in the nodule. Spicule sign (arrows) was observed on longitudinal plane during a second review of ultrasound images postoperatively.

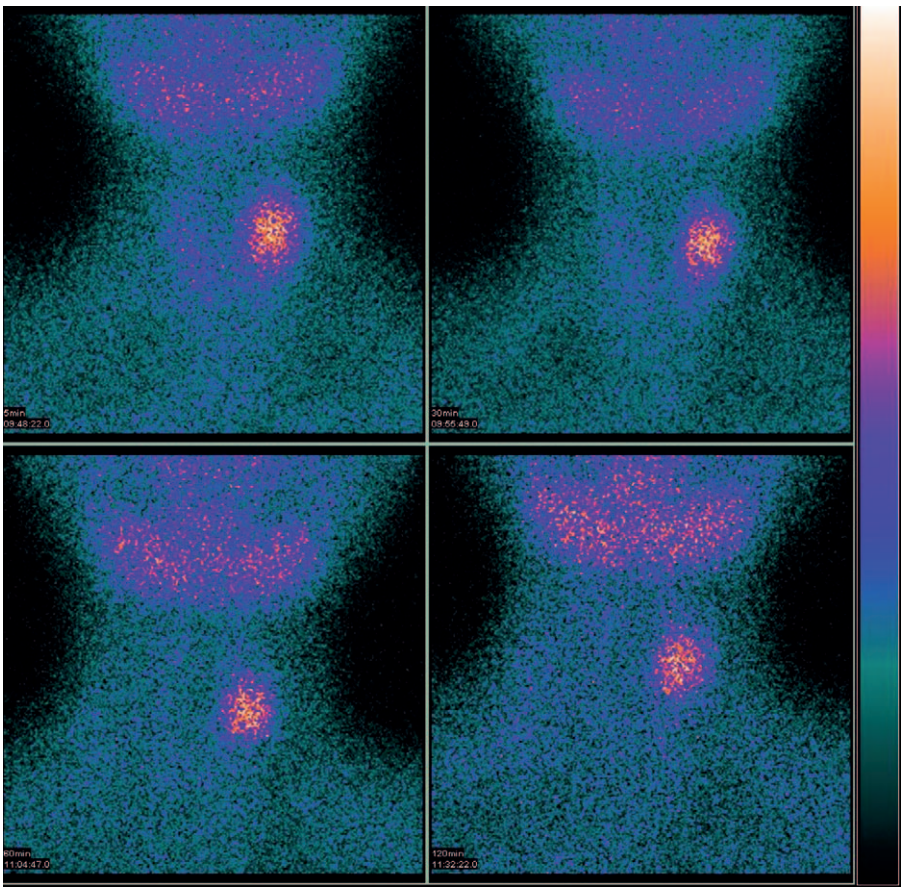

Figure 3. Dual-phase Tc-99m sestamibi scintigraphy. Early (5 and 30 min) and delayed (60 and 120 min) images showed a persistent accumulation of radiopharmaceutical in the left superior parathyroid region (target/nontarget [T/NT] ratios: 2.05–2.14).

3. Discussion

Association between PHPT and acute pancreatitis was first reported by Erdheim in 1903.[6] The etiologic relationship between them was then indicated.[7] The prevalence of acute pancreatitis in patients with PHPT is reported to be 1.5%.[2] PHPT-induced hypercalcemia is considered to be the cause of acute pancreatitis and 3 possible pathophysiological mechanisms were postulated: the deposition of calcium in the pancreatic duct may cause pancreatic duct obstruction; hypercalcemia may lead to conversion of trypsinogen to trypsin within the pancreatic parenchyma triggering autodigestion of the pancreas; genetic variants in SPINK 1 (serine protease inhibitor Kazal type 1) and CFTR (cystic fibrosis transmembrane conductance regulator) genes may increase the risk of developing acute pancreatitis in patients with PHPT.[8] In addition, Singh et al[9] demonstrated that patients with hyperparathyroid-induced hypercalcemic crisis (defined as symptoms and signs of acute calcium toxicity with a corrected calcium level >14–15 mg/dL) showed higher prevalence of pancreatitis as compared to noncrisis patients (13.5% vs 5.7%).

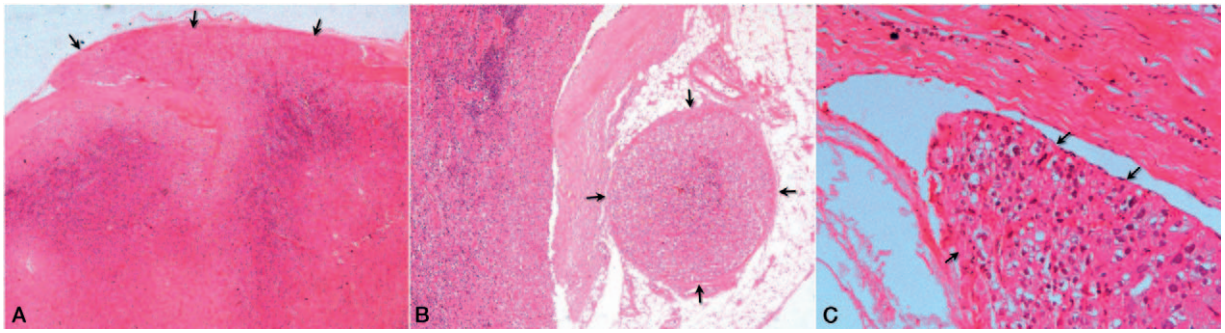

Figure 4. Microscopic appearance. Tumor revealed a solitary growth pattern with capsular and vascular invasion. (A) Transcapsular penetration (arrows) (hematoxylin–eosin stain [H&E], ×20); (B) Nodule with same cellularity and cytological architecture as the main tumor (arrows) outside the tumor capsule (H&E, ×40); (C) tumor thrombus (arrows) in capsular vessel (H&E, ×100).

Table 1

Laboratory findings.

Variables	On admission	Maximal	Postoperative	Normal range
Plasma PTH, pg/mL	NA	2677.7	19.9	15.0–68.3
Serum				
Calcium, mmol/L	2.88	3.36	2.08	2.1–2.55
Amylase, U/L	1200	1200	150	30–110
Urea nitrogen, mmol/L	28.16	28.16	7.2	2.5–1.6
Creatinine, μmol/L	446.9	446.9	138.5	62.0–106.0
Lactate dehydrogenase, U/L	282	391	NA	109–245
Alkaline phosphatase, U/L	732	732	480	40–150

NA = not available; PTH = parathyroid hormone.

Parathyroid carcinoma is a rare endocrine malignancy with an annual incidence of <1/1,000,000.[3] The ratio of affected women to men is 1:1, whereas there is a significant female predominance in benign PHPT.[3] The median patient age is 56 years.[3] The clinical features of parathyroid carcinoma are mainly due to the effects of PHPT.[5] Common presentations include signs and symptoms of hypercalcemia, hyperparathyroid bone disease, and renal involvement, such as nephrolithiasis or nephrocalcinosis.[5] Clues suggesting the presence of parathyroid carcinoma include markedly elevated serum PTH levels (usually >5 times of the upper limit of normal), severe hypercalcemia (usually >14 mg/dL), a palpable neck mass and involvement of the recurrent laryngeal nerve.[10]

When a PubMed search using the keywords "parathyroid carcinoma" and "pancreatitis" for articles published in English was performed, only 11 cases were identified between 1969 and 2016 (Table 2).[11–19] There was a wide diversity in the ages of these patients, varied from 20s to 70s. More than half of the patients were female. In 6 cases, the serum calcium value of the patient was described, 4 of which had a level ≥14 mg/dL. Acute pancreatitis was initial or major symptom in 4 patients, one of which had long-standing recurrent pancreatitis. Available data showed tumor maximal diameters ranged between 2 and 6 cm. Among those cases, 2 patients had ectopic mediastinal parathyroid carcinomas.

Our patient was a young woman in her early 20s and presented with acute pancreatitis other than more common presentations of parathyroid carcinoma, which might be prone to missed or delayed diagnosis. However, since acute pancreatitis is generally associated with hypocalcemia,[1] it is unusual to detect hypercalcemia in a patient with acute pancreatitis, which should always alert physicians to the presence of PHPT or other causes that can lead to hypercalcemia.

Imaging studies of parathyroid gland currently include ultrasound imaging, radionuclide scanning, CT, and magnetic resonance imaging.[20] Tc-99m-MIBI has high affinity for the mitochondria of parathyroid tissue and is the most frequent localization method for PHPT.[10] Radionuclide imaging has advantages in detecting ectopic parathyroid lesions and sites of recurrent or metastatic disease. However, there are not any specific features that are able to distinguish malignant from benign tumors.[20] Though common locations of ectopic parathyroid lesions tend to be areas that are blind-spots for ultrasound,[20] the sensitivity and specificity of which in detecting parathyroid diseases are 70% to 90% and 90% to 98%, respectively, with a positive predictive value of 86% to 98%.[21] Moreover, ultrasound has been reported to assist in the diagnostic challenge of preoperative differentiation between parathyroid carcinoma and benign PHPT.[22] The characteristics of parathyroid carcinoma on ultrasound have been described: parathyroid carcinoma is generally larger than parathyroid adenoma (most reported sizes range from 2 to 7 cm), and tend to be irregularly shaped with lobulated contour; the ratio of depth to width is usually ≥1; carcinomas are predominantly hypoechoic and heterogeneous in echo-texture, cystic changes and calcification can be observed in some cases; surrounding tissue infiltration may appear as a thickened, coarse capsule or an unclear boundary; and irregular radial vessels with no demonstrated supplying vessels have been suggested to be a characteristic type of vascularity in parathyroid carcinoma.[22] The ultrasound findings in our case, such as larger size and heterogeneous hypoechoic echo-texture, are similar to those described in

Table 2

Cases of pancreatitis in patients with parathyroid carcinoma.

Authors	Patient, N	Age	Sex	Calcium	PTH (normal range)	Tumor size or weight
Tseng et al[11]	1	72	M	14.0 mg/dL	168 pg/mL (<50)	2.0 × 1.5 × 1.0 cm
Tkaczyk et al[12]	1	55	M	2.49 mmol/L	2807 pg/mL (10–60)	27 mm in diameter
Kelly[13]	1	NA	F	NA	NA	NA
Wang et al[14]	3	NA	NA	NA	NA	NA
Laks et al[15]	1	33	F	>18 mg/dL	5000 pg/mL (163–347)	NA
Hess et al[16]	1	25	F	15 mg/dL	27,500 pg/ mL (<2000)	6 × 5 × 0.5 cm
Jarman et al[17]	1	47	F	NA	NA	8 g
Walls et al[18]	1	34	F	12.0 mg/dL	NA	4 × 3 × 2.5 cm
Scharf et al[19]	1	22	F	14.6 mg/dL	NA	3.5 × 3 × 2 cm

NA = not available; PTH = parathyroid hormone.

literature, but these features are not specific. The spicule sign observed during the second review of the ultrasound images may suggest the infiltrating pattern growth of tumor, which could have been predictive for the preoperative diagnosis of parathyroid carcinoma or at least suspicion of malignancy.

Surgery is the most effective and only curative treatment for parathyroid carcinoma, and en bloc resection during the initial operation is the criterion standard and provides the best chance for cure and long-term survival.[4] En bloc resection includes parathyroidectomy, ipsilateral thyroid lobectomy, removal of any adherent adjacent tissues, and excision of tracheoesophageal, paratracheal, and upper mediastinal lymph nodes.[4,5] The recurrent laryngeal nerve should be resected if there is a tumor involvement.[4,5]

Like many other endocrine neoplasms, the histopathological distinction between benign and malignant parathyroid tumors is difficult and examination of frozen sections is of little value in distinguishing benign from malignant diseases.[5] In the current case, gross infiltration of adjacent tissue was absent. Parathyroid carcinoma was pathologically diagnosed by postoperative examination of permanent sections, which revealed tumor capsular and vascular invasion.

In conclusion, though acute pancreatitis due to PHPT is uncommon, the presence of PHPT should be taken into account when hypercalcemia occurs in patients with acute pancreatitis. Both radionuclide imaging and ultrasound have advantages and limitations in the diagnosis of PHPT. Severe clinical features and some suspicious findings on ultrasound are predictive for the preoperative diagnosis of parathyroid carcinoma. It is of great importance to differentiate parathyroid carcinoma from benign PHPT as the prognosis is greatly related to the complete removal of the tumor during the first operation.

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