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Acute pancreatitis and parathyroid carcinoma: a case report and literature review

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Abstract. – OBJECTIVE: Parathyroid carcinoma is a rare etiology of primary hyperparathyroidism (PHPT) and subsequent hypercalcemia. Among clinical manifestations of hypercalcemia, acute pancreatitis is very uncommon. Nevertheless, acute pancreatitis may be an initial clinical manifestation of parathyroid cancer.

PATIENTS AND METHODS: We present a case report and literature review on hypercalcemia-induced acute pancreatitis secondary to parathyroid carcinoma.

RESULTS: A 56 years-old man, who had previously received a diagnosis of pancreatic cancer with peritoneal and bone metastasis, complained of persistent postprandial epigastric pain, weight loss (12 kg) and hypercalcemia. He underwent endoscopic ultrasound, which did not identify any solid masses, but a pseudocyst of the pancreas body consistent with a local complication of acute pancreatitis. Plasma levels of parathyroid hormone were markedly increased, and neck ultrasound and scintigraphy confirmed the diagnosis of PHPT. Parathyroidectomy was performed and histological examination revealed parathyroid carcinoma. Searching on PubMed for the keywords "parathyroid carcinoma" AND "acute pancreatitis", from 1969 to March 2021 we found only 12 case reports of acute pancreatitis due to parathyroid cancer. The causal relationship between PHPT and acute pancreatitis has been widely discussed in literature but is still a controversial issue.

CONCLUSIONS: Acute pancreatitis induced by primary hyperparathyroidism due to parathyroid carcinoma is an extremely rare condition. However, when hypercalcemia is found, serum PTH levels should always be determined in order to rule out PHPT and hypercalcemia-induced acute pancreatitis should be suspected in presence of hypercalcemia and abdominal symptoms.

Key Words:
Acute pancreatitis, Hypercalcemia, Primary hyperparathyroidism, Parathyroid carcinoma.

Introduction

The most common cause of hypercalcemia is primary hyperparathyroidism (PHPT), followed by malignant tumours[1]. The spectrum of clinical manifestations of hypercalcemia includes cardiovascular, renal, neurological, psychiatric, gastrointestinal and skeletal involvement[1]. Among gastrointestinal signs, hypercalcemia-induced acute pancreatitis is a rare condition, and it is most often induced by parathyroid adenomas. Pancreatitis related to parathyroid carcinomas is largely less frequent. However, although rare, it may be the first clinical manifestation of parathyroid cancer[2].

Patients and Methods

Here we present a rare case of hypercalcemia-induced acute pancreatitis secondary to parathyroid carcinoma, which was diagnosed in our Center in a patient who had previously received an erroneous diagnosis of pancreatic cancer in another Center. The patient has given informed consent to publish this case report. We then performed a literature review on the topic by searching on PubMed the keywords "parathyroid carcinoma" AND "acute pancreatitis".

Results

Case Report

A 56 years-old man referred to the Emergency Room of Policlinico A. Gemelli of Rome complaining of postprandial epigastric pain, vomiting, fatigue, anorexia and weight loss (12 kg).

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He had recently been hospitalized elsewhere for the same symptoms and he was diagnosed with pancreatic cancer with bone metastasis and secondary hypercalcemia.

During the previous hospitalization, the patient underwent a total body Computed Tomography (CT) scan, which showed hypodense lesions with peripheral contrast enhancement in the tail of the pancreas, multiple peritoneal solid nodules, thrombosis of superior mesenteric vein and multiple small bone lesions suggestive of metastasis. Laboratory tests showed severe hypercalcemia. Subcutaneous enoxaparin at therapeutic dose and pain therapy were started. Bone biopsy was performed to obtain histological characterization of the tumor. He was discharged waiting for the histological examination.

Two weeks after discharge, he came to the Emergency Room of our Hospital for persistent abdominal symptoms. He appeared cachectic, with dehydrated skin and mucosae, but he had a normal urinary output. Laboratory tests showed severe hypercalcemia (calcium 17.8 mg/dL – normal range 8.6-10.2 mg/dL) and increased serum amylase (432 UI/L, normal range <107 UI/L) and lipase levels (288 UI/L, normal range 16-63 UI/L). An abdomen CT scan showed multiple hypodense pancreatic lesions with diffuse peritoneal nodules and thrombosis of the superior mesenteric vein and the left portal branch. Intravenous (IV) fluids, furosemide and long-acting bisphosphonates were administered to treat hypercalcemia. The patient was then admitted to our inpatient Unit.

To improve characterization of the pancreatic lesions, he underwent an endoscopic ultrasound, which did not identify any solid masses, but a pseudocyst of the pancreas body (3x7 cm) consistent with a local complication of acute pancreatitis. In order to rule out other etiologies of hypercalcemia, we decided to determine plasma levels of parathyroid hormone (PTH), which revealed a marked increase (1636.4 pg/mL, normal range 14-72 pg/mL) and led us to hypothesize the diagnosis of PHPT.

Therefore, the patient underwent a neck ultrasound, which demonstrated a hypoechoic nodule size 36 mm with irregular margins, contiguous to the left inferior thyroid pole and consistent with a hyperplastic parathyroid gland. Subsequently thyroid and parathyroid scintigraphy with 99mTc-Technemibi + 99mTc-pertechnetate confirmed a heterogeneous hypercaptation of radiopharmaceutical in the left inferior parathyroid region. Parathyroidectomy was performed and histological examination revealed parathyroid carcinoma.

We then acquired the histological report of bone biopsy of the previous hospitalization, which revealed bone brown tumour, typical of PHPT. About 30 days after the parathyroidectomy an abdomen CT scan was repeated and showed a significant reduction of all the pancreatic and peritoneal nodules previously described (Figure 1).

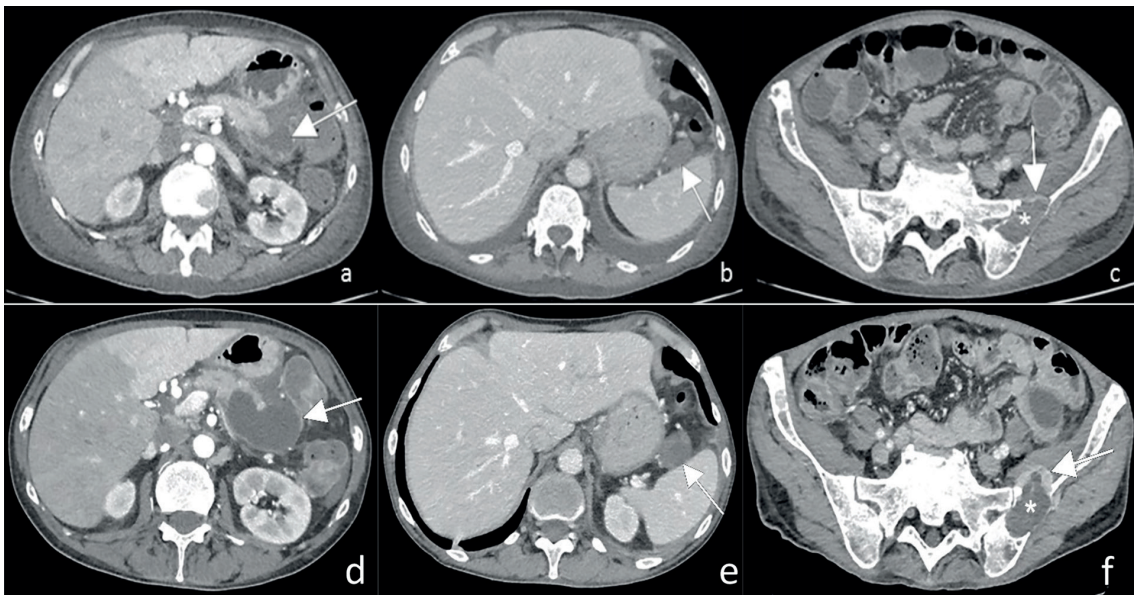

Figure 1. Abdomen CT images during the last hospitalization (**a, b, c,**) showing significant reduction of all the findings compared with CT scan at admission (**d, e, f,**), in particular reduction of the hypodense lesions in the tail of pancreas (**a,** *vs.* **d,**), of a solid nodule placed anterior to the spleen (**b,** *vs.* **e,**), of the peripheral rim of contrast enhancement of a lithic lesion in left iliac wing (**c,** *vs.* **f,**).

Finally, despite the previous diagnostic suspicion of pancreatic cancer, all the laboratory results, imaging and histological findings, supported the diagnosis of PHPT caused by a parathyroid carcinoma complicated with severe hypercalcemia and brown tumors. Pancreatic lesions were fluid collections secondary to hypercalcemia-induced acute pancreatitis, which probably began when the patient described the first symptoms. Portal and mesenteric thrombosis was not neoplastic, but a complication of pancreatic inflammation. In this context, peritoneal lesions appeared to be more likely the outcome of abdominal fluid collections rather than carcinomatosis nodules and we decided to repeat a CT scan within a month to monitor their evolution.

Literature Review

Even though rare, hypercalcemia is a possible cause of acute pancreatitis. The most common cause of hypercalcemia-induced pancreatitis is PHPT, but less frequent etiologies are drugs (such as calcium carbonate)[3,4], cancer (e.g. myeloma[5]; lymphoma[6], promyelocytic leukemia[7]) and granulomatous diseases[7,8].

The causal relationship between PHPT and acute pancreatitis has been widely discussed in literature but is still a controversial issue. Data about pancreatitis rates in patients with PHPT are very different. Bess et al[9] from Mayo Clinic analysed the prevalence of pancreatitis among over 1000 patients affected by PHPT and noted that it was similar to that of the general population. In a study conducted by Khoo et al[10] control subjects without parathyroid disease were found to have a higher rate of pancreatitis than patients with PHPT. However, other authors suggested that different degrees of hypercalcemia are responsible for different rates of pancreatitis. Singh et al[11] demonstrated that patients with PHPT-induced hypercalcemic crisis (serum calcium > 14 mg/dL) presented with pancreatitis more frequently than patients with lower calcium levels. In their retrospective study, Carnaille et al[12] compared patients affected by PHPT with and without pancreatitis and found that serum calcium levels were significantly increased in the first group. More recently, similar results have been observed by Misgar e al[13], who highlighted as the most important reason for the different rates of pancreatitis is the difference in severity of PHPT, suggesting that earlier diagnosis and subsequent treatment of PHPT are most likely associated to an asymptomatic course of the disease.

Indeed, in some cases of undiagnosed PHPT, acute pancreatitis may be its first clinical manifestation[14-17], as in our patient. In the large majority of the cases reported, PHPT-related pancreatitis were caused by parathyroid adenomas[14,16-23]. Only in rare cases the histological examination revealed a carcinoma. We did a literature review searching on PubMed the keywords “parathyroid carcinoma” AND “acute pancreatitis”. From 1969 to March 2021, we found only 12 case reports of acute pancreatitis due to parathyroid cancer, both cervical or ectopical (Table I)[15,24-34]. Almost all these patients were treated with surgical parathyroidectomy. Some of them also presented other clinical characteristics of PHPT, notably nephrolithiasis or bone lesions.

Undiagnosed long-standing PHPT in fact can lead to several degrees of bone damage, from osteoporosis to more severe forms such as osteitis fibrosa cystica and brown tumours, which are very uncommon nowadays and can affect one or multiple skeletal segments. Kunte et al[21] described a case of a young woman with acute pancreatitis and a single brown tumour of the mandible as first manifestations of parathyroid adenoma. In the case presented by Gao et al[15] the patient had multiple bone lesions in the pelvis and femur resulting from a parathyroid carcinoma.

Our patient first referred to our inpatient Unit after a previous diagnosis of pancreatic cancer with bone metastases and secondary severe hypercalcemia.

Patients with active cancer can present elevated serum calcium levels as consequence of the neoplasia itself, a condition called “hypercalcemia of malignancy”. Its most common mechanism is the systemic secretion by malignant tumours of the parathyroid hormone-related protein (PTHrP), which accounts for about 80% of cases of hypercalcemia of malignancy[35]. However, PTHrP is not a routine test in the work-up of hypercalcemia, as laboratory assays are often unreliable and costly and therefore the diagnosis can easily be made on clinical bases[36].

Another mechanism responsible for hypercalcemia of malignancy is osteolysis mediated by osteoclast-activating cytokines, which is usually associated with extensive bone metastases or skeletal cancers, such as multiple myeloma. There rarely is an extrarenal production of calcitriol by the tumour[37].

Nevertheless, being PHPT the most frequent cause of hypercalcemia in general population[38], other causes of hypercalcemia should be ruled out

Table I. Previous cases of acute pancreatitis due to parathyroid carcinoma reported in literature.

Authors (year)	Age	Sex	Serum calcium (normal range)	Serum PTH (normal range)	Tumor localization	Other PHPT manifestations
Jiajue[24] (2020)	37	F	10.7 mg/dl (8.8-10.4)	719 pg/ml (12-68)	Left inferior parathyroid + mediastinum	Kidney stones, osteitis fibrosa cystica
Gao1[5] (2017)	22	F	3.36 mmol/L (2.1-2.55)	2677.7 pg/mL) (15.0-68.3	Left superior parathyroid	Nephrocalcinosis, multiple bone destruction
Pal[27] (2017)	43	M	14.7 mg/dL (NK)	948.7 pg/ml (NK)	Left superior parathyroid	NK
Tseng[28] (2013)	72	M	14.0 mg/dL (< 10.0)	168 pg/mL (< 50)	Mediastinum	None
Tkaczyk[29] (2007)	55	M	2.49 mmol/L (NK)	2807 pg/mL (10-60)	Mediastinum	Nephrolithiasis, renal failure
Rios[30] (2005)	28	M	15.1 mg/dL (NK)	1618.2 pg/mL (12-55)	Left inferior parathyroid	Osteitis fibrosa cystica
Kelly[31] (1991)	NK	F	NK	NK	NK	NK
Laks[32] (1984)	33	F	NK	NK	Multiple parathyroids	Polyuria, fatigue, death
Hess[33] (1980)	25	F	15 mg/dL (NK)	27500 pg/mL (< 2000)	NK	NK
Jarman[34] (1978)	37	F	NK	NK	Left superior parathyroid	NK
Walls[25] (1972)	34	F	10.4 mg/dL (8.2-10.2)	NK	Right superior parathyroid	Osteitis fibrosa cystica, renal failure, death
Scharf[26] (1969)	22	F	14.6 mg/dL (NK)	NK	NK	NK

before considering the diagnosis of hypercalcemia of malignancy and PTH serum levels should always be determined, even in oncologic patients. This helps differentiating between hyperparathyroidism, in which PTH levels are increased, and hypercalcemia of malignancy, in which they are in normal range.

In the case we discussed, dosing PTH serum levels represented the cornerstone which enabled us to clarify the correct cause-effect relationship among patients' signs and symptoms, which otherwise might be misleading. Indeed, PHPT could justify the whole clinical presentation: not only hypercalcemia was secondary to PHPT, but also bone lesions were benign and related to PHPT, as well as nephrolithiasis. Moreover, severe hypercalcemia was responsible for pancreas damage which had caused acute pancreatitis complicated with portal thrombosis and peripancreatic fluid collections and walled-off necrosis.

Conclusions

In conclusion, we presented a case report and literature review of an extremely rare condition, acute pancreatitis induced by PHPT due to parathyroid carcinoma, which had previously been misdiagnosed as pancreatic cancer. Therefore, it should be kept in mind that when hypercalcemia is found, serum PTH levels should always be determined in order to rule out PHPT, even in presence of other possible causes of hypercalcemia. Moreover, even if uncommon, hypercalcemia-induced acute pancreatitis should be suspected when hypercalcemia is associated with abdominal symptoms consistent with pancreatic disease.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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