CASE REPORT

Acute pancreatitis: the onset digestive manifestation, in a patient with adult T-cell leukemia/lymphoma

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Abstract
Acute pancreatitis is a common complication, which occurs with patients suffering from vesicular biliary lithiasis or chronic alcoholism. Hypercalcemia may determine acute pancreatitis, its causes being multiple: primary or secondary hyperparathyroidism, metabolic diseases of the bone, metastatic bone neoplasm, as well as lymphoproliferative syndromes caused by the HTLV-1 virus-adult T-cell leukemia/lymphoma (ATLL). ATLL is a malignant and aggressive lymphoproliferation with the T-cell, associated with the infection caused by the HTLV-1 retrovirus. Organomegaly, cutaneous conditions, and hypercalcemia represent the main characteristics of the disease. From a hematologic point of view, we can notice the atypical lymphocytes (also known as flower cells, due to the shape of their nucleus), with a distinct CD4+ CD25+ phenotype. There have been reported few cases of patients who showed acute pancreatitis in the onset of the disease. We will describe the case of a patient whose diagnosis has not been an easy one, as it showed multiple complications from a very early stage. Conclusions: The atypical onset of ATLL with acute pancreatitis is rarely reported. Its etiology seems to be hypercalcemia but pancreatic infiltration with ATLL cells cannot be ruled out. An attentive investigation of the peripheral blood sample and flow-cytometric tests of peripheral and medullar blood smear are very important for diagnosis. The patient showed from the very beginning severe neurological manifestations which developed to a coma. Causes could have been metabolic as well as CNS infiltration (as shown by the CT examination).

Keywords: adult T-cell leukemia/lymphoma, acute pancreatitis, hypercalcemia.

Introduction
Acute pancreatitis is a common complication, which occurs with patients suffering from vesicular biliary lithiasis or chronic alcoholism. Recently, Cornett DD et al. identified biliary etiology in 68% of the patients suffering from lipidic metabolism disorders and acute pancreatitis, iatrogenic causes in 17% of the cases, idiopathic ones in 10%, alcohol representing 1% of the etiology. As for patients without hyperlipidemia, the biliary etiology has been detected in 34% of the cases, the idiopathic one in 23%, while the alcoholic and iatrogenic causes were found in 14% and 10% respectively [1]. Hypercalcemia may determine acute pancreatitis, its causes being multiple: primary or secondary hyperparathyroidism, metabolic diseases of the bone, metastatic bone neoplasm, as well as lymphoproliferative syndromes caused by the HTLV-1 virus-adult T-cell leukemia/lymphoma (ATLL).

ATLL is a malignant and aggressive lymphoproliferation with the T-cell, associated with the infection caused by the HTLV-1 retrovirus. Organomegaly, cutaneous conditions, and hypercalcemia represent the main characteristics of the disease. From a hematologic point of view we can notice the atypical lymphocytes (also known as flower cells, due to the shape of their nucleus), with a distinct CD4+ CD25+ phenotype. The disease is endemic in Japan, the Caribbean, and some areas of Africa, South America, Iran, and Central Europe.

There have been described four clinical forms of clinical manifestation in ATLL [2]:

• Acute ATLL is characterized by leukemic organomegaly, high levels of LDH frequently associated with hypercalcemia.
• Chronic ATLL, in which we observe lymphocytosis $>4 \times 10^9/L$ with atypical lymphocytes ATLL, skin, lung, liver, and gland lesion. Calcium levels and LDH are within average or under twice the normal.

• Smoldering, characterized by skin and/or lung infiltrations without any other organ lesion and with a normal level of lymphocytes (1–5% ATLL cells), normal serum level for calcium and LDH.

• Lymphoma, characterized by organomegaly with less than 1% of atypical circulating lymphocytes and high levels of LDH and calcium.

There have been reported few cases of patients who showed acute pancreatitis in the onset of the disease. We will describe the case of a patient whose diagnosis has not been an easy one, as it showed multiple complications from a very early stage.

Patient, Methods and Results

A 34-year-old patient, without any previous pathologic or hereditary antecedents, is presented to the hospital with altered health state, one-week history of diffuse abdominal pain, biliary and alimentary vomit, drowsiness and passing cognitive alterations.

On clinical examination, the patient was febrile, with an altered general state. Her skin and mucosa were normally colored, without peripheral adenopathies, upper abdominal increased sensitivity, and liver border at the costal margin. The spleen was not palpable. The WBC count showed a value of 33,000/mm$^3$, with 69% lymphocytes, low platelet count 127,000/mm$^3$, Hb 19.9 g/dL, Ht 53.4%, the serum creatinine level 3.27 mg/dL, the urea level 144 mg/dL, uric acid 19.34 mg/dL. We found elevated levels of amylasemia 700 U/L, GOT 107 U/L, GPT 115 U/L, blood sugar level 127 mg/dL, normal bilirubin.

Imagistic examination showed normal gallbladder without hepatomegaly, and a light splenomegaly. The first hand diagnosis was acute edematous pancreatitis, dehydration, acute renal failure of pre-renal etiology, due to high levels of uric acid (hyperuricemia). Polyglobulia discovered on onset raised suspicions of polycythemia vera.

Abdominal CT examination revealed acute edematous pancreatitis without showing retroperitoneal adenopathy. The splenoportal axis was normal (Figure 1).

Cerebral CT scan showed neurological lesions. Tests for the JAK2 mutation-negative value and osteomedullary biopsy have been performed (Figure 2).

Discussion

The first association of acute pancreatitis with hypercalcemia was described in 1957 by Cope et al. The prevalence of acute pancreatitis in patients with primary hyperparathyroidism (PTHP) is between 1.5–7%, a rate that is not much different from the prevalence of acute pancreatitis in general. However, hypercalcemia can be a factor which leads to acute pancreatitis through three physiopathological mechanisms: the forming of calcium deposits in the pancreatic duct, leading to the obstruction of the duct, the activation of trypsinogen in pancreatic parenchymal cells, promoting the autodigestion of the pancreas, the association of hypercalcemia with variants of SPINK1 (serine protease inhibitor Kazal type 1) and CFTR (cystic fibrosis transmembrane conductance regulator) genes. All these three raise the risk of occurrence of pancreatitis in PTHP patients [3]. Hypercalcemia can also be the consequence of some neoplasms. There have been described many cases of the acute pancreatitis-hypercalcemia-neoplasm association (solid tumor metastasis) [4]. ATLL is a lymphoproliferation of helper/inducer T-cells associated with an infection with HTLV-1.
Clinical manifestations include hepatosplenomegaly, skin, brain, eye, lungs, bone lesions and hypercalcemia. Hypercalcemia may be caused by the mediate resorption of the PTHrP as well as by lymphokines IL1, IL2, IL6, or TNF and represents one of the forms of manifestation of the disease, with a high rate of occurrence among patients [5]. There have been few reports of acute pancreatitis secondary to hypercalcemia occurring in a patient with ATLL [6–9]. Hypercalcemia, with or without lytic lesions, occurs in more than half of patients and it may appear in another third of the cases, as the disease progresses.

There are multiple mechanisms that contribute to the occurrence of hypercalcemia and they have a synergetic action affecting both directly and indirectly the osteoblastic differentiation. Some of these mechanisms are: the activator receptor of the nuclear factor – kB ligand (RANKL); osteoprotegerin (OPG); parathyroid hormone-related protein (PTHrP); proinflammatory cytokines; macrophage inflammatory protein-1 alpha (MIP-1 alpha); Tax nonstructural viral protein; the viral envelope protein Gp-46; and metalloproteinases. RANKL is a surface protein member of the TNF superfamily of proteins, which is overexpressed in ATLL patients, its role being the differentiation of the precursors of osteoclasts, causing the occurrence of hypercalcemia and bone resorption. Osteoprotegerin is the soluble receptor of the TNF family produced by various cells including osteoblasts. Its role would be that of an osteoclastogenesis inhibitory factor and that of stimulating the osteoclast apoptosis. In the ATLL patients, it has been noticed a decrease in the production of osteoprotegerin. PTHrP (parathyroid hormone-related protein) contributes to the resorption of the osteoclasts, the suppression of the activity of osteoclasts, and the increase in the resorption of urine calcium. Patients with ATLL have raised levels of PTHrP. Patients with ATLL show a raised level of urine calcium. The Tax component protein of the HTLV-1 virus has an important role in the high expression of PTHrP gene in the infected cells through the activation of CREB (cellular transcription factor CRE-binding protein). Viral protein gp46-197 is an antigen that imitates the action of osteoprostogesterin thus blocking it, by binding to the same antigenic site. Cytokines IL2, IL1, TNF-α, TGF-β play an important role in the production, secretion and the activity of PTHrP. IL5 plays a synergetic role with PTHrP in the occurrence of hypercalcemia. MIP-1α (macrophage inflammatory protein-1α), chemokines which stimulate osteoclasts, the migration of monocytes (precursors of osteoclasts) and the induction of the RANKL expression in ATLL, show high levels in patients with ATLL. Extracellular matrix metalloproteinases seem to have a role in discovering hypercalcemia in patients with ATLL, by the deregulation of their function by the HTLV-1 virus [10]. Pancreatic infiltration through atypical lymphocytes was reported as another cause of acute pancreatitis in ATLL patients [11].

Conclusions

The initial clinical manifestations imitated the presence of a chronic mieloproliferative syndrome associated with acute pancreatitis and acute kidney failure. An attentive investigation of the peripheral blood sample and flow-cytometric tests of peripheral and medullar blood smear oriented the diagnosis towards a lymphoproliferative syndrome T – ATLL, which explained hypercalcemia and which was consequently confirmed by histopathologic and virusologic exams.

The atypical onset of ATLL with acute pancreatitis is rarely reported. Its etiology seems to be hypercalcemia but pancreatic infiltration with ATLL cells cannot be ruled out.

The patient showed from the very beginning severe neurological manifestations that developed to a coma. Causes could have been metabolic as well as CNS infiltration (as shown by the CT examination).

References


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