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Acute pancreatitis as the initial presentation of acute myeloid leukemia (AML-M2 subtype): A case report

AP Caused By AML

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Abstract

BACKGROUND

Direct infiltration of pancreas and developed acute pancreatitis as an initial symptom for acute myeloid leukemia (AML) is extremely rare. Only once in the literature, the leukemia cells in AML have been implicated as the cause of acute pancreatitis (AP). Pancreatitis caused by a rare predisposing factor is often misdiagnosed as other common causes of idiopathic pancreatitis. Severe acute pancreatitis (SAP) progresses rapidly with a high fatality rate. Therefore, it is important to identify the predisposing factors in the early stage of SAP, evaluate the condition, determine prognosis, formulate treatment plans, and prevent a recurrence. Here, we describe a case of SAP due to AML.

CASE SUMMARY

A 61-year-old man presented to the hospital with fever and persistent abdominal pain. Blood analysis presented significantly elevated serum amylase and severe thrombocytopenia. Computed tomography examination of the abdomen revealed peripancreatic inflammatory effusion. The patient had no AP's common etiologies and risk factors, but concurrent the severe thrombocytopenia that pancreatitis could not explain. Finally, the bone marrow aspirate and biopsy inspection revealed the underlying reason for pancreatitis, AML and FAB AML-M2 type.

CONCLUSION

Direct infiltration of acute leukemia, particularly AML cells, is an infrequent cause of AP. Therefore, although acute pancreatitis is a rare characteristic for acute myeloid leukemia patients as extramedullary infiltration, it should be considered when determining the etiological of AP.

Key Words: Acute pancreatitis; Acute myeloid leukemia; Abdominal pain; Extramedullary infiltration; Etiology; Case report

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Core Tip: Although acute pancreatitis is a rare characteristic for acute myeloid leukemia patients as extramedullary infiltration, it should be considered when determining the etiological of acute pancreatitis. Early diagnosis and etiological management can help avoid ineffective treatments and improve the outcomes. To better diagnose and treat such patients, we reviewed the literature available on leukemia complicated by acute pancreatitis and analyzed its disease mechanisms, clinical symptoms.

INTRODUCTION

Acute pancreatitis (AP) is caused by the premature activation of pancreatic enzymes, which leads to inflammatory disorders of the pancreatic system and pancreatic cell auto-digestion [1]. The patient presented to the emergency department with the complaint of persistent abdominal ache. AP's common etiologies include gallstones, alcohol abuse, medication, and metabolic disorders such as hyperlipidemia, hypercalcemia, and ERCP. Severe AP progresses rapidly with a high fatality rate. Therefore, physicians must identify the inducing factors early to evaluate the condition and devise treatment plans.

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. It is characterized by abnormal proliferation of undifferentiated hematopoietic stem cells in bone marrow with damage to the normal blood cell. Clinical features and prognosis of results show significant variation. Primarily due to poor prognosis and high mortality, it reduces the quality of life. According to a recent study on AML in the United States, the M2 subtype was the most common (25%) in the FAB classification of AML, while the five-year survival rate for patients with AML is 28.3% [2]. The percentage of deaths increases with age.

Current literature concentrates pancreatitis associated with acute leukemia more on the use of chemotherapeutic drugs, and mainly in children with acute lymphoblastic leukemia (ALL). Direct infiltration of acute leukemia, particularly AML cells, is an infrequent cause of AP. Therefore, a better understanding of the extramedullary infiltration characteristic for AML is urgently needed. And when determining the etiological of acute pancreatitis, the possibility of acute leukemia should be considered.

Herein, we present a case of pancreas infiltration in a 61-year-old AML male patient, and through a literature review of previous cases, we analyzed and summarized the features and potential mechanism for the extramedullary infiltration.

CASE PRESENTATION

Chief complaints

A 61-year-old Chinese man was admitted to the emergency department with acute pain in the left upper abdomen with progressive worsening for 3 h.

History of present illness

Symptoms started 3 h before presentation with persistent epigastric pain initially, and then it gradually developed to diffuse abdominal tenderness with nausea, emesis, and lumbar-back radiating pain.

History of past illness

This patient had no history of chronic diseases, such as hypertension, hyperuricemia, hyperlipidemia, and coronary heart disease.

Personal and family history

The patient was a non-smoker and there was no history of alcohol consumption. The patient denied receiving chemotherapy or undergoing recent trauma. Family history was also not significant.

Physical examination

Vital monitoring at admission showed a pulse rate of 111 bpm, blood pressure of 161/111 mmHg, a body temperature of 38.4 °C, and a respiratory rate of 21 breaths/min.

There was no jaundice detected on the skin and sclera. During chest auscultation, decreased breath sounds were heard in bilateral lungs. Abdominal examination disclosed diffuse abdomen tenderness, abdominal muscle tension, and slightly decreased bowel sounds. Cullen's, Gray-Turner's, and Murphy signs were absent.

Laboratory examinations

Initial laboratory testing indicated that WBC count was 7.63 × 10^9/L (reference range: 3.5-9.5 × 10^9/L), with 18.10% monocyte percentage, low platelet count 12 × 10^9/L (reference range: 150-400 × 10^9/L), hemoglobin 12.2 g/dL (reference range: 12-16 g/dL), C-reactive protein (CRP) 0.13 mg/dL (reference range: 0-0.33 mg/dL), elevated level of serum amylase (4288 U/L, reference range: 35-135 U/L), normal bilirubin, triglycerides and serum calcium. The laboratory examination revealed severe thrombocytopenia, mild anemia, increased monocyte count, and significantly increased serum amylase.

The significant decrease in platelet could not be explained based on pancreatitis and infection, thus, blood system diseases must be considered. Histopathological analysis (Figure 1D) and Bone marrow aspirate and biopsy examination (Figure 1C) revealed active bone marrow hyperplasia with increased myeloblasts (approximately 41%). The myeloblasts size varies, and most of them are like round. Medium cytoplasmic volume, stained blue, dark edge color. The nuclei were slightly irregular, pitted and folded, and the nucleolus was fine granular, with mostly 2-4 nucleolus. The proportion of red blood cells was normal, mainly polychromatic normoblast and metarubricyte, and the size of mature red blood cells was different. The proportion of lymphocyte packs is normal, and it is mature lymphocyte. Rare platelets. There was some MPO staining was strongly positive (Figure 1D). Peripheral blood imaging depicted no significant increase in WBC count. myeloblasts were more common, with a similar morphology result as bone

marrow (Figure 1B). FAB AML-M2 type seems more likely, taking acute leukemia into account. Cytogenetic analysis of the bone marrow showed a 46 XY genotype (Figure 1A) .

On flow cytometry, myeloblasts (68.93%) were positive for CD 34, 117, 38, 64, 11c, 33, 13, and 7 and negative for CD 15, 36, 14, 16, 19, 3, 20, 56 and CD 10. Monoblasts (19.36%) were positive for CD 14, 15, 38, 7, 64, 36, 11c, 33, and 13 and negative for CD 20, 19, 3, 56, 7, 9 and10. The gene mutation tests about the myeloid malignancies showed CEBPA double mutation, CSF3R mutation and STAG2 mutation. CEBPA and CSF3R mutations appear at the same time were associated with negative prognostic factors in AML. The gene tests were also performed with probes specific for more than 50 items, including RUNX-1 fusion and JAK2 fusion genes, the results of these studies were normal.

Imaging examinations

Computed tomography of the abdomen demonstrated pancreatitis with diffuse edema of the pancreas, peripancreatic effusion, gallbladder stones (Figure 1A).

Contrast-enhanced thorax and abdomen CT in the next day suggested: (1) Bilateral pleural effusion and adjacent atelectasis;(2) pancreatitis accompanied by peripheral inflammatory exudation, uneven enhancement of pancreatic parenchyma. There were also hypodense lesions infiltrating the pancreas and slightly thicker adjacent duodenal wall; and (3) ascites (Figure 2B).

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FINAL DIAGNOSIS

Based on the patient's medical history, clinical characteristics, and diagnostic results, the final diagnosis was acute myeloid leukemia, severe acute pancreatitis (extramedullary infiltration).

TREATMENT

After controlling infection, fluid resuscitation, blood component transfusion, and symptomatic antipyretic treatment, the inflammatory indicators decreased, abdominal

pain and bloating alleviated, with the resumption of oral intake. However, the patient still had intermittent fever with the onset of dyspnea, shortness of breath, and wheezing. Arterial blood gas analysis indicated respiratory failure (PO2= 6.44 kPa, PCO2= 5.84 kPa, oxygenation index was 230). After non-invasive ventilator support, the oxygenation index was above 200, and the patient's shortness of breath and wheezing were improved. Pancreatitis remained relatively stable. The patient was hospitalized for nine days and continue to treat AML in another hospital. He received chemotherapy of idarubicin combined with cytarabine (IA "3 + 7" regimen) treatment in the hospital.

OUTCOME AND FOLLOW-UP

Leukemia and pancreatitis both improved after chemotherapy. After 2 cycles of chemotherapy, the lesions in his pancreas disappeared (Figure 3). The patient achieved a full recovery and complete remission (Figure 4). with platelet recovery. The patient has been alive for 1 years since the initial development of AML. Pancreatic walled-off necrosis developed in the healed pancreas after the treatment of pancreatitis. There was no significant increase in amylase, no obvious abdominal pain or distension, no recurrence of pancreatitis, and change in abdominal mass.

DISCUSSION

Pancreatitis associated with acute leukemia has been reported mainly in children with acute lymphoblastic leukemia (ALL). Most of which were linked with the use of asparaginase as chemotherapeutic drugs. Pancreatitis has also been reported in AML patients using cytarabine [3,4] or all-trans retinoic acid [5-7] and other combined chemotherapy regimens[8]. Pancreatitis caused by chemotherapy medications, on the other hand, is usually mild and can be improved if the chemotherapeutic drugs are suspended. In addition, bone marrow transplantation has also been a risk factor for pancreatitis[9-11]. A few cases of AP with adult T-cell leukemia (ATL) were induced by hypercalcemia[12] . There were cases of AP with direct infiltration of leukemia cells in ALL[13-15], one of which confirmed atypical lymphocytic infiltration at the pathological

level using fine-needle aspiration biopsy[13]. Although the other reports were not supported by pathological evidence, with the progress of induction therapy, regression of leukemic infiltration was seen in the pancreas. Acute leukemia, whether direct infiltration or in combination with chemotherapeutic drugs, can result in AP. But in AML, the pancreas is a rare organ of extramedullary infiltration. Only once in the literature, the leukemia cells in AML have been implicated as the cause of AP. In Japan, a patient with AML developed acute mimicking autoimmune pancreatitis[16].

In the case report, the patient was AML-M2 type which can complicate with extramedullary manifestations[17].The patient was initially thought to have biliary pancreatitis because of the gallstone found in the abdomen CT, but the patient had no bile duct stones. Serum bilirubin, GGT, and ALP were normal, and there was no evidence of cholangitis; therefore, the occurrence was unlikely to be caused by a stone. The patient's blood lipids were not elevated, with no prior drinking history; thus, alcohol or hyperlipidemia was ruled out. Then, after a follow-up inspection, he was diagnosed with AML, revealing the underlying reason for pancreatitis. Serum calcium levels at admission were within the normal range; the patient had no history of chemotherapy, so chemotherapy-related adverse reactions were also eliminated. On the top of that, after chemotherapy for leukemia, there was no recurrence of pancreatitis. Based on the above details, it was presumable that the leukemic infiltration of the pancreas brought upon pancreatitis in this patient.

The extramedullary manifestations of leukemia can affect any organ, resulting in diversified early manifestations of leukemia, with separate organ damage or prominent local manifestation as the initial symptoms. AP caused by leukemic cell infiltration to the pancreas is rare in AML, and the mechanism is still uncertain. Studies have shown that AML cells can accelerate the progression of leukemia by reshaping a supportive malignant microenvironment[18], which results in an invasion of the pancreas and other extramedullary organs. CXCR4/CXCL12 signaling axis, matrix metalloproteinases (MMPs), and urokinase-type plasminogen activator system (uPAs) mainly were focused on studies while investigating malignant tumors microenvironment in AML. Higher

CXCR4 expression in hematopoietic stem cells suggesting an increase in recurrence rate and significantly poor prognosis[19,20]. The bone marrow plasma MMP-9 Level is significantly higher in AML patients with extramedullary infiltration, showing that the premature production of MMP-9 may contribute to leukemic cells infiltration to extramedullary organs[21]. The uPAs induces plasminogen activation, which plays a vital role in tissue remodeling, proteolysis, invasion, and metastasis. Lanza *et al*[22]demonstrated that urokinase plasminogen activator receptor (uPAR) expression increased in patients with AML with invasive manifestations.

There was a high risk of hemorrhage after needle biopsy because of the low platelet count, so typical pathological changes such as leukemic cell infiltration to the pancreas could not be confirmed. But AP should be considered in AML patients with acute, persistent epigastric pain, whether or not there was amylase elevation. In the absence of fine-needle aspiration biopsy, the highly plausible possibility of direct infiltration of leukemia cells should be sought if other causes were excluded, as early detection and timely treatment of leukemia could improve the outcome of pancreatitis. If not handled properly, pancreatitis caused by a rare cause can develop into severe pancreatitis with systemic inflammatory response syndrome (SIRS), organ dysfunction with rapid progression, poor prognosis, and high risk of death. It is harmful and difficult to diagnose, so clinicians must pay greater attention.

Although extramedullary infiltration of AML is generally regarded as an indicator of poor prognosis, this conclusion is still debatable[23-25]. Due to limited data available, it is difficult to determine the prognostic significance of pancreatic involvement in patients with AML. Therefore, for leukemia patients with extramedullary invasion of uncommon sites such as the pancreas, this may not indicate more aggressive than other common sites, but treatment and diagnosis can be delayed. Especially in the said case, the rare AP as the first extramedullary infiltration manifestation led to misdiagnosis or missed diagnosis.

CONCLUSION

This case report exposed AP is related to AML and highlighted the rare but significant etiology. Many advancements have been made in diagnostic techniques and clinician awareness to identify rare predisposing factors of AP. Early diagnosis and etiological management can help avoid ineffective treatments and improve the outcomes.

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