Early diagnosis of asparaginase-associated pancreatitis based on elevated serum elastase-1 levels: Case reports

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Abstract. L-asparaginase (L-asp) is a well-known anticancer agent used in the treatment of acute lymphoblastic leukemia (ALL) in children. However, it is also known to induce several acute complications, such as acute pancreatitis. This is a presentation of two pediatric acute lymphoblastic leukemia (ALL) cases of asparaginase-associated pancreatitis (AAP) diagnosed at an early stage based on elevated serum elastase-1 levels, in the presence of normal serum amylase levels. Early diagnosis and treatment of AAP, although imperative, is occasionally difficult if only standard diagnostic procedures are followed. Elastase-1 is a potentially useful marker for the early diagnosis of AAP. Therefore, the measurement of elastase-1 levels, in addition to amylase and lipase levels, is recommended in L-asp-treated patients.

Introduction

L-asparaginase (L-asp) is a well-known anticancer agent used for lymphoid malignancies. Although it is one of the key drugs in the treatment of acute lymphoblastic leukemia (ALL) in children, it is also known to induce several acute complications, including coagulopathy, hypersensitivity, hepatic dysfunction, hypertriglyceridemia, hyperammonemia and pancreatitis. In patients with clinical symptoms such as abdominal pain, nausea and emesis, acute pancreatitis is suspected on the basis of elevated levels of serum amylase and/or lipase, along with abnormal findings on imaging studies. Early diagnosis and prompt treatment of acute pancreatitis is imperative. However, it may not always be possible using standard diagnostic procedures, such as serum amylase measurement and abdominal ultrasonography/computed tomography (US/CT).

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This is a report of two pediatric cases of asparaginase-associated pancreatitis (AAP) diagnosed in its early stage on the basis of elevated serum elastase-1 levels in the presence of normal amylase levels.

Case reports

Case 1. A 5-year-old boy with B-precursor ALL had received multi-agent chemotherapy according to the L-0416 protocol of the Tokyo Children's Cancer Study Group (TCCSG) and complete remission was achieved following induction chemotherapy. The patient underwent subsequent chemotherapies without severe complications. Nine months after the onset of the disease, he received sequential chemotherapy comprising dexamethasone (DEX; 6 mg/m^2 x 14 days), vincristine (VCR, 1.5 mg/m^2 weekly x 4 weeks), adriamycin (ADR, 25 mg/m^2 weekly x 4 weeks) and L-asp (6,000 U/m^2 weekly x 4 weeks). Three days after the administration of the third dose of L-asp the patient suddenly developed posterior reversible encephalopathy syndrome and had to be treated with anticonvulsant, antihypertensive and sedative agents. During this intensive treatment, pleural effusion and ascites gradually developed and mechanical ventilation was required. The serum amylase levels were normal and CT and US revealed no abnormality in the pancreas. However, acute pancreatitis was suspected based on the elevation of serum elastase-1 levels to 936 ng/dl [upper limit of normal (ULN)] on the seventh and final day of L-asp administration (Fig. 1), when pleural effusion and ascites were prominent and presumably associated with acute pancreatitis. Elevated serum lipase levels were also detected on the following day. Consequently, treatment for acute pancreatitis was initiated with octreotide, famotidine and nafamostat. Eleven days after the detection of elevated serum elastase-1 levels, serum amylase levels increased to 278 mg/dl (2.2 times the ULN). Thereafter, the condition of the patient gradually improved without any late sequelae. The cumulative dose of L-asp administered was 222,000 U/m^2.

Case 2. A 10-year-old boy with B-precursor ALL had received multi-agent chemotherapy according to the L-0416 protocol of TCCSG. The first remission was achieved without any severe complications. Six months after the onset of the disease, the patient received chemotherapy comprising DEX (6 mg/m^2 x 14 days), VCR (1.5 mg/m^2 weekly x 4 weeks),

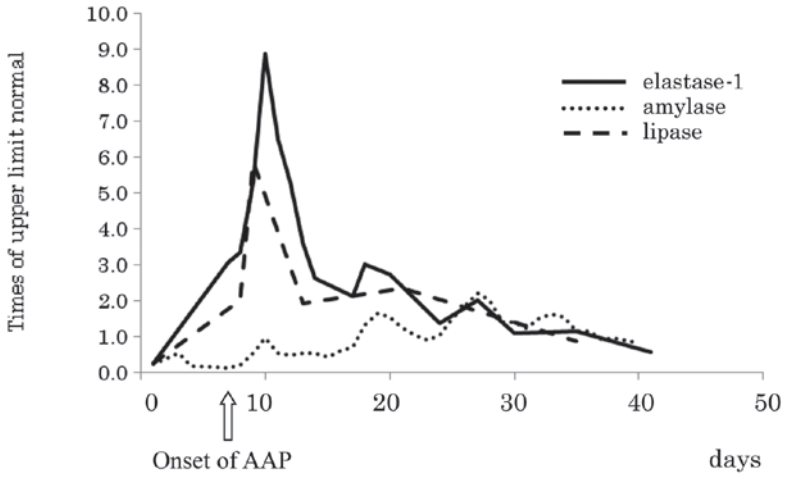

Figure 1. Laboratory course from the day of the final L-asparaginase administration in case 1. On the seventh day, elastase-1 levels were elevated ≤3 times the upper limit of normal in the presence of normal amylase levels. AAP, asparaginase-associated pancreatitis.

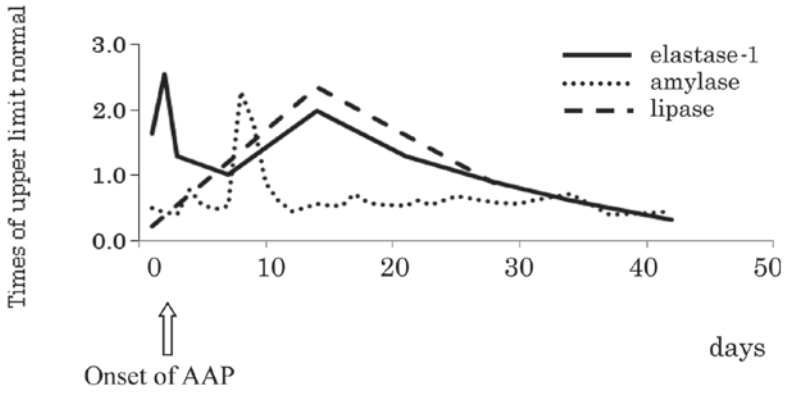

Figure 2. Laboratory course from the day of the final L-asparaginase administration in case 2. On the second day, only the elastase-1 level was elevated ≤1.6 times the upper limit of normal in the presence of normal amylase and lipase levels. AAP, asparaginase-associated pancreatitis.

ADR (25 mg/m^2 weekly x 4 weeks) and L-asp (10,000 U/m^2 weekly x 4 weeks). Two days after the administration of the third L-asp dose, the patient complained of abdominal pain and emesis. Serum amylase and lipase levels were normal and imaging studies, namely CT, US and magnetic resonance imaging, revealed no abnormalities. However, elevated serum elastase-1 levels to 765 ng/dl were observed (Fig. 2), which led to the suspicion of AAP. Consequently, octreotide, famotidine, fentanest and nafamostat were administered along with parenteral nutrition. Seven days after the elevation of elastase-1 levels, serum amylase levels increased to 288 mg/dl (2.3 times the ULN). Therefore, we were able to diagnose AAP in its early stage. Thereafter, the condition of the patient improved rapidly without any late sequelae. The cumulative dose of L-asp administered was 72,000 U/m^2.

Discussion

L-asp is a well-known anticancer agent used for the treatment of lymphoid malignancies. Although it is one of the key drugs in the treatment of ALL in children (1), it is known to induce several complications, including coagulopathy, hypersensitivity, hepatic dysfunction, hypertriglyceridemia, hyperammonemia and pancreatitis. Of these, AAP has been reported to occur in 3-18% of children with ALL receiving chemotherapy (2-7). Acute pancreatitis *per se* may be a life-threatening disease (8,9). When a patient develops AAP, chemotherapy must be interrupted for several months or more and subsequent administration of L-asp, as recommended in the protocol, should also be discontinued. Therefore, the overall survival rate is poorer in patients with compared to those without AAP (10,11).

Serum amylase and lipase levels and findings of imaging studies are commonly used for the diagnosis of acute pancreatitis (7,12,13). Amylase and lipase are the pancreatic enzymes listed in the metabolites list of Common Terminology Criteria for Adverse Events as defined by the National Cancer Institute. Elastase-1 is one of the pancreatic enzymes whose secretion is elevated due to pancreatic damage (14,15). Whether elastase-1 is a useful marker in the diagnosis of acute pancreatitis remains to be elucidated through thorough investigations.

Previous studies reported that elastase-1 is seemingly less specific and may not be correlated with disease severity (16,17). By contrast, another study suggested similar or superior sensitivity of elastase-1 when compared with that of amylase or lipase in cases of acute pancreatitis (18). A study conducted by

Shimizu *et al* (19) reported subclinical pancreatitis accompanied by the elevation of elastase-1 levels in L-asp-treated ALL patients, who exhibited no symptoms of pancreatitis and had normal amylase and lipase levels. Although no patient with definitively diagnosed pancreatitis was included in that study, the usefulness of elastase-1 levels in the early diagnosis of AAP was emphasized.

The two cases presented in this study were diagnosed with definitive pancreatitis by the clinical symptoms and the subsequent elevation of serum amylase levels. Therefore, elastase-1 may be a beneficial marker for subclinical as well as manifested pancreatitis in its early stage.

Although early diagnosis and treatment of acute pancreatitis is imperative, it is occasionally difficult solely by using standard diagnostic methods. Approximately 1-26% of AAP patients may suffer from late complications such as pseudocyst and abscess formation (3,8). In our study, the patients recovered rapidly without any complications, probably due to the mild and self-limited nature of their AAP. However, early detection and prompt treatment contributed, to some extent, to the rapid improvement and lack of late sequelae.

In conclusion, serum elastase-1 appears to be a useful marker for the early diagnosis of pediatric ALL complicated by AAP. Therefore, in addition to amylase and lipase levels, the measurement of elastase-1 levels is recommended when L-asp-treated patients develop abdominal pain or other symptoms suggestive of the presence of pancreatitis.

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