Asparaginase-Induced Acute Necrotizing Pancreatitis Resulting in Chronic Pancreatitis and Pseudocyst in an Adult with Acute Lymphocytic Leukemia

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ABSTRACT

L-Asparaginase is one of the main chemotherapy regiments for acute lymphocytic leukemia (ALL) management. Acute pancreatitis is one of the serious side effects of l-asparaginase administration and may lead to interruption of chemotherapy cycle. Long term complications may be devastating for patients which include of pseudocyst pancreas and chronic pancreatitis. Asparaginase induced pancreatitis is rare among adult due to the nature of ALL which commonly occurred in children population. The pathophysiology of asparaginase induced pancreatitis is still unclear. Here we present 18-year-old male with ALL and asparaginase induced acute necrotizing pancreatitis which complicated to chronic pancreatitis and pseudocyst.

Keywords: *pancreatitis, acute lymphocytic leukemia, asparaginase*

ABSTRAK

L-asparaginase merupakan salah satu regimen kemoterapi utama untuk tatalaksana leukemia limfositik akut (LLA). Pankreatitis akut merupakan salah satu efek samping serius dari penggunaan l-asparaginase sehingga dapat menyebabkan terhentinya siklus kemoterapi. Komplikasi jangka panjang dapat menurunkan kualitas hidup pasien yaitu berupa timbulnya pseudokista pankreas dan pankreatitis kronik. Pankreatitis akibat asparaginase merupakan kasus yang jarang pada populasi dewasa, salah satunya dikarenakan prevalensi LLA yang lebih sering ditemukan pada pasien anak. Patofisiologi dari pankreatitis akibat asparaginase belum diketahui secara pasti. Dalam tulisan ini, kami melaporkan seorang pria berusia 18 tahun dengan LLA dan pankreatitis akut nekrotikans akibat asparaginase yang berkomplikasi menjadi pankreatitis kronik dan pseudokista.

Kata kunci: *pankreatitis, leukemia limfositik akut, asparaginase*

INTRODUCTION

Acute pancreatitis is commonly caused by biliary stone obstruction; however, approximately 0.1–2% of acute pancreatitis cases may be drug induced.[1] L-asparaginase is used as chemotherapy regiment for acute lymphocytic leukemia (ALL) and correlated with acute pancreatitis.[2] While, most of drug induced pancreatitis cases are mild to moderate severity; some of the acute intermittent porphyria (AIP) cases may lead to short-term and long-term complications. Short-term AIP complications can be defined as pancreatic necrosis and pseudocyst development; while long-term AIP complications can be defined as diabetes and chronic pancreatitis. Altogether this short and long-term AIP complications may lead to increased risk for patient's morbidity, mortality, and decreased life quality. The occurrence of adult AIP is also rare, due to the nature of ALL which commonly occurred in children population.[1,2] Here we present an 18-year-old male patients with asparaginase induced acute necrotizing pancreatitis which complicated to chronic pancreatitis and pseudocysts.

CASE ILLUSTRATION

An 18-year-old male patients was admitted to the emergency department with severe epigastric pain that radiating to the back and frequent vomiting. His past medical history was remarkable for ALL and had undergone chemotherapy. His body weight was 58 kg, height 165 cm, and body surface area of 1.63 m^2. In induction phase, at first week he was given methotrexate intrathecal 15 mg, vincristine 1.5 mg/m^2 IV, daunorubicin 30 mg/m^2 IV. In the second week, he was given vincristine 1.5 mg/m^2 IV and daunorubicin 30 mg/m^2 IV. At the third week, he was given methotrexate intratechal 15 mg, vincristine 1.5 mg/m^2 IV, daunorubicin 30 mg/m^2 IV, and L-asparaginase 7500 IU/m^2 IV (given twice, separated by 1 day). At the fourth week, he was given vincristine 1.5 mg/m^2 IV, daunorubicin 30 mg/m^2 IV, and L-asparaginase 7500 IU/m^2 IV (given twice, separated by 1 day). At the fifth week, methotrexate intratechal 15 mg, vincristine 1.5 mg/m^2 IV, daunorubicin 30 mg/m^2 IV, and L-asparaginase 7500 IU/m^2 IV (given twice, separated by 1 day). Five days after the last administration of l-asparaginase, he complained current complaint which were severe epigastric pain, nausea, and frequent vomiting. At admission, his vital signs were blood pressure of 130/80 mmHg, pulse rate of 110 beats per minute, respiration rate of 20 times per minute, body temperature of 37.0 °C, and oxygen saturation of 98% on room air. His visual-analog-scale (VAS) was 7–8.

The patient showed moderately ill-looking appearance and body mass index of 16.2 kg/m^2, anemic conjunctiva, and palpable tenderness on epigastric region without muscle guarding. No cullen and grey-turner sign were observed. The laboratory investigation showed Hb 9.5 gr/dL, white blood cell 11,200/μL, lipase level 1344 U/L, amylase level 874 U/L, sodium level 127 mEq/L, potassium level 3.38 mEq/L, and albumin 3.28 gr/dL. Abdominal ultrasound examination showed no gallstone and dilated biliary tract were seen. His APACHE-II score was 9 and his Ranson criteria was zero. He was diagnosed as mild acute pancreatitis induced by L-asparaginase. He was put on fluid resuscitation, parenteral nutrition, analgetic, and symptomatic drugs. He was planned for abdominal- computerized tomography (CT)-scan with contrast.

On the follow up, his general condition was improved, the pain was decreased, and his intake tolerance was improved. The pancreatic enzyme level was gradually decreased on day four of hospitalization to lipase 412 U/L and amylase 302 U/L. The abdominal-CT-scan with contrast examination revealed cystic lesion sized 4.5 cm x 3.9 cm at pancreas tail with peripancreatic fluid and fat stranding, suggestive for acute necrotizing pancreatitis non infected with peripancreatic fat infiltration and pseudocyst (Figure 1).

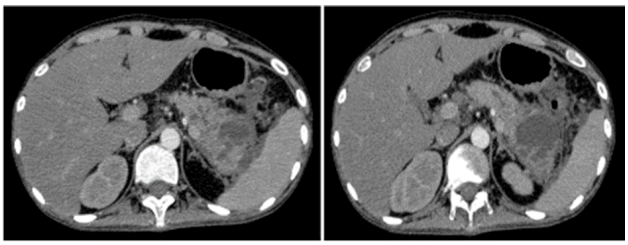

Figure 1. Abdominal CT scan with contrast examination on fourth day of hospitalization

Consultation to digestive disease surgery department was made and he was planned for pancreatic necrotomy on 4 weeks after the onset. The patient was discharged on the seventh day, pain at visual analog scale (VAS) 2 on fentanyl patch, amylase 183 U/L, and lipase 102 U/L. During the outpatient follow up visit, the patient still complained recurrence epigastric pain, nausea and vomiting. The lipase was 245 U/L and amylase was 130 U/L. He was re-admitted on the day before operation. The necrotomy was performed.

On the weekly follow up visit post operation, he still complained recurrent epigastric pain which ranged VAS 2–4, recurrent nausea, and still needed opioid medication to control his pain. The laboratory examination showed persistently high pancreatic enzyme level, amylase ranged 120–158 U/L, and lipase ranged 182–248 U/L. Follow up abdominal-CT-scan showing hypodense mass 4.2 x 5.6 cm suggestive for pseudocyst at pancreatic tail (Figure 2).

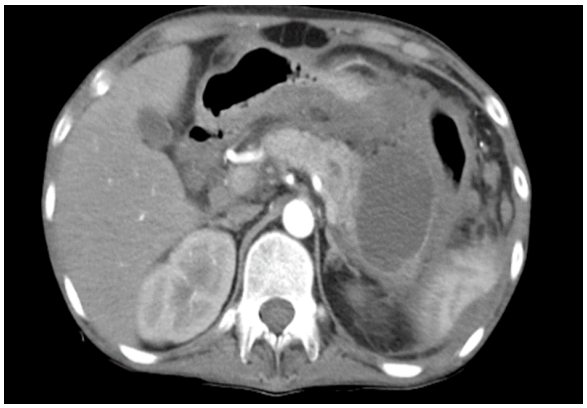

Figure 2. Follow up abdominal-CT-Scan

Based on those findings, we suspected him for chronic pancreatitis and pseudocyst complication. We planned to manage him conservatively and observed for the pseudocyst with the surgery department.

DISCUSSION

Asparaginase induced pancreatitis is rarely found in adult patient, due to the ALL disease is more prevalent among children. However, study showed that adult and adolescence had 5.2 times increased risk for having AIP and persisting AIP complications 6.7 times more likely. Prevalence of AIP was reported between 6.7% and 18%.[2] Study from Nordic Society of Pediatric Hematology and Oncology (NOPHO) showed there were 20% of AIP occurred in ALL patients aged 18–45 years old.[3]

The onset of AIP was reported variable. Kearney et al found that AIP most commonly developed within first ten weeks of asparaginase administration, which ranged from days to weeks. This finding raised the possibility of AIP may occur not fully related with dose accumulation effect, but more likely be explained due to underlying predisposition.[4] The mechanism of AIP has not been fully understood. Asparaginase was depleting the asparagine body deposit therefore disrupting the plasma amino acid synthesis and balance especially in high protein turnover organ such as pancreas. This mechanism may lead to depressed exocystosis process in acinar pancreatic cell, which generally thought may lead to autodigestion of pancreatic tissue and inflammation.[2,5,6] Genetic predisposition and polymorphism were also being thought playing role.[2,7] Several risk factors have been implicated for higher risk developing AIP. Systematic review by Oparaji et al, found that older age, asparaginase formulation type, higher ALL risk stratification, and higher asparaginase dosing was associated with AIP occurrence.[8] Chen et al found that AIP occurrence is more related to dose intensity of L-asparaginase, rather than accumulated dosage.[9]

The clinical manifestation of AIP was similar to acute pancreatitis. Therefore, detailed history taking to establish the temporal relationship should be performed. Pancreatic enzyme level should be examined whenever AIP was suspected. Imaging modalities such as abdominal ultrasound was useful to exclude biliary stone related acute pancreatitis. While, abdominal CT-scan and magnetic resonance imaging (MRI) were useful to detect the pancreatic necrosis, pseudocyst, and other complications. Monitoring of amylase and lipase serum level was needed.[2,7] In our case, persistent symptom and elevated pancreatic enzyme level were pointing to the occurrence of AIP complications.

Raja et al have made the algorithm for AIP diagnosis and management AIP.[2] The management of AIP is mainly supportive such as fluid resuscitation, nutritional support, pain management and other. However, asparaginase administration must be stopped whenever AIP was suspected.[2,10] Octreotide or somatostatin which act to inhibit secretion of pancreatic enzymes, theoretically may be helpful in acute pancreatitis management because it may limit the pancreatic inflammation. Study showed the effectivity of octreotide usage in two ALL patient who had AIP. The patients were showing improved clinical symptoms and laboratory findings.[11] Similar finding was also reported by Wu et al.[12]

Asparaginase induced pancreatitis cases usually resolved as mild to moderate disease. However, AIP can also lead to acute severe complication such as multiorgan failure. Severe course has been reported in up to 15% of AIP patients.[13] Other complications can be divided as short-term and long-term AIP complications. Short term complications were defined as pancreatic necrosis and pseudocyst development which mainly occurred during within 4 weeks of acute pancreatitis. Pancreatic necrosis may become source of infection and lead to increased mortality risk. Necrotomy can

be safely performed on four weeks after onset in order to wait for the walled off pancreatic necrosis development. Pseudocyst was generally managed conservatively and monitored regularly. The long-term AIP complications may be defined as diabetes and chronic pancreatitis which may impact the long-term of patient's life quality.[2,3,10,14]

Re-introduction of asparaginase is associated with higher risk development of recurrent AIP.[2,4] The presence of pseudocyst was an absolute contraindication for asparaginase re-introduction. Asparaginase may be re-introduced if the patients have no acute pancreatitis symptoms and pancreatic enzyme level below three times the upper normal limit.[2]

In conclusion, ALL adult patient is at higher risk for developing AIP and having persistent complications. Early recognition and prompt treatment of AIP are needed. Long term complications of AIP such as chronic pancreatitis may impair patient's life quality.

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