INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

2022 July; 28(3): 337-342
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Pancreatitis in Acute Lymphoblastic Leukemia

Putu Yudi Adnyani, I Nyoman Wande, Sianny Herawati

Department of Clinical Pathology, Faculty of Medicine, Udayana University/Sanglah Hospital, Denpasar, Indonesia. E-mail: yudismaradayita@gmail.com

ABSTRACT

Pancreatitis is inflammation of the pancreatic parenchyma and diagnosed based on symptoms of heartburn accompanied by increased levels of pancreatic enzymes. Acute pancreatitis in acute lymphoblastic leukemia is usually caused by therapy but can also be caused by other factors. A 13-year-old female patient diagnosed with acute lymphoblastic leukemia complained of heartburn, which was could be felt piercing the back. The patient also experienced nausea, vomiting, decreased appetite, difficulty in bowel movements, and fever. Physical examination found an increase in body temperature, anemic conjunctiva, multiple neck gland enlargements, and enlargement of the liver. The results of complete blood tests showed leukocytosis, anemia, and thrombocytopenia. The results of an examination of bone marrow aspiration showed a picture of the bone marrow in accordance with Acute Lymphoblastic Leukemia (ALL-L2). Clinical chemistry tests showed an increase in amylase, lipase, SGOT, BUN, creatinine, LDH, ferritin, calcium, and procalcitonin. The patient has not received chemotherapy for ALL yet. Acute pancreatitis in ALL is usually caused by chemotherapy but in some cases, it can also be caused by sepsis, which was one of the complications of ALL. Acute lymphoblastic leukemia patients who experience acute pancreatitis showed a poor prognosis.

Keywords: Acute pancreatitis, acute lymphoblastic leukemia, sepsis

INTRODUCTION

Pancreatitis is an acute condition of inflammation in the pancreatic parenchyma. Acute pancreatitis can be diagnosed based on typical abdominal pain, an elevated pancreatic enzyme, or imaging.[1] The cause of acute pancreatitis in children is usually from drugs, infection, trauma, metabolic, systemic illness, and anatomical differences such as choledochal cyst and an abnormal unity of the pancreato-biliary junction.[2] Acute pancreatitis in patients with Acute Lymphoblastic Leukemia (ALL) is usually caused by therapy given such as the use of L-Asparaginase, which is a chemotherapy drug for patients with ALL.[3] This case will discuss a case of acute pancreatitis due to infection, not because of drug therapy.

CASE REPORT

A female aged 13-years-old was admitted to the emergency room of Sanglah Hospital with the main complaint of abdominal pain. The pain was first felt in the solar plexus 3 days before admission and got more painful 8 hours before admission. The pain radiated to the lower back and got worse if there was pressure on the stomach. The patient was constipated 3 days before admission, with difficulty passing brownish stool, there was no blood was detected. The patient was nauseous and threw up a day before admittance, the patient threw up 5 to 10 mL each time, for a total of 10 times, sometimes blood and mucus could be found. The patient also had a fever, felt fatigued, and had appetite loss. Gum and nose bleeding were denied. The patient had a history of ALL but has never undergone chemotherapy. There was a history of Outpatient Clinic and admittance to the hospital. The patient was a second child, with normal birth delivery and had a good history of growth and development with complete immunization. Similar complaints were not found in the family history.

Physical examination showed a weak general appearance, alert with a low nutritional state. Heart rate 108x/minute, respiratory rate 24x/minute, the temperature of 37.8C. Head and neck examination showed anemic eyes, and multiple gland enlargements on the right side of the neck at least 1-2 cm with a rubbery consistency, moveable with no tenderness. The thoracic examination was within normal limits. The abdomen was distended and there was a decrease in peristaltic movements. Palpation found a liver enlargement at 4 cm beneath the costae arc and 4 cm beneath the xiphoid. The spleen was hard to evaluate.

Complete blood count results are shown in Table 1. There was leukocytosis, lymphocytosis, normochromic normocytic anemia, and thrombocytopenia when the patient is admitted to the hospital.

There was the elongation of the extrinsic pathway of coagulation factors, hyperfibrinogenemia, and an increased level of D-dimer in hemostasis results (Table 2).

A peripheral blood smear is shown in Table 3. There are bicytopenia with leukocytosis suspected of acute leukemia dd/ALL. Bone marrow aspiration was conducted 2 days before admittance showing acute ALL-L2 (Figure 1). There is 70% lymphoblast infiltration with heterogenic morphology and clefts in the nucleus of lymphoblasts.

Clinical chemistry results are shown in Table 4. There was an increase in SGOT 92.6 U/L, amylase 441.6 U/L, lipase 2,991.8 U/L, BUN 35.30 mg/dL, creatinine 2.43 mg/dL, procalcitonin 11.13 ng/mL, ferritin 4,853 ng/dL, and LDH 7,952 U/L. There was a decrease in globulin 2.50 and random blood sugar 77 mg/dL on June 1st, 2019. Electrolytes showed an increase in calcium, reaching 13.1 mg/dL (Table 5). A blood culture done on May 31st, 2019 showed that there was no bacterial growth.

Table 1. Complete blood count

Parameter	Results		Reference Range
	30/5/2019	6/6/2019	
WBC (10^3/µL)	**28.01**	6.85	4.1-11.0
% Eosinophil (%)	0.30	0.35	0.0-5.0
% Basophil (%)	0.56	0.61	0.0-2.0
% Neutrophil (%)	**6.47**	**16.82**	47-80
% Lymphocyte (%)	**87.49**	**80.21**	13-40
% Monocyte (%)	5.18	2.01	2.0-11.0
RBC (10^6/µL)	4.04	**2.24**	4.0-5.2
HGB (g/dL)	**10.90**	**6.34**	12.0-16.0
HCT (%)	**33.81**	**18.70**	36-46
MCV (fL)	83.61	83.42	80.0-100.0
MCH (pg)	26.96	28.27	26.0-34.0
MCHC (g/dL)	32.25	33.89	31-36
RDW (%)	12.37	13.05	11.6-14.8
PLT (10^3/µL)	**12.6**	**14.58**	140-440
MPV (fL)	**11.70**	**6.24**	6.80-10.0

Table 2. Hemostasis results

Parameter	Results 9/6/2019	Reference Range
PPT (seconds)	**26.4**	10.8-14.4
INR	**2.48**	0.9-1.1
APTT (seconds)	33.7	24-36
Fibrinogen (mg/dL)	**592.00**	140-450
D-dimer (FEU/mL)	**13.21**	< 0.5

Table 3. Peripheral blood smear

Parameter	Results (30/5/2019)
Erythrocytes	A large proportion of the cell population is normochromic normocytic poikilocytosis (microcyte (+), spherocyte (+), ovalocyte (+)
Leukocytes	Appears to increase in number, differential count appears to have lymphocytosis, a large nucleated cell resembling lymphoblasts were found with a total of 60%, vacuolization (-), toxic granules (-)
Thrombocytes	Appears to decrease in number, clumping (-), giant platelet (-)
Conclusion	Bicytopenia with leukocytosis suspected of acute leukemia dd/ALL

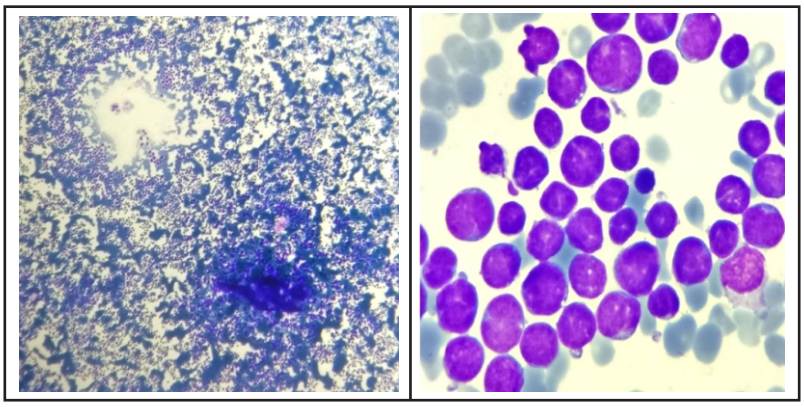

Figure 1. Bone marrow appearance: A. Hypercellular at 100 x magnification; B. Lymphoblast morphology at 1000x magnification

Table 4. Clinical chemistry results

Parameter	Results				Reference Range
	31/5/19	3/6/19	5/6/19	10/6/19	
AST (U/L)	**92.6**			**267.1**	11.00-27.00
ALT (U/L)	12.50			**82.90**	11.00-34.00
Complete bilirubin					
Total bilirubin (mg/dL)	0.43			**5.08**	0.30-1.10
Direct bilirubin (mg/dL)	0.24			**4.77**	0.00-0.30
Indirect bilirubin (mg/dL)	0.19			0.31	
Alkali Phosphatase (U/L)	131			**251**	0-187
Total Protein (g/dL)	6.1			5.9	6.00-8.00
Albumin (g/dL)	3.60			3.30	3.50-5.20
Globulin	**2.50**			**2.60**	3.2-3.7
Gamma GT (U/L)	21			**409**	7.00-32.00
Amylase (U/L)	**441.6**				25.00-120.00
Lipase (U/L)	**2,991.8**			51.2	13-60
BUN (mg/dL)	**35.30**	**53.40**			8.00-23.00
Creatinine (mg/dL)	**2.43**	**2.63**			0.50-0.90
Procalcitonin (ng/mL)		**11.13**		**30.75**	<0.15
Ferritin (ng/dL)			**4,853.0**		13-68
LDH (U/L)			**7952**		240-480

Table 5. Serum electrolyte results

Parameter	Results			Reference Range
	31/5/19	3/6/19	5/6/19	
Serum potassium (mmol/L)	3.91	**2.46**	**3.00**	3.50-5.10
Serum sodium (mmol/L)	138	140	**150**	136-145
Serum chloride (mmol/L)	100.2	102.2	**111.5**	94-110
Calcium (mg/dL)	**13.1**	**11.6**	10.3	9.20-11.00
Magnesium (mg/dL)				1.6-2.6

A plain abdominal X-ray showed a ground glass appearance in the upper right and left abdomen that pressed the intestinal system to the caudal (suggesting hepatosplenomegaly).

This patient was given 3 bags of 175 mL Thrombocyte Concentrate (TC) until the thrombocytes reached 50.000. Hypercalcemia was corrected with NaCl 0.9% (2x infusion) 54 macro drops per minute, 40 mg Furosemide infusion every 8 hours, and 1,950 mg Ceftriaxone infusion every 12 hours dripped in 50 mL D5% that must be finished in 30 minutes.

DISCUSSION

Acute lymphoblastic leukemia is a proliferation and malignant transformation of a lymphoid progenitor cell in the bone marrow, blood, and extra-medullary. Acute lymphoblastic leukemia is more likely in children aged 2–5 years old and reaches the second peak over 50 years old.[4,5] Clinical manifestation from ALL is related to malignancy and bad lymphoid cell differentiation in the bone marrow, peripheral blood cells, and extramedullary. The description that is shown is unspecific with a combination of symptoms and signs of bone marrow failure such as anemia, thrombocytopenia, and leukopenia. General symptoms are fever, weight loss, night sweating, bleeding easily, fatigue, shortness of breath, and infection. Extramedullary involvement generally occurs and causes lymphadenopathy, splenomegaly, and hepatomegaly in 20% of patients. Central nervous system involvement happens in 5–8% of patients with cranial nerve deficit symptoms.[4,6] Cell T ALL can be accompanied by a mediastinal mass. Diagnosis is established with 20% or more lymphoblasts in the bone marrow or peripheral blood. Morphologic examination, flow cytometry, immunophenotyping, and cytogenesis are needed for confirming the diagnosis and risk stratification. Lumbar puncture with CSF analysis is the standard examination to evaluate central nervous system involvement. If central nervous system involvement is confirmed, MRI must be conducted. Other tests that must be done are a complete blood count with cell differentiation and a blood smear to evaluate the other hematopoietic cells. The coagulopathy profile and serum clinical chemistry of ALL patients must also be tested. Uric acid, calcium, phosphate, and LDH should be documented to monitor tumor lysis syndrome. Acute lymphoblastic leukemia classification according to the French American British (FAB) morphology criteria is divided into three subtypes, based on cell size, cytoplasm, nucleolus, vacuolization, and basophilia. The FAB classifications are ALL-L1, L2, and L3.[4]

A patient newly diagnosed with ALL showed laboratory results as follows anemia, neutropenia, and thrombocytopenia with a variated number of leukocytes between 0.1-1,500 x 10^3/µL. Serum LDH concentrations increased in a large number of ALL and were related to tumor burden.[6] An increase in uric acid is also usually found and shows an increase in purine catabolism. Infiltration of leukemia in the kidney is marked by the increase in creatinine, urea nitrogen, phosphate, and uric acid levels. In 0.5% cell B precursor ALL, it is found that t (17;19) (q22; p13.3) with an E2A-HLF fusion is related to disseminated coagulopathy, hypercalcemia, and a bad prognosis. Liver dysfunction due to leukemic infiltration happens in 10-20% of patients and is usually mild.[7]

A 13-year-old female patient with symptoms of fatigue and fever denied nose or other signs of bleeding. Physical examinations showed poor nutritional status, anemic conjunctiva, multiple enlargements of neck glands, and liver enlargement in the abdomen. Radiological imaging proved the presence of hepatosplenomegaly. Complete blood count showed anemia, leukocytosis, and thrombocytopenia. The age, symptoms, and physical and laboratory examinations were in line with a diagnosis of ALL. The bone marrow aspiration strengthened the diagnosis and narrowed it to ALL-L2. There was an increase in the patient's LDH in line with the theory that states that in ALL, LDH increases due to the tumor burden, and 50% of patients of ALL have LDH levels between 300 and 1,000 IU/L. LDH levels are usually related to the number of WBC and blasts.[6] Infiltration of leukemia to the kidney and liver shows an increase in creatinine, urea nitrogen, and SGOT.

Calcium levels in this patient increased to 13.1 mg/dL. Hypercalcemia is a metabolic abnormality that is rarely found in children. Hypercalcemia can be caused by metabolic disorders, nutrition, drug influence, genetics, inflammation, and malignancy factors.[8] Hypercalcemia can also be caused by the excretion of a protein resembling the parathyroid hormone by lymphoblasts and the infiltration of leukemia to the bone that can happen through 3 mechanisms, as follows: osteolysis from direct invasion of tumor cells into the bone, the increase of bone resorption by osteoclasts through the humoral factor produced by the tumor, and hypercalcemia absorption by vitamin D activation, but hypercalcemia in malignancy is a complication that is very rare in children and the incidence rate is 0.4–1.3% from cancer with the most common cause being ALL at this age.[8] Hypercalcemia is reported as the early manifestation of malignancy in ALL children, before the discovery of blasts in peripheral blood smear.[9] Hypercalcemia is classified based on the levels of total serum calcium, mild hypercalcemia is 10.5–11.9 mg/dL, moderate hypercalcemia is 12–13 mg/dL and severe hypercalcemia is > 14 mg/dL.[9,10] Serum calcium levels over 12 mg/dL are related to unspecific symptoms such as lethargy, depression, anorexia, nausea, vomiting, polyuria, and polydipsia. Patients with calcium levels over 15 mg/dL may experience renal failure and

cardiovascular abnormalities with arrhythmia and coma. This patient had a decrease in appetite, nausea, and vomiting since a day before admittance. This patient had moderate hypercalcemia with calcium levels of 13.1 mg/dL. A reference stated that in patients with hypercalcemia caused by malignancy, an increase in calcium levels may have a poor clinical outcome in ALL patients.[11]

Acute pancreatitis is defined as an inflammation of the pancreatic parenchyma that is shown clinically by the presence of a sudden onset of abdomen and back pain followed by an increase of pancreatic enzymes in the blood and urine.[3]

Acute pancreatitis diagnosis based on the Atlanta criteria is the presence of two of three criteria that comprise typical abdominal pain, serum lipase or amylase activity for at least 3 times the normal upper limit, and characteristic Computed Tomography (CT) findings. Risk factors of acute pancreatitis in children are biliary tract disease (gall stones, biliary sludge, pancreas divisum, annular pancreas), medication use (valproic acid, asparaginase, prednisone, metronidazole, tetracycline, and mesalamine), systemic disease, abdominal trauma, metabolic disorders (diabetic ketoacidosis, hypertriglyceridemia, hypercalcemia), and inborn errors of metabolism.[1,12]

Acute pancreatitis diagnosis is based on clinical signs and confirmed by laboratory and/or radiology. The symptoms of acute pancreatitis in children that often occur are abdominal pain and/or irritability, followed by epigastric tenderness, nausea, and vomiting. Ultrasonography is the chosen examination for children considering the safety, it's not invasive, and the ability to detect biliary etiology. The abdominal CT scan can help the diagnosis of acute pancreatitis complications (fluid build-up, necrosis, bleeding).[1] Acute pancreatitis can variate from mild (death numbers less than 1%, usually recovers in a couple of days) to severe (death rate more than 30%). The highest death rate is in patients with the hemorrhagic pancreas, multiorgan dysfunction or failure (shock, kidney failure, pulmonary insufficiency), and necrotic pancreas. Infection and abscess can increase the death rate in the necrotic pancreas.[1,12] It is not easy to predict acute pancreatitis because the scoring for adults is not implemented on children. The newest study shows that serum lipase 24 hours from the appearance, with levels over 7 times the normal limit, can help as an acute pancreatitis marker in children.[1] The severity of acute pancreatitis can be determined by the Labour and Welfare of Japan (JPN score), that comprises of : base excess ≤ -3 mEq or shock; PaO2 ≤ 60 mmHg or respiratory failure; BUN ≥ 40 mg/dL or creatinine ≥ 2.0 mg/dL or oliguria < 0.5 mL/kg per hour; LDH ≥ 2x upper normal limit; thrombocyte ≤ 1x 10^5/mm^3; Calcium ≤ 7.5 mg/dL; CRP ≥ 15 mg/dL; positive SIRS score ≥ 3; Age < 7 years old and/or weight < 23 kg. The cut-off is to determine the degree of severity if they fulfill at least 3 criteria.[2]

The laboratory results of this patient showed an increase of amylase and lipase 3 times the upper normal limit. Ultrasonography could not be conducted on this patient due to hepatosplenomegaly, causing difficulty in evaluating the pancreas. This patient already fulfilled 2 out of 3 elements of the Atlanta criteria, confirming the diagnosis of acute pancreatitis. Acute pancreatitis in ALL patients is usually a complication from therapy such as L-asparaginase.[3] This patient hasn't received chemotherapy so acute pancreatitis due to medication could be ruled out. Sepsis and hypercalcemia are other risk factors for acute pancreatitis. The increase in procalcitonin levels is proof of sepsis in this patient. Neutropenia is a primary risk factor that is related to infection; the severity and frequency of infection increase with an absolute neutrophil count below 500 cells/µL. Other risk factors are disturbances in cellular and humoral immunity, damage to normal defence mechanisms, and the use of blood vein catheters or other medical equipment. Multiple risk factors can happen in the same patient.[13]

Acute pancreatitis severity in this patient according to JPN score can be seen from the BUN of 35.30 mg/dL, creatinine 2.43 mg/dL, LDH 7,952 U/L, and thrombocyte of 12.6 x 10^3/µL. This patient died with shock and DIC as the cause of death, this is in line with the theory that states that the most severe complication of acute pancreatitis that often causes death is shock caused by multiorgan failure.

CONCLUSION

This case describes a case of acute pancreatitis in an Acute Lymphoblastic Leukemia patient. Acute pancreatitis in ALL is usually caused by chemotherapy drugs, but in patients who haven't received chemotherapy, pancreatitis may be caused by infection and hypercalcemia which are complications of ALL. This case shows an ALL patient with acute pancreatitis with a bad prognosis.

REFERENCES

1. Pohl JF, Uc A. Pediatric pancreatitis. Curr Opin Gastroenterol, 2015; 31(5): 380-386.
2. Abu-El-Haija M, Kumar S, Quiros JA, Balakrishnan K,

Barth B, *et al*. The management of acute pancreatitis in the pediatric population: A clinical report from the NASPGHAN Pancreas Committee. J Pediatr Gastroenterol Nutr, 2018; 66(1): 159-176.
3. Stefanovic M, Jazbec J, Lindgren F, Bulajic M, Lohr M. Acute pancreatitis as a complication of childhood cancer treatment. Cancer Medicine, 2016; 5(5): 827-836.
4. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: A comprehensive review and 2017 update. Blood Cancer Journal, 2017; 7(6): e577.
5. Mahmood K, Ubaid M, Rizvi ST. Multiple osteolytic lesions causing hypercalcemia: A rare presentation of acute lymphoblastic leukemia. Case Report in Medicine, 2017; 2017: Article ID 2347810.
6. Elbossaty WFM. Lactate Dehydrogenase (LDH) as prognostic marker in acute leukemia "quantitative method" . J Blood Disord Transfus, 2017; 8: 1
7. Larson RA. Acute Lymphoblastic Leukemia. In: Kaushansky K, Lichtman MA, *et al*., editors. Williams Hematology. 9th Ed., New York, Mc Graw Hill Education, 2016; 1505-1526.
8. Martins AL, Moniz M, Nunes PS, Abadesso C, Loureiro HC, *et al.* Severe hypercalcemia as a form of acute lymphoblastic leukemia presentation in children. Rev Bras Ter Intensiva, 2015; 27(4): 402-405.
9. Hyun HS, Park PG, Kim JC, Hong KT, Kang HJ, *et al*. A case of severe hypercalcemia causing acute kidney injury: An unusual presentation of acute lymphoblastic leukemia. Child Kidney Dis, 2017; 21:21-25.
10. Goldner W. Cancer-related hypercalcemia. Journal of Oncology Practice, 2016; 12(5): 426-433.
11. Chen W-P, Chiang W-F, Chen H-M, Chan J-S, Hsiao P-J. Preventive healthcare and management for acute lymphoblastic leukemia in adults: Case report and literature review. Healthcare, 2021; 9: 931.
12. Husain S, Srinath A. What's unique about acute pancreatitis in children: Risk factors, diagnosis and management. Nat Rev Gastroenterol Hepatol, 2017; 14: 366-372.
13. Rolston KVI. Infection in patients with acute leukemia. In: Maschmeyer G, Rolston KVI, editors. Infections in hematology. New York, Springer, 2015; 3-24.