

Case Report

Diabetic Ketoacidosis and Persistent Hyperglycemia as Long-term Complications of L-asparaginase-induced Pancreatitis

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Diabetic ketoacidosis (DKA) and pancreatic pseudocysts are rare complications following treatment of hematological malignancies with L-asparaginase (L-asp). Persistent hyperglycemia with recurrent DKA presenting as a long-term complication of L-asp-induced pancreatitis is even rarer. A 21-year-old man with pre-B-type acute lymphoblastic leukemia (ALL) developed pancreatic pseudocysts, DKA and persistent hyperglycemia after L-asp therapy. The patient was treated with oral hypoglycemic agents (OHA) for sugar control thereafter. Ten months later, an other episode of DKA developed during relapsed ALL without having obvious precipitating factors. Insulin was then instituted for control of his blood sugar until death. The leukemic process may play some role in glucose homeostasis and may be considered as a precipitating factor for DKA. The patient finally died of disease progression of ALL and sepsis 2 years after the initial diagnosis of ALL.

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L-asparaginase (L-asp) has been used for the treatment of such malignant hematological disorders as acute lymphoblastic leukemia (ALL) and lymphomas. Serious side effects of L-asp include hepatotoxicity, pancreatitis, renal failure, hyperglycemia, coagulopathy, central nervous system (CNS) disorders and hypersensitivity reaction.¹ Diabetic ketoacidosis (DKA) and pancreatic pseudocysts may occur on rare occasions, and hyperglycemia is usually transient.¹⁻¹¹ Except for the diabetogenic effect of L-asp, the leukemic process itself, through mechanisms as yet undetermined, may impair glucose metabolism as well. Here we report a rare case of ALL who developed recurrent DKA and persistent hyperglycemia after treatment with L-asp.

Case Report

A 21-year-old man sought medical attention for persistent fever in January 1999 and was diagnosed to have ALL of pre-B cell type. He had no family history of diabetes mellitus or other endocrinological disorders. Complete remission (CR) was achieved after induction therapy with vincristine, daunomycin and prednisolone. Additionally, CNS prophylaxis with intrathecal methotrexate (MTX) and cranial irradiation were instituted. After intrathecal MTX therapy, treatment with *Escherichia Coli*-derived L-asp (Leunase) at a dose of 18,000 IU intramuscularly every other day was given. One day after the 8th dose of L-asp, the patient complained of nausea, vomiting and

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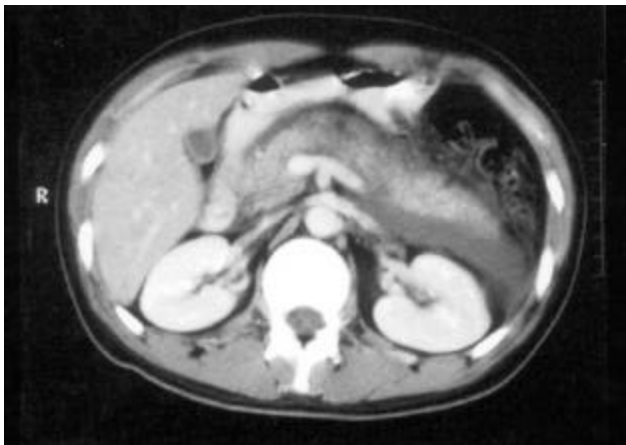


Fig. 1. CT scan 2 days after the last dose of L-asp showing enlarged pancreas with irregular surface and focal fluid accumulation over the para-pancreatic region.

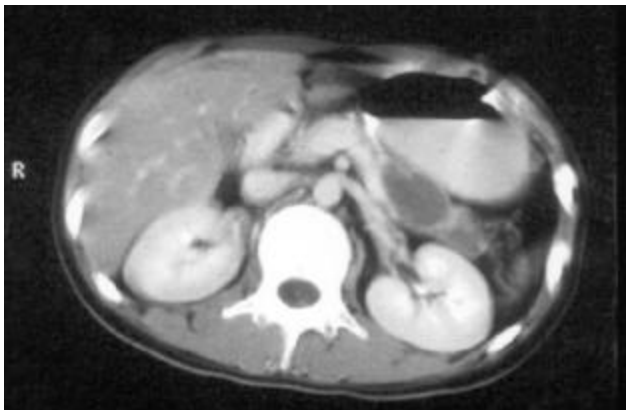


Fig. 2. Follow-up CT scan 1 month later showing pancreatitis with pseudocyst formation over the tail area.

epigastric discomfort. Physical examination showed decreased bowel sounds and local tenderness over the epigastric region without rebound tenderness. Pertinent laboratory findings showed an amylase level of 363 U/L (normal range: 30-110 U/L), a lipase level of 1,199 U/L (normal range: 23-300 U/L) and a triglyceride at 97 mg/dL (normal range: 35-150 mg/dL). Abdominal computed tomography (CT) scan demonstrated an enlarged pancreas with irregular surface and focal fluid accumulation over the para-pancreatic region (Fig. 1). The patient was treated with supportive measures for L-asp-induced pancreatitis for 2 weeks and his condition improved. He then received consolidation therapy with prednisolone,

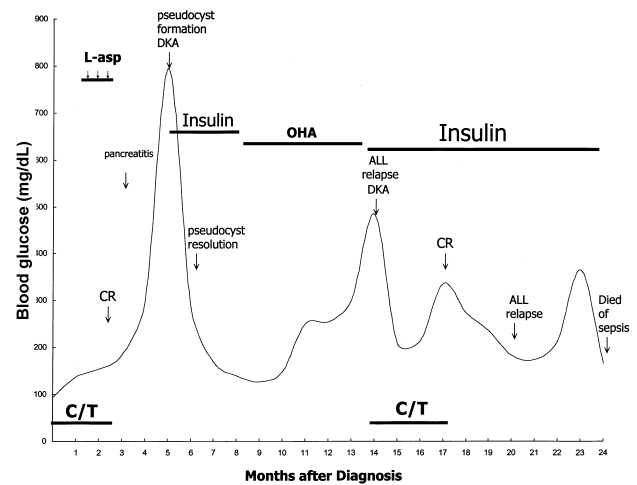


Fig. 3. Summary of the hospital course and variation of blood glucose level. ALL = acute lymphoblastic leukemia; CR = complete remission; C/T = chemotherapy; DKA = diabetic ketoacidosis; L-asp = L-asparaginase; OHA = oral hypoglycemic agents.

vincristine, methotrexate, and mercaptopurine. Unfortunately, he developed shortness of breath and abdominal pain 1 month later. Arterial blood gas analysis showed a pH of 6.994, a PCO_2 level of 23.5 mmHg, HCO_3^- at 5.6 mmol/L, and a base deficit of -24.4 mmol/L. Blood glucose was 764 mg/dL and serum ketone body was 3+. Concurrent serum amylase was 167 U/L (normal range: 30-110 U/L). An abdominal CT scan showed pancreatitis with a pseudocyst forming over the tail area, about 6×3 cm² in size (Fig. 2). DKA was impressed. The patient was then treated aggressively for DKA and pancreatic pseudocyst formation, and his clinical condition improved following rehydration, parenteral nutrition, nasogastric decompression, intravenous insulin, bicarbonate supplement and empiric antibiotics. The pancreatic pseudocyst resolved gradually, and abdominal ultrasonography revealed normal appearance of the pancreas 16 days later. Random blood glucose still fluctuated between 200 mg/dL and 300 mg/dL. Oral hypoglycemic agents were administered. During the subsequent months, he refused any further maintenance therapy. Ten months after the last dose of L-asp, his ALL relapsed and he was found to have another episode of hyperglycemic ketoacidosis. He then received treatment for his

hyperglycemic ketoacidosis and ALL again with mitoxantrone and cytosine arabinoside (Fig. 3). Although the clinical condition improved and his ALL was in second complete remission, the hyperglycemia persisted and insulin injection was needed for blood sugar control. Unfortunately, his ALL relapsed in his CNS and bone marrow in November, 2000, and he died of septic shock 2 years after the diagnosis of ALL. The clinical course of his ALL and blood glucose level are delineated in Fig. 3.

Discussion

Hyperglycemia is a well-documented complication of L-asparaginase therapy for ALL.^{1-5,11} The reported incidence of hyperglycemia ranges from 2.5-23%^{1,2,7,11} and episodes usually resolve within an average of 12 days.⁵ The symptoms vary from mild glucose intolerance to severe or even fatal DKA. Acute pancreatitis, which occurs in 2-16% of cases, is another serious side effect of L-asparaginase treatment.^{6,12} L-asparaginase-related life-threatening pancreatitis, sometimes with the development of pseudocysts and death, have repeatedly been reported in the medical literature.¹²

We reviewed the English medical literature and were able to identify 12 cases (including the present case) of DKA related to L-asparaginase therapy (Table 1).^{1-3,6,8,10,11,13,14} A number of pathogenic mechanisms of L-asparaginase-related hyperglycemia have been proposed, such as inhibition of insulin biosynthesis, impaired insulin secretion, a reduction in insulin receptors, concurrent hyperglucagonemia and pancreatic islet cell damage.^{4,11,15,16} All reported cases of hyperglycemia and DKA after L-asparaginase therapy were reversible and transient except 2, including the present one. One case with persistent diabetes and ketoacidosis was reported, but that case died 6 weeks after L-asparaginase therapy.¹⁰ There is no conclusive study about the duration of the diabetogenic effect of L-asparaginase. In the present case, persistent hyperglycemia, recurrent DKA and relapsed ALL developed 10 months after the last dose of L-asparaginase. The pathogenesis of this long-term complication may be permanent damage of beta cells due to pancreatic pseudocysts. Such late DKA had never

been reported in the literature because almost every leukemia patient suffering from severe L-asparaginase-induced pancreatitis died before such long-term complications would appear.

DKA is a potentially fatal complication, and its management should include volume replacement, electrolyte supplementation and intravenous insulin. Early recognition of risk factors and precipitating factors for L-asparaginase-related DKA is important. In our review, 8 of 12 patients who developed DKA after L-asparaginase might have had precipitating factors such as acute pancreatitis, pancreatic pseudocysts, and infection,^{2-3,6,8,11,13,14} in addition to the diabetogenic effect of L-asparaginase itself. Dacou-Voutetakis *et al.* also suggested that leukemic process itself, through mechanisms as yet undetermined, could impair glucose metabolism.¹⁷ This suggestion may explain why our case developed DKA during relapsed ALL without having obvious precipitating factors. Furthermore, some investigators found that over 10 years of age, obesity, Down syndrome, family history of diabetes mellitus and high initial leukocyte count might predispose hyperglycemia in those patients who received L-asparaginase.⁷

Recently, 2 other preparations of asparaginase became available: (1) *Erwinia carotovora*-derived L-asparaginase; and (2) polyethylene glycol-L-asparaginase. Several investigations suggested that these 2 agents have fewer side effects and fewer hypersensitivity reactions.^{16,18} Ridgway *et al.* reported asparaginase-induced hyperglycemia would be attenuated after substitution of the *Erwinia* L-asparaginase for *E. coli* L-asparaginase.¹⁸ However, more studies of pharmacokinetics, toxicity, dose modification, drug interaction and protocol design are needed.

In conclusion, L-asparaginase-induced pancreatitis could lead to long-term impairment of pancreatic function, such as DKA and persistent hyperglycemia, if patients live long enough. Postprandial blood glucose, urinary glucose, urinary ketone body and serum pancreatic enzymes should be closely monitored after L-asparaginase therapy. Early recognition of the precipitating factors for DKA is important to prevent L-asparaginase-related fatal consequences, and the leukemic process itself may be considered as one of the predisposing factors.

Table 1. Summary of DKA associated with L-asp therapy reported in the literature

Case no.	Age (yr)/Sex	Diagnosis	Symptoms and signs	Onset after the last dose of L-asp (days)	Associated clinical manifestation	Therapy	Long-term sequelae	Outcome	References
1	12/F	ALL	Nausea, vomiting, polyuria, polydipsia, vaginal pruritus	20	Oral and vaginal candidiasis	Insulin and supportive treatment	Nil	CR	13
2	56/M	ALL	Cardiopulmonary embarrassment	11	Acute hemorrhagic pancreatitis	Supportive resuscitation	Nil	Died	6
3	30/M	ALL	Vomiting, diarrhea, dyspnea, oliguria	1	Pneumonia	Insulin, supportive resuscitation, antibiotics	Nil	Died	8
4	10.5/F	ALL	Lethargy, irritable, polydipsia, polyuria, Kussmaul respiration	2	Nil	Insulin and supportive treatment	Persistent hyperglycemia, ketouria	Died	10
5	10/F	AL	Lethargy, irritable, polydipsia, polyuria, Kussmaul respiration	2	Small abscess on the right upper eyelid	Insulin, supportive resuscitation, antibiotics	Nil	CR	3
6	13/M	AL	Polyuria	5	Neutropenia, small rectal fissure	Insulin, supportive treatment, antibiotics	Nil	CR	14
7	9/M	ALL	NS	NS	Pancreatitis, secondary peritonitis	Insulin, supportive treatment, antibiotics	NS	NS	2
8	11/F	ALL	NS	NS	Nil	Insulin and supportive treatment	NS	NS	2
9	NS	AL	NS	4	Nil	NS	NS	Died	1
10	NS	AL	NS	NS	Nil	NS	NS	Alive	1
11	10/M	ALL	Nausea, vomiting, abdominal pain, conscious change	Days and 2 weeks	Acute pancreatitis, perianal abscess	Insulin, supportive treatment, antibiotics	Nil	CR	11
12	21/M	ALL	Epigastric pain, nausea, Vomiting	6 weeks and 10 months	Pancreatitis, pseudocyst formation	Insulin, supportive treatment, antibiotics	Persistent diabetes, recurred DKA	CR	This case

ALL = acute lymphoblastic leukemia; CR = complete remission; AL = acute leukemia; NS = not stated.

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