Diabetic Ketoacidosis With L-asparaginase Therapy

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Diabetic ketoacidosisis as a complication of L-asparaginase therapy in children with acute leukemia is rare. Hyperglycemia may occur in about 10% of cases receiving L-asp, which may present as mild glucose intolerance to severe hyperglycemia. We report two children with acute lymphoblastic leukemia who developed diabetic ketoacidosis after treatment with L-asparaginase.

Key words: *Child, Complications, Diabetic ketoacidosis, L-asparaginase*.

L-asparaginase therapy for acute lymphoblastic leukemia (ALL) is associated with hyperglycemia(1,2); rarely it may even present catastrophically as diabetic ketoacidosis (DKA).

CASE REPORT

***Case 1*:** An 11-years old male child diagnosed with T-cell ALL was given induction chemotherapy with vincristine 1.5 mg/m^2 slow intravenous/weekly, L-asparaginase 10000 IU/m^2 intravenous/bi-weekly, prednisolone 60 mg/m^2/day orally, doxorubicin 25 mg/m^2/weekly for four doses and methotrexate intrathecal 12 mg weekly. The induction period was continued for 6 weeks. After remission, maintenance therapy was started and repeat marrow examination was done as per treatment protocol. After seven days, the patient developed abdominal pain with unexplained dehydration. Investigations showed hyperglycemia (blood glucose 646 mg/dL), serum amylase 1024 units/L and serum lipase 840 units/L, with ketonuria and acidosis (pH 7.1). Ultrasonography of abdomen showed swollen pancreas. The child was managed as for diabetic ketoacidosis with intravenous fluids, insulin infusion, and parenteral broad-spectrum antibiotics, but succumbed to the illness 3 days later.

***Case 2*:** A 12-year-old male child with ALL-L2 was started on induction chemotherapy, as in the previous case. Patient achieved remission after induction therapy and was put on maintenance therapy. After two months on maintenance therapy, patient developed abdominal pain and hypogastric swelling. Ultrasonography of the abdomen showed retroperitoneal mass suggestive of pseudo-pancreatic cyst with inflamed swollen pancreas and necrosis of tail of the pancreas. Blood glucose was normal (86 mg/dL). After three months of maintenance therapy, the child developed unexplained weight loss with persistent abdominal pain and fever. Investigations showed hyperglycemia (blood glucose 486 mg/dL), ketonuria, and acidosis. He was diagnosed as a case of DKA and managed with fluid correction, insulin infusion, actrapid, mixtard and supportive management including parenteral antibiotics. However, as the glycemic control was not adequate, the patient was started on glargine 5U subcutaneous twice daily along with actrapid. On follow up, he is maintaining his blood sugar on glargine and actrapid for last few weeks.

DISCUSSION

Hyperglycemia is a well-documented complication of L-asparaginase therapy for ALL [2-6]. The reported incidence of hyperglycemia ranges from 2.5-23% [1-4] and episodes usually resolve within an average of 12 days after last dose of L-asparaginase [6]. A number of pathogenic mechanisms have been proposed, such as inhibition of insulin biosynthesis, impaired insulin secretion, a reduction in insulin receptors, concurrent hyperglucagonemia, and pancreatic islet cell damage [5,7-9]. Dacou-Voutetakis, *et al*. [9] also suggested that leukemic process itself, through mechanisms as yet undetermined, could impair glucose metabolism [9].

We were able to identify five individual case reports and studies reporting DKA after L-asparaginase therapy in children with ALL. In the largest case series, DKA occurred in 6 out of 797 patients (incidence 7.5/1000) [10]. Cetin, *et al*. [4] documented DKA in 2 out of 136 (1.47%) children receiving L-asparaginase for ALL. In the past 3 years, out of 86 patients of ALL treated with L-asparaginase, two children developed DKA (2.3%).

In previously reported cases, DKA developed days to weeks after L-asparaginase therapy [2,4,8,10]. Our first

case developed DKA seven days after the last dose and in second case, the interval between the last dose of L-asparaginase and development of the pseudocyst and development of DKA were 2 and 3 month, respectively. There is no conclusive evidence about the duration of diabetogenic effect of L-asparaginase. In both our cases, both patients who developed DKA might have had precipitating factors such as acute pancreatitis, pancreatic pseudocysts, in addition to the diabetogenic effect of the drug itself.

We conclude that regular monitoring of blood sugar and periodic screening for DKA is required particularly in patients older than children with ALL who have been treated with L-asparaginase.

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