HEALTH SCIENCES AND DISEASES
The Journal of Medicine and Health Sciences

Case Report

Diabetes Secondary to Chemotherapy in Acute Lymphoblastic Leukemia. A Report of 2 Cases

Diabète secondaire à une chimiothérapie pour leucémie lymphoblastique aigue

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Keywords :acute lymphoblastic leukemia, juvenile diabetes; chemotherapy
Mots clés : leucémie lymphoblastique aigue , diabète juvénile, chimothérapie.

ABSTRACT

Diabetes is a rare complication of chemotherapy, especially in children. In the present work, we report 2 cases of diabetes induced by chemotherapy and their short-term evolution.

RÉSUMÉ

Le diabète est une complication peu fréquente de la chimiothérapie. Dans ce travail, nous reportons deux cas de diabète secondaire à une chimiothérapie pour leucémie aigue lymphoblastique.

INTRODUCTION

The use of well-designed, effective treatment protocols during the last few decades, which include L-asparaginase and prednisone among other chemotherapeutic agents, has greatly improved the long term outcome of pediatric acute lymphoblastic leukemia (ALL). These drugs are used in remission induction, and intensification phases in all pediatric protocols leading to long-term event-free survival rates of about 80% [1-2]. L-Asparaginase is reported to cause hyperglycemia in about 10% of patients and acute pancreatitis. These secondary effects are the most common reasons for stopping treatment with L-asparaginase [2-4]. Glucocorticoids are the most common cause of medication-induced hyperglycemia and diabetes mellitus, clinical conditions that can occur as a result of impaired insulin secretion or action or the destruction of pancreatic beta cells [5-6]. Few cases of medication-induced hyperglycemia or diabetes mellitus have been reported in the medical literature, and none has been reported from Saharan Africa. We therefore report two cases of diabetes which developed during the course of chemotherapy in the hematology oncology unit of the Mother and Child Centre of the Chantal Biya Foundation.

CASE PRESENTATIONS

CASE 1

A 6-year old female patient was referred to the endocrinology service with complaints of upper abdominal pains, polyuria and polydipsia. She had been diagnosed with T-cell acute lymphoblastic leukaemia (ALL) 3 months ago at the hematology-oncology unit. Induction therapy had been initiated according to the FRALLE 2000A protocol: Methotrexate intrathecal 12mg, Vincristine 1.5mg/m2/day; Doxorubicine 40mg/m2/day; L-Asparaginase 6000IU/m2 (9 doses), Dexamethasone 6mg/m2/day (5mg for 28 days, tapering off on days 30–36). She was referred to us 19 days after starting therapy and had already received 5 doses of L-asparaginase and 7 days of dexamethasone. There was no family history of diabetes or autoimmunity.

On physical examination, she was lethargic, afebrile, moderately dehydrated, with tachycardia and Kussmaul type breathing. Laboratory examinations revealed elevated HbA1c (8.5%), blood glucose of 574mg/dl (34.87mmol/L), as compared to an initial blood glucose level of 74mg/dl (4.1mmol/L) at time of diagnosis of

ALL. Serum amylase of 307 IU/l (normal) and lipase levels of 1992IU/l (12times above normal values), against initially normal values of serum amylase (39IU/l) and lipase (37IU/l). Urine dipstick revealed ketones 1+ (15mg/dL) and glucose 1+ (250mg/dL). The serum electrolyte levels were normal

The diagnosis of acute pancreatitis secondary to diabetic ketoacidosis with was made. Management consisted of 0.1IU/kg/h of rapid-acting insulin sub-cutaneously till negation of ketones in urine and rehydrated using 0.9% saline at 3L/body surface area/24h into which 1.5g of potassium chloride was added per litre of saline. No enteral feeding for 24h. After five hours, the blood glucose level was normal, there was absence of ketones in urine. Clinically, polyuria and polydipsia had stopped and there were no signs of dehydration, but there was persistent abdominal pains. The patient was put on intermediate-acting insulin twice daily at a dose of 1 IU/kg/24h (2/3 of total dose in the morning and 1/3 in the evening). Her blood glucose was controlled 7 times per day.

Chemotherapy was continued according to protocol with use of L-asparaginase and dexamethasone. She was discharged on 0.2IU/kg/day intermediate-acting insulin.

CASE 2

A 13-year old female patient followed up at the hematology oncology unit for acute lymphoblastic leukaemia (ALL) classified high risk, diagnosed seven months ago, was referred to the intensive care unit (ICU) with difficulty of breathing, polyuria, and altered consciousness.

She had been undergoing chemotherapy according to the GFAOP (Groupe Franco-Africain d'Oncologie Pédiatrique) 2005 Protocol. Induction therapy comprised intrathecal Methotrexate 15mg, Vincristine 1.5mg/m², Asparaginase 10.000UI/ m² (6 doses), Dexamethasone 6mg/ m² (days 8-22). She had no family history of diabetes or autoimmunity. She was transferred to the ICU on day 26 of her induction phase, 5 days after starting L-Asparaginase (had received 2 doses), and on a weaning dose of dexamethasone 3mg twice daily. An endocrinology consult was requested.

Physical exam revealed an unconscious patient (Glasgow coma scale of 9/15) with intense pallor and severe dehydration (heart rate 140cycles per minute, blood pressure 100/50mmHg). The patient was afebrile with Kussmaul breathing pattern.

Laboratory investigations revealed a full blood count with hemoglobin at 3.5g/dl, white blood cells at 4000/mm3, platelets at 58000/mm3. Blood glucose of 468mg/dl (25.98mmol/L), urine dipstick: ketones 3+ (80mg/dL) and glucose 2+ (500mg/dL). Serum amylase, lipase and electrolyte levels were all normal.

The patient was transfused 500ml of whole blood within 4 hours, and managed as a case of diabetic ketoacidosis secondary to chemotherapy. She was rehydrated at 3L/ml/24h with 0.9% saline and 1.5g of potassium chloride added per liter of saline. Sub-cutaneous rapid insulin at 0.1UI/kg/h was administered. Absence of ketones in urine occurred 6hours afterwards. The patient regained consciousness 16 hours after inception of therapy. She was transferred to the hematology oncology unit on intermediate-acting insulin at a dose of 1UI/kg/24h twice daily.

She continued chemotherapy according to protocol and was weaned off dexamethasone. However, her blood glucose levels remained persistently high despite the fact that L-asparaginase and dexamethasone had been stopped. She continued with insulin with decreased requirements of insulin of 0.5UI/kg after 10weeks. She has gone through the consolidation and intensification phases of chemotherapy and is presently in the maintenance phase. She was discharged on insulin therapy and is doing well.

DISCUSSION

Our first case depicts a combination of two rare complications that can be seen during the remission induction phase of treatment in ALL patients. After the diagnosis of acute pancreatitis secondary to diabetic ketoacidosis was made, the patient was weaned off dexamethasone within a week. However, high blood glucose levels persisted with ongoing use of L-asparaginase. One week after L-Asparaginase was stopped, control blood glucose, serum amylase and lipase levels were normal. When she started the re-intensification phase chemotherapy with Dexamethasone for the first 8 days there was a rise in her blood glucose levels (average 2.45mg/dl) which made us increase her insulin doses from 0.2IU/kg/day to 0.5IU/kg/day. We came to the conclusion that in this patient, L-asparaginase and glucocorticoids are both incriminated in her hyperglycemia and may be transient.

The elevated HbA1c of 8.5% also reveals a period of hyperglycemia prior to presentation although there is no past history of diabetes or autoimmunity in the family.

There is a reported prevalence of 16.2% pancreatic toxicity during treatment with L-asparaginase, which can lead to hyperglycemia and diabetes mellitus in 2.5% - 23% of patients [2,7,8].

Hyperglycemia caused by L-asparaginase may be influenced by concomitant use of steroids [9]. We find hyperglycemia associated with the use of L-asparaginase and glucocorticoids in 10-15% of pediatric patients with ALL, with a prevalence of DKA of only 0.8% [10].

We didn't have risk factors for the development of DKA such as age and obesity in our first patient, but it is possible that the combination of L-asparaginase, glucocorticoids and acute pancreatitis acted as synergistic factors for the development of DKA. We also had a resolution of our patient's glycemia to normal levels each time the causative agent was stopped, which may insinuate a self-limiting, transient process.

In our second case, age was a risk factor for the development of DKA, and a combination of L-asparaginase and glucocorticoids use. The patient had persistently high blood glucose levels regardless of the phase of chemotherapy she was undergoing and the drugs being used.

CONCLUSION

Physicians treating ALL patients should be aware of the possibility of the development of complications like acute pancreatitis and diabetic ketoacidosis associated with L-asparaginase and glucocorticoid use. We therefore recommend monitoring for hyperglycemia and acute pancreatitis during chemotherapy in these children, in order to reduce the adverse events linked to these complications. In the case where one must continue with the drug that induced diabetes, concomitant insulin therapy is the best option.

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