Severe Hypoglycemia in a Patient with Acute Renal Failure due to Tumor Lysis Syndrome

Alla Shnaider MD, Anna Basok MD, Boris Rogachev MD, D. Tovbin MD and Marcus Mostoslavsky MD

Department of Nephrology, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

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Several mechanisms have been described in the literature to explain the incidence of hypoglycemia in hematologic malignancies. These include: increased glucose metabolism in neoplastic tissue, synthesis of insulin-like growth factor-II by tumors, insulin autoimmune syndrome, and high levels of cytokine production following chemotherapy. However, little data are available on hypoglycemia in patients with tumor lysis syndrome. We present a patient with acute renal failure due to tumor lysis syndrome that appeared after treatment with fludarabine for chronic lymphocytic leukemia. At the same time, severe life-threatening hypoglycemia was diagnosed. With improvement in the clinical and laboratory status, the patient's hypoglycemia was resolved. Our report describes a case of a rarely seen syndrome and submits several hypotheses that might explain this phenomenon, while still leaving it open for further clarification.

Patient Description

A 60 year old woman was admitted to the Department of Nephrology at the Soroka Medical Center because of muscle weakness, paresthesia in the toes and fingers, and vomiting. The patient had suffered from chronic lymphocytic leukemia for several years with recent lymphoma transformation. She had been treated with fludarabine 3 days prior to admission without appropriate hydration. Physical examination revealed signs of hypovolemia such as orthostatic hypotension, plane jugular veins and aneuria. Body temperature was normal.

On admission, laboratory findings showed: blood urea nitrogen 170 mg/dl, creatinine 6.1 mg/dl, sodium 132 mEq/L, potassium 9.9 mEq/L, serum pH 7.07, HCO_3 6 mEq/L, glucose 29 mg/dl, uric acid 45 mg/dl, calcium 6.3 mg/dl, phosphorus 37 mg/dl, lactate dehydrogenase hormone 427–590, white blood cells 1,440, hemoglobin 10.0 g/dl, platelets 137. Electrocardiogram revealed idioventricular rhythm, flattening of P waves, and widening of the QRS complex.

After initial treatment for hyperkalemia in the emergency ward, hemodialysis was performed and hydration initiated. At admission, severe symptomatic hypoglycemia was detected (glucose 29 mg/dl) and intravenous dextrose was started with fast correction of glucose levels, which again fell below 30 mg/dl immediately after cessation of treatment.

Hypoglycemia persisted during the first 5 days of hospitalization, with subsequent complete resolution. Hemodialysis was discontinued after three sessions, with significant improvement in the patient's clinical status and marked improvement in renal function. The patient was not known to suffer from diabetes mellitus. The laboratory data are presented in Table 1.

Table 1. Patient's laboratory results

Tests	Hypoglycemic time	After* resolution	Normal values
Creatinine (mg/dl)	6.1	0.91	0.5–1.1
Blood urea nitrogen (mg/dl)	170	22	6–20
Uric acid (mg/dl)	45	4.4	3.4–7
Phosphorus (mg/dl)	37	3.5	2.7–4.5
Glucose (mg/dl)	29	93	60–115
Insulin (μ/ml)	15	17	5–25
C-peptide (ng/ml)	21.6	3.58	0.8–4
IGF-1 (nmol)	17.2	15	11.6–48.4
Cortisol (g/dl)	23	10	5–25
IL-6	Undetectable levels	Undetectable levels	
TNF	Undetectable levels	Undetectable levels	

* 2 months after the hypoglycemic episode.

Comment

It is well known that hypoglycemia may be seen in the clinical course of several tumors. We present a case of acute renal failure due to severe tumor lysis syndrome accompanied by life-threatening hypoglycemia with high levels of C-peptide, inappropriately high for hypoglycemia. Sepsis was ruled out as a possible cause of the hypoglycemia. Furthermore, neither the patient nor any member of her family was known to have been treated by oral hypoglycemic drugs at any time. An assay for sulfonylurea was therefore not considered necessary in this case.

The most common cause of hypoglycemia is increased glucose metabolism in neoplastic tissue with a high histologic grade of malignancy and a high proliferation rate, as in lymphoma and other hematologic malignancies [1,2]. However, our patient had normal glucose levels prior to chemotherapy, and hypoglycemia appeared only after commencement of chemotherapy and the development of the tumor lysis syndrome.

The role of IGF-II has been investigated in a variety of tumors such as hepatocellular carcinoma and non-islet cell tumors [3]. Furthermore, IGF-II is known to have insulin-like activity that may reduce glucose plasma levels, but high IGF-II levels are usually accompanied by low insulin values, which was not the case in our patient. Hence, although IGF-II levels were not

IGF = insulin-like growth factor

measured in our patient, this mechanism can be ruled out as a possible cause of the hypoglycemia. There are reports in the literature of insulin autoimmune syndrome with hypoglycemia, hyperinsulinemia, and insulin and pro-insulin binding autoantibodies in patients who had not been exposed to exogenous insulin in the past [4]. Usually plasmapheresis is used to reduce the antibody pool. In our patient the hypoglycemia resolved spontaneously without the need for additional therapy.

It is known that several cytokines (interleukins 1 and 6, tumor necrosis factor) may induce hypoglycemia, loss of body weight, and anorexia. Investigations have shown that IL-1 may be responsible not only for elevated insulin levels but also for elevated glucagon levels. This remains a controversial issue. Although it was anticipated that high levels of cytokine-interleukins would be found in a patient with tumor lysis syndrome treated by chemotherapy, in our patient IL-1 and TNF-α levels in the serum were normal.

Extrapancreatic production of insulin by tumor cells was unlikely since the insulin and glucose levels normalized soon after resolution of the renal failure. Furthermore, the patient was not treated by drugs known to stimulate endogenous insulin production in the pancreas.

Despite the fact that renal failure may be a possible explanation for the C-peptide and insulin elevation due to reduced clearance of insulin in the kidney [5], hypoglycemia is an unusual occurrence in this setting. Thus, the mechanism underlying the hypoglycemia needs further investigation.

IL = interleukin

TNF = tumor necrosis factor

References

1. Lapela M, Leskinen S, Minn HR, et al. Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorine-18-fluorodeoxyglucose. *Blood* 1995; 86(9):3522–7.
2. Durig J, Feidler W, de Wit M, Steffen M, Hossfeld DK. Lactic acidosis and hypoglycemia in a patient with high-grade non-Hodgkin's lymphoma and elevated circulating TNF-alpha. *Ann Hematol* 1996;72(2):97–9.
3. Mizuta Y, Isomoto H, Futuki Y, et al. Acinar cell carcinoma of the pancreas associated with hypoglycemia: involvement of "big" insulin-like growth factor-II. *J Gastroenterol* 1998;33(5):761–5.
4. Chen CH, Huang MJ, Huang BY, et al. Insulin autoimmune syndrome as a cause of hypoglycemia – report of four cases. *Chang Keng I Hsueh* 1990;13(2):134–42.
5. Ramires G, O'Neill WM Jr, Bloomer HA, Jubiz W. Serum C-peptide in renal failure following stimulation of pancreatic secretion. *Clin Nephrol* 1979;11(6):297–301.

Correspondence: Dr. A. Shnaider, Dept. of Nephrology, Soroka Medical Center, P.O. Box 151, Beer Sheva 84101, Israel.
Phone: (972-8) 640-0477
Fax: (972-8) 640-003