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Case Report

Severe and persistent hypoglycemia with lactic acidosis in an elderly lady with type 2 diabetes mellitus and lymphoma\leukemia: A rare case report

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ABSTRACT

We present here a case of hypoglycemia and lactic acidosis in an elderly diabetic lady with underlying leukemia\lymphoma. Possible mechanisms responsible for both hypoglycemia as well as lactic acidosis are discussed. The case emphasizes the need for thorough chasing of all clinical leads obtained from history taking, physical examination, as well as laboratory evaluation in order to avoid getting misled by apparently obvious diagnosis. To the best of the author's knowledge, this is the first time such a case is reported in Indian literature.

1. Introduction

Hypoglycemia, a known complication of malignancy, has etiologies like production of an insulin-like substance by malignant cells, impaired liver function secondary to tumor infiltration, glucose consumption by malignant cells, and autoantibodies to the insulin receptor resulting in insulin-like effects. The proposed mechanisms for lactic acidosis, another known complication in patients with hematological malignancies, include over expression of hexokinase, reduction in hepatic lactate clearance, elevated levels of TNF-α, thiamine deficiency, or microvasculature embolization resulting in hypoperfusion and anaerobic metabolism [1].

The concurrence of hypoglycemia and lactic acidosis is rare. The differential diagnosis includes hematological malignancies, septicemia, renal insufficiency, mitochondrial dysfunction, malaria and certain drugs including biguanides. The concurrence of hypoglycemia and lactic acidosis has high mortality rate in spite of thorough investigations and early treatment.

2. Case report

A hemodynamically stable 74-year old female was admitted in an extremely exhausted and drowsy state with history of severe loss of appetite and severe weakness for 2 days. The patient was a known diabetic for 12 years, for which, she was taking glimepiride (1 mg) twice a day until 2 days prior to her hospitalization. Physical examination revealed a massive and firm-to-hard hepatomegaly, there were no other positive findings. An ultrasonography of the abdomen showed hepatomegaly with fatty changes, and a small calculus in gall bladder. A computed tomography scan of abdomen confirmed USG findings, showing fatty infiltration of liver with hepatomegaly, and thickened gall bladder wall with fluid accumulation around it suggestive of cholecystitis, but no gall stones.

Based on the history, physical examination, laboratory investigations (Table 1), the primary working diagnosis was hypoglycemia precipitated by reduced food intake with some contributions from glimepiride, though it was discontinued 2 days earlier. Possible additional contribution towards hypoglycemia due to hepatic malignancy, particularly leukemia\lymphoma was suspected.

2.1. Management

The patient was initiated on 25% glucose (50 mL bolus), followed by 5% glucose intravenously (80 mL\h). Despite continuous intravenous infusion with intermittent boluses of 25% glucose from time to time in addition to oral feeds, she repeatedly developed hypoglycemia and her clinical status improved only partially and temporarily over the next 3 days. Her sequential capillary blood glucose readings done at 2–4 hourly intervals after initial venous plasma glucose reading at admission were 47 mg%, 85 mg%, 40 mg %, and 29 mg% respectively.

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Table 1
Laboratory investigations.

Laboratory investigation	Day 1	Day 4	Day 5	Normal value
Random plasma glucose at admission	56 mg/dL (random)		116 mg/dL (fasting)	<200 mg/dL
Serum creatinine	1.11 mg/dL		2.69 mg/dL	0.6–1.4 mg/dL
Serum bilirubin	1.42 mg/dL		6.7 mg/dL	0.0–1.0 mg/dL
Serum alkaline phosphatase	102 IU/L		197 IU/L	80–306 IU/L
SGOT	425 IU/L		1060 IU/L	0–49 IU/L
SGPT	455 IU/L		520 IU/L	0–49 IU/L
Hemoglobin	11.5 g/dL	9.8 g/dL		12–16 g/dL
Total WBC count	8600 cells/mm^3	26800 cells\mm [3]	40600 cells\mm [3]	5000–10000 cells\mm [3]
Serum electrolytes	Within normal limits			
Differential WBC count	Within normal limits	82% neutrophils, with 15% band forms, 18% lymphocytes	65% neutrophils, with 13% band forms	
Peripheral smear	Normal			
Serum alpha feto protein	Not detectable			<10 ng/mL
Serum protein electrophoresis	No monoclonal gammopathy			
Serum lactate		>20.0 mmol\L		0.7–2.1 mmol\L
Serum pyruvate		0.29 mmol\L		0.36–0.57 mmol\L
Fasting serum insulin		4.7 uIU\mL		6-27 uIU/mL
HbA1c	7.6%			<5.7%

The patient deteriorated rapidly, developed acidotic deep rapid breathing, and continued to have repeated hypoglycemia. On day 4, deterioration in clinical status accelerated and arterial blood gas showed severe metabolic acidosis (Table 2). Her IGF levels could not be measured due to lack of facilities. The patient did not respond to intravenous sodium bicarbonate given 6 hourly. Her blood sample was sent for culture and she was put on empirical antibiotic treatment with parenteral piperacillin–tazobactam and meropenem.

On day 5 her clinical condition worsened, she had acidotic breathing and acute hepatic failure. Eventually she developed hypotension and bradycardia and died. Considering her age, very rapid deterioration in her health and a strong possibility of hematological malignancy, the patient's relatives had given “Do not resuscitate” instructions; thus, ventilatory support and hemodialysis was not given. Post mortem liver biopsy was performed after obtaining informed consent from relatives. Histological examination revealed liver involvement by lymphoma\leukemia in diffuse nodular and sinusoidal pattern, diagnostic of haematolymphoid leukemia\lymphoma.

3. Discussion

There are various pathogenetic mechanisms that explain hypoglycemia in patients with malignancies. Excessive production of insulin or insulin-like substances by cancer cells, increased glucose consumption by large tumors, or alteration in glucose homeostasis are the underlying causes of hypoglycemia in malignant conditions [2]. Metabolic disorders such as type B lactic acidosis occur in patients with hematological malignancies such as lymphoma, leukemia and multiple myeloma [3,4].

Table 2
Arterial blood gas findings at different time points.

Day	pH	pCO_2(mm Hg)	pO_2(mm Hg)	HCO_3act (mmol/L)
Day 2	7.359	16.0 ↓	83.5	8.8
Day 3	7.258 ↓	20.2 ↓	92.8	8.8
	7.259 ↓	28.0 ↓	75.1	12.3
Day 4	7.238 ↓	14.1 ↓	63.6 ↓	5.9
	7.278 ↓	29.8 ↓	85.2	13.7
Day 5	7.164↓	22.6 ↓	90.2	8.0
	7.143↓	21.8 ↓	56.3 ↓	7.3

Reference range.
pH, 7.35–7.45.
pCO_2, 32.0–45.0.
pO_2, 75.0–100.0.

In malignancies, though rare, the association of hypoglycemia and lactic acidosis is well-documented, particularly in lymphoproliferative tumors like lymphomas. This is pronounced due to an ardent consumption of glucose via the glycolytic pathway affiliated with lactate production, even under aerobic circumstances, and is endorsed as the “Warburg effect”. An alternate fascinating likelihood explaining this effect is an oncogenic switch, which shifts metabolism in the direction of a glycolytic state [1].

Lactic acidosis associated with hematological malignancy carries grave prognosis [5], and resolves only if the lymphoma\leukemia is successfully treated. Chan et al. reviewed literature on 28 cases of lymphoma-induced lactic acidosis and reported their own case. Eleven of these 28 patients had hypoglycemia [6]. In addition, a solitary case of Burkit's lymphoma associated with lactic acidosis and hypoglycemia has been reported [7].

Though few clinical and laboratory features of our patient closely resembled those described in literature, there were some differences. In our case, symptoms were very acute and deterioration in condition was very rapid. A known long standing diabetes status also differentiated our case. There was a strong possibility of getting misled, at least temporarily, due to “known diabetes on sulphonylurea” status. Moreover, the diagnosis of lymphoma\leukemia was not known at the time of presentation and was established only post mortem. [Normal fasting plasma insulin level ruled out glimepiride induced hypoglycemia.] The persistent hypoglycemia in spite of continuous intravenous glucose infusion could be explained by a phenomenon of infused glucose, acting as a raw material for lactate production by hepatic tumor cells.

Similar to our findings, Doolittle et al. reported nine patients with lymphoma-associated lactic acidosis, wherein extensive hepatic tumor involvement was seen at autopsy [8].

4. Conclusions

Lactic acidosis and concurrent hypoglycemia are ominous signs in patients with lymphoma and leukemia and carry high mortality. Prompt diagnosis of lactic acidosis and underlying hematological malignancy, and early treatment is the only way to achieve

complete resolution of lactic acidosis and concurrent hypoglycemia. The described case emphasizes the need for thorough chasing of all clinical leads obtained from history taking, physical examination, as well as laboratory evaluation in order to avoid getting misled by apparently obvious diagnosis.

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