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Case Series

Non symptomatic hypoglycemia in cancer patients: a case series in a tertiary care cancer hospital

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ABSTRACT

Sever hypoglycemia when blood glucose level <54 mg/dl is a grave condition and patients manifest with impaired cognitive function. Glucose is the key energy source for brain. In normal physiological condition glucose metabolized aerobically to produce energy in the form of ATP after glycolysis. In hypoglycemia like in condition of starvation or in any pathologically low blood glucose level, brain depends on ketone bodies to fulfill its energy requirement. In cancer patients due to Warburg effect there is aerobic fermentation of glucose leads to production of ketone bodies and lactic acid, which fulfill the energy requirement of brain and patients doesn't show symptoms of hypoglycemia

Keywords: Hypoglycemia, Warburg effect, Ketone bodies

INTRODUCTION

Hypoglycemia, blood glucose level <54 mg/dl is clinically significant when cognitive function is impaired and requires blood glucose correction.[1] It is common condition in starvation and in known diabetic patients who are on insulin therapy or on oral hypoglycemic drugs. Hypoglycemia commonly presents with symptoms of altered sensorium, fatigue, irritability, coma and altered gait. Hypoglycemia is a life-threatening condition in both healthy as well as in person with comorbidities and it needs immediate dextrose infusion. Glucose is an indispensable source of energy in the form of ATP for normal physiological activity of brain function. In hypoglycemia due to depletion of ATP, the normal physiology of brain is altered and symptoms of hypoglycemia are manifested.

Here is the case series of three patient having malignancy who came to hospital without any symptoms of hypoglycemia but incidental finding of low plasma glucose on routine blood work up. Though hypoglycemia may be artifactual in leukemia patient due to in vitro glycolysis by abnormal leucocytes, but in the reported cases none of the patients had leukemia, and sample for glucose analysis was collected in fluoride vial, which prevents *in vitro* glycolysis.[2] Blood glucose level of all three patients was <54 mg/dl in two sample replicates collected at the same time. All the three patients were fully conscious and well oriented with normal gait. Test for the biochemical parameters (LFT, KFT, blood sugar) have been performed on Siemens dimension EXL 200, hematological parameters (Hemoglobin, TLC, platelet count) were done on Siemens ADVIA 2120i and tumor markers were analyzed on Siemens ADVIA Centaur CP.

CASE SERIES

Case 1

A 40-year female came with history of fever and loss of weight since last one year, diagnosed as metastatic carcinoma pancreas with no history of diabetes mellitus. CECT abdomen showed multiple lesions in both lobes of liver with mass lesion in pancreatic body with retro

pancreatic extension. Her peripheral blood examination report is shown in Table 1.

Table 1: Test parameters of case 1.

Tests	Results
Biochemistry report	
RBS	36 mg/dL
AST	33.8 U/L
ALT	12.0 U/L
Serum total protein	6.62 g/dL
Serum albumin	3.25 g/dL
Serum total bilirubin	0.69 mg/dL
Serum urea	18.4 mg/dL
Serum creatinine	0.82 mg/dL
Immunoassay report	
Serum CEA	46.79 ng/mL
Serum CA19.9	99691.8 U/mL
Hematology report	
Haemoglobin	10.60 g/dL
WBC count	13.01×10^9/L
Platelets	519×10^9/L

Case 2

A 41-year male was diagnosed with pancreatic malignancy with metastatic multicentre hepatocellular carcinoma. CECT was suggestive of tail of pancreas mass with loss of fat planes, hepatic and splenic metastasis with regional and retroperitoneal metastatic adenopathy. Peripheral blood examination showed the following results as shown in Table 2 and blood culture showed no growth of any organisms after 5 days of incubation.

Table 2: Test parameters of case 2.

Tests	Results
Biochemistry report	
RBS	22 mg/dL
AST	77 U/L
ALT	236 U/L
Serum total protein	6.4 g/dL
Serum albumin	2.7 g/dL
Serum total bilirubin	0.40 mg/dL
Urea	16 mg/dL
Creatinine	0.75 mg/dL
Immunoassay report	
Serum CA-19.9	20.10 U/mL
Serum CEA	5.6 ng/mL
Serum AFP	1.6 ng/mL
Hematology report	
Haemoglobin	13.10 g/dL
WBC count	8.78×10^9/L
Platelets	327×10^9/L

Case 3

A 75-year male was diagnosed as carcinoma prostate and no history of diabetes mellitus. CECT scan of the thorax, abdomen and pelvis was suggestive of metastatic hepatic lesions noted in both the lobes of liver along with retroperitoneal and pelvic adenopathy. He was operated for TURP and came for routine health check-up. On routine blood examination the results were as follows shown in Table 3.

Table 3: Test parameters of case 3.

Tests	Results
Biochemistry report	
RBS	34 mg/dL
AST	74 U/L
ALT	111 U/L
Serum total protein	7.2 g/dL
Serum albumin	3.2 g/dL
Serum total bilirubin	0.42 mg/dL
Urea	55 mg/dL
Creatinine	2.42 mg/dL
Immunoassay report	
Serum PSA	313.81 ng/mL
Hematology report	
Haemoglobin	11 g/dL
WBC count	6.75×10^9/L
Platelets	182×10^9/L

DISCUSSION

Hypoglycemia is a life-threatening condition in both healthy as well as in person with comorbidities. In a normal physiology brain utilises glucose as energy source while in hypoglycemia it switches to utilise ketone bodies to fulfil its energy requirement.[3] In case of starvation or any pathological condition which leads to hypoglycemia brain utilises ketone as the main source of energy which helps survive the individuals even under very low blood glucose levels.[4,5] Monocarboxylate transporters (MCTs) present on the membrane of endothelial cells and astrocytes allow lactate and ketone bodies to cross blood brain barrier which are the main substitute fuels for the brain.[6] In normal cell glycolysis is followed by aerobic oxidation of pyruvate in Krebs cycle to generate energy equivalents in the form of NADPH and FADH.[7] Cancer cell follow a different aerobic glycolysis where pyruvate is converted to 3-hydroxy-butyrate and L-lactate which act as fuel for tumour growth and metastasis.[8] In tumour cells the normal aerobic glucose metabolism is shifted to specialised fermentation leading to formation of ketones due to Warburg effect.[9] Otto Warburg observed that glucose uptake by cancer cells was more than that the surrounding cells. Moreover, cancer cells ferment glucose to produce lactate in the presence of sufficient oxygen.[10] It is a modified form of cellular metabolism found in cancer cells, leads to conversion of pyruvate into lactate with generation of ketone bodies. Pavlides et al made an observation that 3-hydroxy-butyrate (a ketone body) in cancer patients is about four times more than the normal individuals.[11] Many recent studies also suggest that changes in the cellular environment increases the demand

of ATP, which is fulfilled by rapid aerobic glycolysis.[12] It can be concluded that in cancer patients' asymptomatic hypoglycemia is caused due to Warburg effect in the absence of other underlying causes. It is thus important to investigate the causes of asymptomatic hypoglycemia on time, especially in cancer patients.

CONCLUSION

Unlike normal cells Cancer cells divide rapidly and form a microenvironment of hypoxia so that these-cell can survive in oxygen deficient environment. It is also observed that glucose uptake in cancer cells are more than normal cells and cancer cells perform a specialised type of glucose metabolism i.e., aerobic fermentation of glucose leading to formation of ketone from pyruvate. These ketones are act as fuel for cancer cells. Cancer patients can survive even in hypoglycaemic condition, due to presence of ketones as energy source.

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