

Case Report

Confirmed Hypoglycemia Without Whipple Triad: A Rare Case of Hyper-Warburgism

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Abbreviations: ACH, Ademolus classification of hypoglycemia; ALS, acid labile subunit; ATP, adenosine 5'-triphosphate; BG, blood glucose; CT, computed tomography; FDG, ¹⁸F-fluorodeoxyglucose; GH, growth hormone; HbA_{1c}, glycated hemoglobin; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IV, intravenous; NADPH, nicotinamide adenine dinucleotide phosphate; NICTH, non-islet cell tumor hypoglycemia; PET, positron emission tomography.

Received: 14 August 2020; Editorial Decision: 12 November 2020; First Published Online: 21 November 2020; Corrected and Typeset: 15 December 2020.

Abstract

Spontaneous hypoglycemia in nondiabetic patients poses a diagnostic challenge. Hypoglycemia in malignancy has several etiologies; an extremely rare mechanism is the Warburg effect causing excess lactate production and avid glucose consumption. We describe the clinical course of a 52-year-old man admitted for chest wall mass and severe but asymptomatic hypoglycemia. Laboratory workup was obtained for insulin vs noninsulin-mediated hypoglycemia, and biopsy of the chest wall mass and ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) scan were performed. D10 infusion and intravenous/oral steroids started for severe hypoglycemia. Chemotherapy was initiated after biopsy, and blood glucose (BG) and lactate levels followed with clinical response in tumor size and changes in PET/CT. Investigations were significant for venous BG in the 40s (Ademolus Classification of Hypoglycemia grade 2 hypoglycemia), plasma insulin of less than 2 μU/mL (2–20 μU/mL), C-peptide of 0.2 ng/mL (0.8–6.0 ng/mL), insulin-like growth factor 2 (IGF-2) of 113 ng/mL (333–967 ng/mL), serum lactate of 16 mmol/L (0.5–2 mmol/L), and albumin of 2.3 g/dL (3.4–5.4 g/dL). Biopsy showed diffuse large B-cell lymphoma, and PET revealed highly FDG-avid disease in the chest, abdomen, and pelvis, but no FDG uptake was seen in the brain. Hypoglycemia and lactic acidosis improved remarkably after chemotherapy. PET/CT at 4 weeks showed complete metabolic response with reappearance of physiological FDG uptake in the brain. Noninsulin-mediated hypoglycemia was likely due to the combination of profound malnutrition and rapid glucose use by cancer cells. The patient presented with exaggerated

Warburg effect (hyper-Warburgism), evident by extreme glucose consumption, severe lactic acidosis, and large tumor burden on PET/CT. Absence of cognitive symptoms was probably due to use of lactate by the brain. Chemotherapy corrected these abnormalities rapidly, and must be instituted in a timely manner.

Key Words: hypoglycemia, lactic acidosis, Warburg effect, lymphoma, chemotherapy

Spontaneous hypoglycemia in patients without diabetes poses a diagnostic challenge and its cause remains unelucidated in many cases. Hypoglycemia in malignancy can have several underlying etiologies: hepatic or adrenal insufficiency, insulin or insulin receptor autoantibodies, production of an insulin-like substance by malignant cells, or large tumor burden causing excessive glucose consumption [1, 2]. Paraneoplastic secretion of insulin or insulin-like growth factors (IGF-1, IGF-2, or partially processed precursors of IGF-2 ['big'-IGF-2]) is frequently associated with tumors of mesenchymal, epithelial, and neuroendocrine origin [3]. The occurrence of lactic acidosis in malignancy is a well-described entity especially in lymphoproliferative disorders like lymphomas [4-6] but its association with severe asymptomatic hypoglycemia is an extremely rare phenomenon [7, 8].

This association can be explained by the Warburg effect, wherein metabolism in cancer cells shifts toward glycolytic pathways from oxidative phosphorylation, even under aerobic conditions, leading to excessive glucose consumption with concomitant excess lactate production [9]. The Warburg effect has been documented for more than 90 years and extensively studied, but despite the interest, its function in tumor biology is not fully understood. ^{18}F -fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) scan is a functional/metabolic imaging method used to assess tumor burden and is largely based on the principle of the Warburg effect [10]. Here we report a challenging case of severe but asymptomatic hypoglycemia with severe lactic acidosis in a patient with diffuse large B-cell lymphoma (non-Hodgkin lymphoma). The Whipple triad may not be applicable to all cases of hypoglycemia as some medical literature suggests [11]. Our case report further supports this scientific fact in a nondiabetic population with hypoglycemia. We also briefly review the Warburg effect, its pathophysiology, and its role in tumor proliferation.

1. Case Description

A 52-year-old man with a history of hypertension and chronic obstructive pulmonary disease was admitted to the county hospital for complaints of an 80-pound (36-kg) weight loss, severe malnutrition, and right chest wall

mass and right arm swelling. He reported a progressively increasing chest wall mass for the past 5 months, but profoundly worsening in the 1 week prior to presentation along with symptoms of fatigue, loss of appetite, and right arm swelling. However, he denied fever, night sweats, neuroglycopenia, or any adrenergic symptoms. He had no classic signs of hypoglycemia and no behavioral or cognitive impairment. Physical examination revealed tachycardia, white patches on the oral mucosa and posterior tongue, and an indurated mass on the right chest wall with extensive swelling of the right upper limb. Initial laboratory investigations were significant for blood glucose (BG) of 41 mg/dL (60-100 mg/dL) (Ademolus classification of hypoglycemia [ACH] grade 2 hypoglycemia) [12, 13], serum lactate of 16 mmol/L (0.5-2 mmol/L), bicarbonate of 15 mEq/L (20-24 mEq/L), anion gap of 26 mEq/L (3-10 mEq/L), albumin of 2.3 g/dL (3.4-5.4 g/dL), and normal renal and liver function tests including coagulation profile. There were no signs of sepsis, acute hypoxemia, or circulatory failure. An arterial blood gas obtained showed a pH of 7.42 and oxygen saturation of 97.8%. A computed tomography (CT) of the chest/abdomen/pelvis showed bilateral pleural effusions; a large, ill-defined heterogeneous mass along the anterior chest wall; and a 2.5-cm lesion in the liver.

Fingerstick glucose readings were persistently in the 20s (ACH grade 3 hypoglycemia) [12, 13] with no sustained response to multiple boluses of intravenous (IV) dextrose and glucagon. The patient was started on a dextrose 5% drip and IV methylprednisolone drip that maintained his BG levels in the 100s. The IV methylprednisolone and dextrose drip were titrated down and stopped to investigate the cause of the hypoglycemia. The patient's BG dropped to 39 mg/dL (ACH grade 3 hypoglycemia) [12, 13] and corresponding laboratory values showed a plasma insulin level of less than 2 $\mu\text{U}/\text{mL}$ (2-20 $\mu\text{U}/\text{mL}$), C-peptide of 0.2 ng/mL (0.8-6.0 ng/mL), and a ketone level of 0.2 mmol/L (< 0.4 mmol/L). IGF-1 and IGF-2 were 26 ng/mL (61-200 ng/mL) and 113 ng/mL (333-967 ng/mL), respectively. Glycated hemoglobin (HbA_{1c}) was 4.9%. Cortisol level could not be checked because he was on high-dose steroids. He underwent ultrasound-guided biopsy of the chest wall mass, with pathology showing diffuse large B-cell lymphoma. Brain magnetic resonance imaging did not

show any intracranial lesions. The patient was restarted on dexamethasone 1 mg twice daily for recurrent hypoglycemia and was discharged with follow-up at the local comprehensive cancer center per his wishes.

One week after discharge, the patient presented to the tertiary care cancer center with complaints of persistent weakness, low appetite, and with a continued uncomfortable right chest wall mass and worsening of the aforementioned right arm swelling. Laboratory investigations were again significant for BG of 36 mg/dL (60-100 mg/dL) (ACH grade 3 hypoglycemia) [12, 13], potassium of 5.1 mg/dL (3.5-5 mg/dL), lactate dehydrogenase 7735 mg/dL (313-618 mg/dL), and a fingerstick glucose of 52 mg/dL (ACH grade 2 hypoglycemia) [12, 13]. Given the biopsy-proven lymphoma and significant clinical tumor burden, chemotherapy with rituximab, dose-adjusted etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone (DA EPOCH) was initiated day 1 of hospitalization. He was started on D5 infusion with IV dextrose boluses for severe hypoglycemia. However, his BG values remained persistently low (36-54 mg/dL) (ACH grade 3 hypoglycemia to ACH grade 2 hypoglycemia) [12, 13] despite intervention, and peak lactate was 15.4 mmol/L (0.5-2 mmol/L) (Fig. 1). D5 infusion was changed to D10 and he was transferred to the intensive care unit. By day 3, his BG levels started improving on the D10 infusion (see Fig. 1). After 8 hours of normal glucose levels, the D10 infusion was discontinued to facilitate a ^{18}F -FDG-PET/CT scan for evaluation of tumor burden.

The ^{18}F -FDG-PET/CT scan revealed extraordinary diffuse, high-volume infiltrative disease of soft tissue in the

chest, abdomen, and pelvis as well as skeletal involvement of the left vertex, upper and midfrontal-parietal skull, and proximal right femoral diaphysis identifying a stage IV bulky disease (Fig. 2A). Interestingly, the brain showed profoundly low metabolic activity with areas of gray matter measuring a standardized uptake value of 0.9 to 1.2. Chemotherapy with DA EPOCH and intrathecal methotrexate prophylaxis was continued, with clinical evidence of decreased tumor size. BG values now ranged from 100 to 200 mg/dL, without dextrose infusions or steroids, and lactate levels started decreasing, reaching 8.7 mmol/L by day 5 (see Fig. 1). The patient was subsequently transferred back to the medical wards without any complication and discharged after completing the first cycle of chemotherapy. A repeat ^{18}F -FDG-PET/CT obtained approximately 4 weeks post chemotherapy completion showed complete metabolic response with the reappearance of physiological uptake of FDG in the brain (Fig. 2B). At 6 weeks' follow-up in the lymphoma clinic, his serum lactate level normalized (1.2 mmol/L), serum albumin was 2.7 g/dL, and BG was 191 mg/dL. Thereafter, his serum albumin levels still ranged from 2.4 to 3.0 g/dL but he remained euglycemic. The patient subsequently completed 6 cycles of chemotherapy without any signs of disease relapse.

2. Discussion

Hypoglycemia can be a manifestation of a large tumor burden in malignancy. Most patients with hypoglycemia are symptomatic, especially when BG is less than 55 mg/dL (ACH grade 2-4 hypoglycemia) [12, 13]. However, our

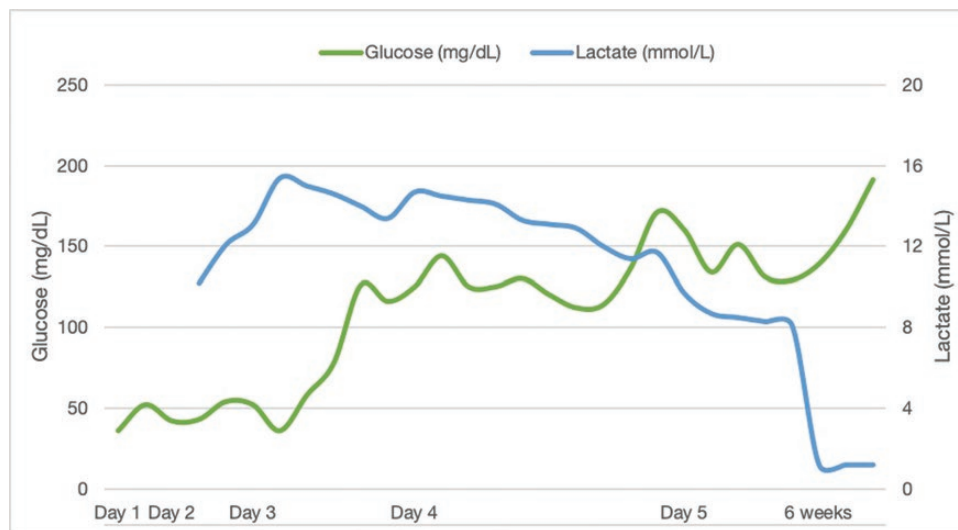


Figure 1. Blood glucose (in green, milligram per deciliter [mg/dL]) and lactic acid (in blue, millimole per liter [mmol/L]) values during comprehensive cancer center hospitalization. The patient started chemotherapy (dose-adjusted etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone [DA EPOCH]) day 1 of hospitalization. D5 infusion converted to D10 infusion on day 2. Blood glucose levels started improving by day 3 and serum lactate levels decreasing gradually, reaching 8.7 mmol/L by day 5. Lactate levels normalized at week 6, when checked in clinic at follow-up. A, Prechemotherapy scan. B, Scan at 4 weeks (after first cycle).

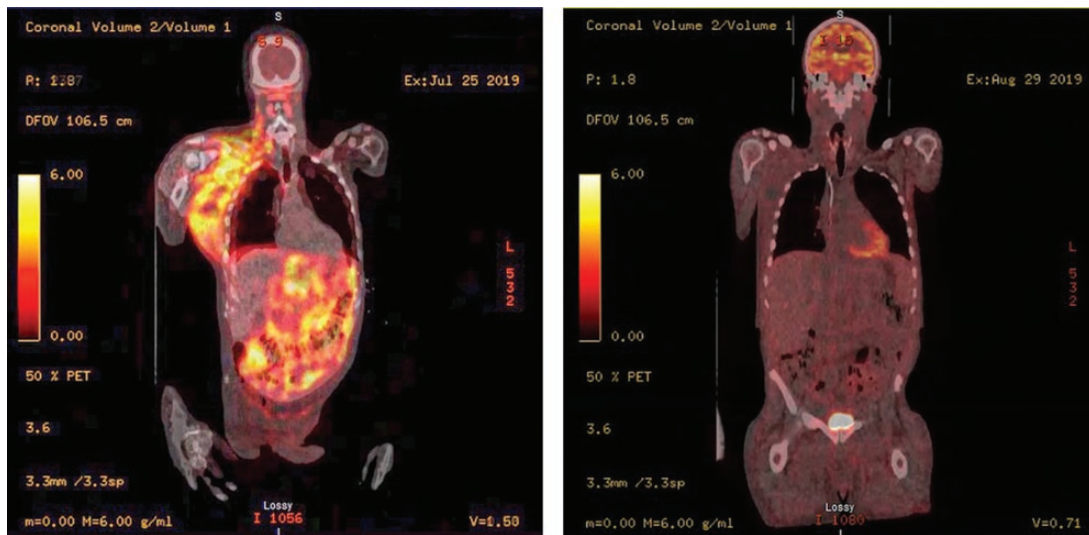


Figure 2. A and B, ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography imaging prior to and post chemotherapy treatment showing complete metabolic response and return of physiological FDG uptake in brain.

patient presented with severe hypoglycemia with BG in the 30s to 40s (ACH grade 3 and grade 2 hypoglycemia) [12, 13] requiring continuous IV dextrose infusion and IV steroids, but no typical neuroglycopenic or adrenergic symptoms. Although his HbA_{1c} was 4.9%, which estimates the BG to be approximately 94 mg/dL, his clinical condition deteriorated severely in the 5 to 7 days prior to presentation, suggesting that the development of hypoglycemia was an acute event. Therefore, HbA_{1c} , which estimates the average BG over 3 months, might not be truly reflective of his current glycemic status, and also hypoglycemia is very poorly correlated with HbA_{1c} and tends to be episodic. His severe malnourished state with an albumin of only 2.3 g/dL is certainly a confounding factor in the evaluation of hypoglycemia. It is not uncommon for patients with malnutrition to present with persistent low venous glucose largely due to poor glycogen stores and decreased metabolic precursors (largely amino acids) to provide for gluconeogenesis substrates. The fact that his BG improved considerably with chemotherapy despite any change in nutritional status could argue against this etiology. However, we cannot say this with certainty because the time course for glycemia recovery is likely to be earlier than malnutrition recovery. Therefore, severe malnutrition and pronounced inanition in our patient could still be a contributing factor in his persistent hypoglycemia. Other nonneoplastic conditions that can cause hypoglycemia, like sepsis, circulatory insufficiency, and acute hypoxia, and liver and renal dysfunction, were ruled out.

Insulin and C-peptide levels were appropriately suppressed at the time of hypoglycemia, ruling out hyperinsulinemia as cause of hypoglycemia. IGF-2 has been shown to have insulin-like bioactivity and, by acting

on insulin-sensitive tissues, can result in sustained hypoglycemia [14]. Elevated levels of IGF-2 or partially processed precursors of IGF-2 ('big' IGF-2) cause hypoglycemia in patients with non-islet cell tumor hypoglycemia (NICTH), seen commonly with solid tumors of mesenchymal and epithelial origin [15]. Most IGF-1 and IGF-2 exist in a ternary complex with IGF binding proteins (IGFBP-3 or IGFBP-5) and an acid labile subunit (ALS); this complex has limited biological activity [16]. However, big IGF-2 associates less readily in these complexes. In IGF-2-omas, binary complexes of IGF-2, and/or big-IGF-2 (circulating freely or in binary complexes), exhibit greater capillary permeability, readily cross the endothelial barrier, and cause hypoglycemia by binding to the insulin receptors IR-B/A and also inhibit growth hormone (GH) production [16]. Because ALS and IGFBP-3 are GH dependent, plasma levels of total IGF-1 and IGF-2 can decrease as a consequence of reduced GH secretion. In fact, levels of total IGF-2 can be elevated, normal, or even low in patients with NICTH, but IGF-2 precursors are often elevated [17]. Big IGF-2 can be detected by radioimmunoassays using antibodies against the E-domain [18, 19] or thin-layer chromatography [20]; however, these assays are not readily available commercially. As such, an elevated ratio of IGF-2/IGF-1 might help with the diagnosis. A ratio of greater than 10:1 is considered to be diagnostic for IGF-2-associated hypoglycemia [3, 15]. In our patient, IGF-2 and IGF-1 levels were both low, often seen in severe cachexia, but the IGF-2/IGF-1 ratio was 4:1. Unfortunately, immunohistochemistry on the tumor tissue using antibodies against the E-peptide region could not be performed in our institute. Therefore, an IGF-2/IGF-1 ratio of less than 10:1 and nonresponsiveness of BG to glucagon injections on admission imply that the possibility of IGF-2

or big IGF-2 secretion by the tumor is less likely, but definitive evidence is lacking.

Lactic acidosis is a known complication of malignancy. It is considered to be type-B lactic acidosis in the presence of euolemia and normal oxygenation. This was the case with our patient, who had no underlying evidence of hypoxia and circulatory shock. A limitation of this case report is that thiamine levels were not checked at the time of elevated lactate levels. Various mechanisms have been proposed for lactic acidosis associated with lymphoma: increased hepatic production of lactate due to overexpression of enzyme hexokinase leading to high rates of glycolysis [7], decreased hepatic lactate clearance, paracrine actions of tumor necrosis factor- α [21], or microvasculature embolization [22]. Lactic acidosis in non-Hodgkin lymphoma portends a poor prognosis and is associated with high mortality rates. However, severe lactic acidosis associated with severe asymptomatic hypoglycemia in a case of diffuse large B-cell lymphoma is a rare occurrence.

An intriguing possibility that explains this association is the Warburg effect leading to excessive glucose consumption and increased lactate production [9, 23]. In the 1920s, Otto Warburg showed that cultured tumor tissues had high rates of glucose uptake and lactate secretion even in the presence of oxygen [24]. Under normal conditions, glucose is metabolized to carbon dioxide through oxidative phosphorylation with pyruvate as an intermediate in the mitochondrial tricarboxylic acid cycle [25]. Under anaerobic conditions, pyruvate is reduced to lactate producing only 2 mol of adenosine 5'-triphosphate (ATP). However, in cancer cells, certain oncogenic mutations shift the metabolism toward glycolytic pathways from oxidative phosphorylation even under aerobic conditions (the term *aerobic glycolysis*), leading to excess lactate production [23, 24, 26]. The lack of proportion between glycolysis and respiration, that is, "fermentation" of glucose into lactate by tumor cells even in the presence of sufficient oxygen and functioning mitochondria [27] is what sets Warburg effect apart.

The metabolism of glucose to lactate via glycolysis yields only 2 mol of ATP compared to 36 mol generated by catabolism of glucose in the mitochondrial tricarboxylic acid cycle [28]. There are many theories proposed as to why would the proliferating cancer cells shift to a less efficient metabolism (aerobic glycolysis). One proposed theory is that proliferating cancer cells have additional requirements extending beyond ATP production. Cancer cells need macromolecules like amino acids and lipids for tumor growth. Glucose as a major energy substrate supplies significant carbon, free energy, and reducing equivalents to support cell division and therefore, must be diverted to macromolecular precursors like acetyl-coenzyme A [25].

Committing majority of the glucose to oxidative phosphorylation for ATP generation limits the production of acetyl-coenzyme A and nicotinamide adenine dinucleotide phosphate (NADPH) required for macromolecular synthesis. The Warburg effect allows cells to feed several nonmitochondrial pathways (such as pentose phosphate pathway, NADPH, and glycerol synthesis), and maintain large pools of glycolytic intermediates that favor biosynthetic pathways [26].

The Warburg effect serves as the principle behind PET/CT scanning, which uses FDG, a marker for glucose metabolism to detect and monitor cancer growth [10]. Our patient's ^{18}F -FDG-PET/CT scan showed markedly enhanced FDG uptake in the chest, abdomen, pelvis, and diffuse skeletal involvement indicative of increased glucose uptake and metabolism in these areas owing to significant tumor burden at these sites. The Warburg effect leads to shunting of glucose from noncancerous cells to the cancer cells to meet energy and biosynthetic demands, and this can cause consumptive hypoglycemia because of increased uptake and rapid use of glucose by the tumor cells. We believe the hypoglycemia in our patient was attributable to direct glucose consumption by the tumor as illustrated by the presence of avid FDG uptake in tumor sites and minimal uptake in other tissues on ^{18}F -FDG-PET/CT scan (see Fig. 1A). Near-absent FDG uptake in the insulin-responsive target tissues (mainly muscle and brain) and lack of response to glucagon again argue against the possibility of insulin or IGF-2/big IGF-2-mediated hypoglycemia in this case.

Also interesting to note is the profoundly low metabolic activity within the gray matter of the brain seen on PET/CT scan. This brings us back to our patient's original presentation of being completely asymptomatic of hypoglycemia despite his BG in the 40s. Near-absent FDG uptake in the brain and asymptomatic hypoglycemia indicate an alternative source of energy for the brain, thus preserving its function and providing neural protection. Various studies have indeed shown evidence that lactic acid can be a major metabolic fuel for the brain both in hypoglycemic and euglycemic conditions [29-31]. Therefore, lactate, rather than glucose, probably served as an alternative fuel for the brain in our hypoglycemic patient and prevented neuroglycopenic symptoms. However, the metabolic pathways by which lactate is used in the brain are not completely defined.

Acute hypoglycemia should be managed by dextrose infusions and/or IV/oral steroids while waiting for the hypoglycemia and malignancy workup to be complete. However, aggressive dextrose infusions might not considerably improve BG values but instead worsen lactic acidosis by preferentially "feeding the tumor" and increasing

lactate production from the tumor [32, 33]. It would not be until chemotherapy is initiated that these metabolic derangements are rectified completely. Although steroids can have an immediate benefit on correcting hypoglycemia, tumor lysis in a rapidly proliferating lymphoid malignancy must be carefully monitored. This should particularly be kept in mind while waiting for tissue diagnosis, because many of these patients are started on steroids for severe and recurrent hypoglycemia in the emergency department or intensive care unit. In cases of insulin or insulin-like-mediated (paraneoplastic secretion of IGF-2/big IGF-2) hypoglycemia, therapies like long-term IV glucagon infusions [34] or GH therapy [35] can be used for treatment of hypoglycemia.

In conclusion, most of the hypoglycemia in large tumor-related situations is often multifactorial. In our patient, suppressed insulin, low C-peptide, an IGF-2/IGF-1 ratio of less than 10:1 and lack of response to glucagon suggest noninsulin/IGF-2-mediated hypoglycemia. Hypoglycemia was likely due to the combination of profound malnutrition and direct glucose consumption by the tumor through the Warburg effect. Severe hypoglycemia with lack of neuroglycopenic symptoms and near-absent FDG uptake in the brain suggest the use of lactate (rather than glucose) as an alternative metabolic fuel for the brain, preserving its function. Our patient presented with an exaggerated Warburg effect (hyper-Warburgism) as demonstrated by extreme glucose consumption, severe lactic acidosis, and large tumor burden on ¹⁸F-FDG-PET/CT. It is crucial to investigate the causes of spontaneous hypoglycemia in a timely fashion, especially in the setting of malignancy, and understand the pathophysiology of the Warburg effect underlying it. The findings of lactic acidosis and hypoglycemia improved remarkably once chemotherapy started. For chemosensitive cancers, chemotherapy should be initiated promptly without any delay to disrupt the Warburg effect and restore the metabolic abnormalities.

Acknowledgments

Manu Raj Pandey critically reviewed the manuscript and participated in editing.

Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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