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Clinical Effect of the Warburg Effect in Stage IV Hepatocellular Carcinoma

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Abstract

The Warburg effect is a metabolic phenomenon observed in cancer cells and is characterized by aerobic glycolysis instead of mitochondrial oxidative phosphorylation as the primary mechanism of cellular energy generation. The exact benefit of such a metabolic switch is poorly understood, as aerobic glycolysis is thermodynamically more inefficient than mitochondrial oxidative phosphorylation. Here, we present a case of a 40-year-old male with advanced stage 4 hepatocellular carcinoma with chronically low glucose levels measured in the 20s to 40s and completely asymptomatic. Upon examination, findings of sympathetic hyperactivity in the setting of hypoglycemia were absent, and mentation was completely intact. This occurred in the absence of any states or medications known to induce hypoglycemia; concurrently, the patient demonstrated hyperphagia, suggesting increased metabolic demand in the setting of an immense, overwhelming tumor burden. During these hypoglycemic intervals, the patient's coagulation profile, including PT and international normalized ratio, remained within normal limits, suggesting sufficient residual hepatic parenchyma and glucogenic capacity. The patient's glucose remained extremely low, refractory to correction with multiple dextrose, D5, and D10 administrations. This suggests chronic systemic habituation to malignant cell consumption of serum glucose leading to adaptations to this hypoglycemia in highly metabolically active organs, such as the brain, heart, liver, and kidneys. This report highlights the clinical utility of recognizing this metabolic state in the setting of advanced-stage malignancy with significant tumor burden and how it affects hospital glucose management. Its early recognition will lead to improvements in meeting the patient's metabolic demands while avoiding paradoxical exacerbation of lactic acidosis when providing guideline-directed oncological treatment. This metabolic state may function as a surrogate marker, in conjunction with serum markers and imaging studies, for clinical identification of advanced stage malignancies and for treatment escalation.

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1. Introduction

The Warburg effect, WE, first described by Dr. Otto Warburg in the 1920s, describes the biochemical phenomenon of increased glycolysis in cancer cells, even in the absence of hypoxia, and of aerobic glycolysis with functioning mitochondria [1]. It is primarily associated with rapid tumor growth, extensive tumor burden, and typically advanced-stage malignancy [1,2]. The precise mechanism by which WE occurs is not known. A cellular hallmark is increased glucose uptake and utilization via glycolysis, with lactate production and resultant hyperlactatemia [1,2]. Several studies have analyzed and confirmed the promoting effects of aerobic glycolysis on tumor cell proliferation, immune evasion, angiogenesis, and disease progression and metastasis [1,2]. Here, we present a clinical case of a 40-year-old male who presented with non-neuroglycopenic hypoglycemia and hyperlactatemia, revealing aerobic glycolysis of the Warburg effect in stage four hepatocellular carcinoma. To our knowledge, this is the first clinical report to capture the Warburg effect in HCC. We also briefly review the literature on the bioenergetic phenotype of aerobic glycolysis and its relationship to tumorigenesis.

2. Case Presentation

Serum CEA and CA 125 were normal, CA19-9 of 119 units/mL [reference range: 0-35 units/mL], and AFP of 167,200 ng/mL [reference range: 0-40 ng/mL]. Serological Hepatitis B evaluation revealed positive HBsAg and anti-HBc antibodies, with an HBV viral load of 166,000 IU/mL [reference range negative: <10 IU/mL]. Hepatobiliary surgery and gastroenterology were consulted with an IR-guided liver biopsy, leading to tissue pathology revealing a primary diagnosis of hepatocellular carcinoma, HCC; taken together with the pulmonary findings, this rendered a diagnosis of stage four HCC. Radiation and hematology-oncology were consulted regarding the initiation of chemotherapy for stage four HCC.

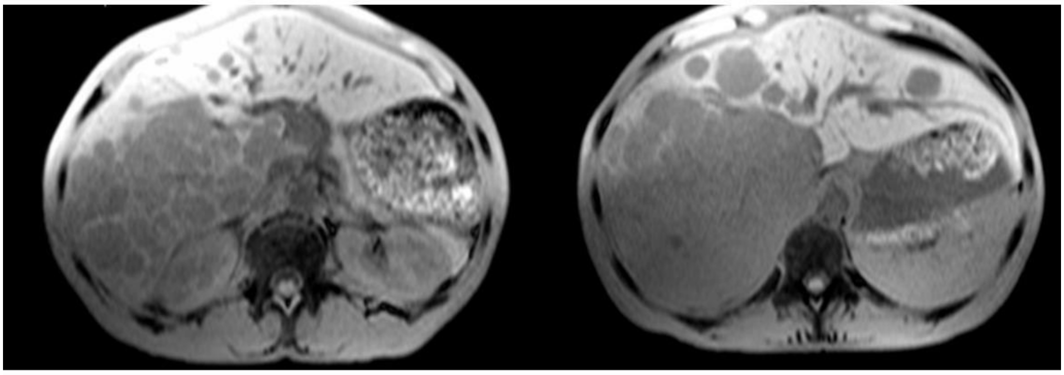

Figure 1. Triple phase contrasted MRI of the abdomen with hepatic protocol that reveals diffuse enhancing masses with a dominant 23 cm x 14 cm enhancing mass occupying the entirety of the right hepatic lobe.

3. Discussion

In non-cancerous cells, glucose is metabolized via glycolysis, generating pyruvate. Under conditions of adequate oxygen, pyruvate is translocated into the mitochondria and enters the tricarboxylic acid (TCA) cycle for the generation of adenosine triphosphate (ATP) via oxidative phosphorylation and metabolism to CO_2 [3]. During hypoxia, normal cells metabolize pyruvate via lactic acid fermentation to rapidly produce ATP for cellular energy and regenerate NAD^+, which is necessary for the repeated cycling of anerobic glycolysis [3]. The Warburg effect is a cancer cell-specific bioenergetic metabolic phenotype characterized by the predominance of glycolysis with lactate fermentation over mitochondrial oxidative phosphorylation in the absence of hypoxia. Our current understanding of this malignant, specific energetic strategy remains limited, with persistent inquiry into how a less efficient mechanism of ATP production promotes disease progression. Tumor cells originate from within tissue structures known as tumor microenvironments, TMEs. TMEs are characterized by the presence of both healthy host cells and tumor cells, embedded in a tissue matrix that is consistently subjected to fluctuating degrees of hypoxia and tissue acidity [4]. This commonly occurs in response to a mismatch between tumor cell proliferation and the vascular delivery of nutrients necessary to sustain proliferating cells rapidly [4]. Given the tissue structure of solid organ malignancies and decreased proximity to vascular density, there remains an increasing gradient of hypoxia towards the center of solid organ tumors [5,6]. The vascular supply, and therefore oxygen and glucose delivery, to solid organ tumors, such as HCC, is greatest in the outer tumor layers [5,6]. This creates highly competitive niches that constantly select for cancer cells that can adapt to a range of extracellular acidities, oxygenation, and reduced nutrient delivery via the vasculature [5,6]. This

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increase in metabolic stress stimulates the development of varying bioenergetic strategies amongst cancer cells.

Several mutations are identified to confer the acquisition of aerobic glycolysis, such as overexpression of tumor necrosis factor alpha, TNFa, hexokinase, hypoxia inducible factor 1 alpha, HIF1a, and insulin-like growth factors, IGF, FLT3 tyrosine kinase, and c-myc [7–10]. These mutations, with their bioenergetic heterogeneity, confer metabolic plasticity on cancer cells, enabling them to thrive and proliferate in harsh environments such as the TME. Several studies have identified the Warburg effect as a bioenergetic strategy in combination with mitochondrial dysfunction to support rapid cellular proliferation within TMEs [11–13]. This occurs because WE-induced aerobic glycolysis increases glucose-derived carbon utilization for anabolic pathways, thereby supporting rapid tumor cell growth rather than introducing carbon into the TCA cycle for respiration to CO2 [14]. Once tumor cells acquire mutations that enable the metabolic switch to aerobic glycolysis, intracellular lactate accumulates, which is then secreted and further acidifies the TME [15–17]. Mechanistically, increased tissue acidity can directly induce DNA damage and alter the enzymatic activity of DNA repair enzymes, causing impaired DNA repair responses [15–17]. Acidified TMEs coupled with increasing hypoxia from tumor-vascular mismatch caused by WE enhanced tissue proliferation cyclically contribute to a vicious unending sequence of cancer cell expansion, immunoevasion, and metastatic invasion [15–17]. Once cancer cells metastasize to secondary sites, they can engage in dysregulated aerobic glycolysis to support the rapid cellular growth required to establish a tumorigenic focus, generate yet another TME, and contribute to the cycle of malignancy.

The patient presented with asymptomatic hypoglycemia and nonspecific abdominal discomfort with no associated weight loss. During the hypoglycemic intervals, the coagulation profile, including prothrombin time, PT, and international normalized ratio, INR, remained within normal limits, suggesting sufficient residual hepatic parenchyma and glucogenic capacity. The absence of signs and symptoms suggesting an underlying malignancy or findings indicating a paraneoplastic syndrome introduced diagnostic uncertainty. However, the persistence of hypoglycemia and hyperlactatemia alongside exclusion of etiologies for refractory hypoglycemia prompted reevaluation and broadening of differentials. Clinical consideration of malignancy-associated metabolic dysfunction incited further differential evaluation, leading to the clinical suspicion and eventual tissue diagnosis of HCC. The absence of neuroglycopenic symptoms is related to the brain's capacity to utilize lactate as a primary source of ATP generation, in conjunction with other chronic adaptations to hypoglycemia in highly metabolically active organs, such as the heart, liver, and kidneys [18,19]. In rare instances, the only apparent indicators of an occult malignancy are the bioenergetic metabolic phenotypes of tumor cell metabolism in otherwise clinically silent and well-compensated disease. This reinforces the importance of early consideration and recognition of malignancy-related metabolic phenotypes, as the criteria for identifying metabolic disturbances secondary to WE have not yet been clearly defined. The development of sudden refractory hypoglycemia and hyperlactatemia, inconsistent with other etiologies in the setting of advanced-stage HCC, diagnostically supports the identification of aerobic glycolysis of the WE. Aerobic glycolysis confers proliferative and subsequently metastatic potential to cancer cells, indicating a bioenergetic cellular profile highly suggestive of malignancy progression. WE metabolic profiles may serve as a clinical biomarker prompting clinicians to deepen their evaluation for malignancy, particularly in patients with spontaneous refractory hypoglycemia and lactic acidosis.

The molecular and laboratory signatures of the WE can therefore lead to higher early detection rates of malignancies, thereby improving long-term patient prognosis by enabling earlier initiation of appropriate treatment. Alongside the guidance of oncology specialists, the patient began treatment with the PD-L1 blocker durvalumab with close ambulatory follow-up, revealing a resolution of spontaneous hypoglycemia and normalization of hyperlactatemia with continued treatment. Although the WE is typically associated with advanced-stage malignancy, this case underscores the importance of a multispecialty approach to guide treatment and achieve the best possible patient outcomes. Clinician awareness of WE-induced aerobic glycolysis remains paramount, as continued

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treatment with intensive glucose replacement will drive increased lactate production by tumor cells. This will further exacerbate lactic acidosis and contribute to the harsh extracellular conditions of TME's that select for neoplastic cells and mediate progression of existing tumors. Attempted correction of hypoglycemia while not clinically recognizing the metabolic signature of the WE can therefore precipitate production of large amounts of serum lactate, leading to severe lactic acidosis with rapid clinical decompensation. Medical management of Warburg effect-induced hypoglycemia and hyperlactatemia remains unoptimized, with the only effective long-term treatment strategies being early recognition, diagnosis of malignancy, and initiation of effective treatment.

4. Conclusions

The Warburg effect is a cancer cell-specific bioenergetic metabolic phenotype characterized by the predominance of glycolysis with lactate fermentation in the absence of hypoxia. We describe a patient with advanced-stage HCC who presented with and persistently demonstrated spontaneous, asymptomatic hypoglycemia with concurrent hyperlactatemia and lactic acidosis. This case demonstrates the diagnostic challenges and complexities encountered when clinically evaluating severe persistent asymptomatic hypoglycemia. There is often a significant diagnostic delay in the recognition of Warburg Effect-induced hypoglycemia, and aggressive treatment with glucose can potentiate the effects of TMEs and more acutely precipitate the development of life-threatening lactic acidosis. It is the primary purpose of this report to increase clinical awareness of the WE in the hope that clinicians maintain a high index of suspicion for malignancy-specific metabolic changes, as maximized patient prognosis and quality of life rely on early detection and initiation of multispecialty treatment, including intensive oncologic therapy.

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