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Case Report

The Warburg Effect a Diagnostic Challenge in Oncological Critical Care - Case Presentation and Literature Review

Roosemberg F*; Martinez E; Abril P; Bermeo D; Garcia C; Chung M; Bowen A; Bolaños O
Department of Critical Care, SOLCA Guayaquil, Ecuador

***Corresponding author:** **Roosemberg F**
Department of Critical Care, SOLCA Guayaquil, Ecuador.
Email: fernando_roosemberg1@hotmail.com

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Abstract

Purpose of the study: The Warburg effect is the result of the metabolic adaptation of malignant neoplastic cells; it represents a challenge for the intensivist as it presents with hypoglycemia and severe metabolic acidosis with type B hyperlactatemia refractory to treatment. The purpose of the study was, through the presentation of a clinical case, to emphasize the importance of recognizing tumors associated with the Warburg effect and its early oncological treatment to revise the metabolic disorder and minimize the rate of complications.

Materials and methods: Presentation of a clinical case of a 61-year-old male patient with a diagnosis of diffuse medium to large cell non-Hodgkin lymphoma, high-grade immunophenotype B, who presented hypoglycemia and severe metabolic acidosis with type B hyperlactatemia refractory to treatment, was presented. Multiple differential diagnoses leading to the Warburg effect diagnosis

Results: After starting induction of chemotherapy with the R-CVP scheme (rituximab 593 mg, cyclophosphamide 1185 mg, vincristine 2 mg and dexamethasone 16 mg), resolution of the metabolic treatment of the Warburg effect was evident.

Conclusions: The Warburg effect occurs in tumors with a high tumor burden, generating a metabolic disorder refractory to conventional treatment. Early initiation of chemotherapy allows the resolution of the condition that can generate high mortality.

Keywords: Warburg syndrome; Neoplastic stem cell; Malignant lymphoma

Abbreviations: PI3K: Phosphoinositide 3-Kinase Inhibitors; Akt: Protein Kinase B; mTor-: Mammalian Target of Rapamycin; HIF-1ª: Hypoxia-Inducible Factor-1; PTEN: Phosphatase and Tensin Homologue Deleted on Chromosome 10; p53 gene**;** VHL: Von Hippel-Lindau Gene; ROS: Reactive Oxygen Species; HSP90: Heat Shock Protein 90; cMYC proto-oncogenes; Ras gene; Raf gene; GLUT-1: Glucose Transporter 1; GLUT-3: Glucose Transporter 3; HK: Hexokinase; PFK: Phosphofructokinase; PDK-1: Pyruvate Dehydrogenase Kinase 1; LDH-A: Lactate Dehydrogenase A; PDH: Pyruvate Dehydrogenase; HCO3: Bicarbonate; BCL2: B-Cell Lymphoma 2**.**

Introduction

The Warburg effect is a pathological condition primarily associated with the metabolic adaptation of malignant neoplastic cells necessary for their maintenance and progression. While it has been described in other contexts, it is mostly linked to lymphomas [1]. Few cases have been reported, with mortality rates ranging from 70% to 80% in the first month [2]. Diagnosis poses a challenge for intensive care physicians due to severe metabolic acidosis with refractory hyperlactatemia, necessitating a deepening of medical knowledge for timely management.

Case report

A 61-year-old male patient with a diagnosis of diffuse large B-cell non-Hodgkin lymphoma, high-grade B-cell immunophenotype (C-YMC positive 70%, BCL2 negative), without oncologi-

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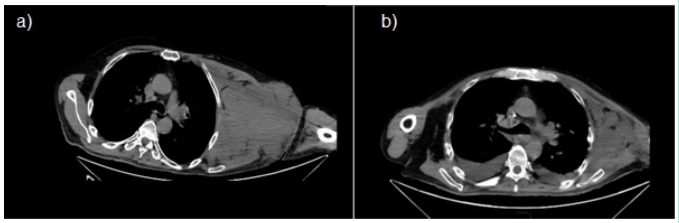

Figure 1: a) Initial chest Computed Tomography (CT) scan reporting left supraclavicular lesion with soft tissue density lymph node conglomerate without contrast enhancement measuring 127 x 115 x 118 mm, causing displacement of muscular and vascular structures. b) Follow-up chest CT scan at 10 days: significant decrease in previous lesion approximately 50% measuring 74 x 71 x 70 mm.

cal treatment, presented to the emergency department with a 24-hour history of malaise, dyspnea on minimal exertion, and use of accessory muscles without oxygenation alteration. Imaging and laboratory tests revealed leukocytes 12890, neutrophils 80%, lymphocytes 7%, eosinophils 1%, procalcitonin 0.17 ng/ml, hemoglobin 13.3 g/dl, hematocrit 36.5%. Biochemical analysis showed hypoglycemia (35 mg/dl), urea 22.5 mg/dl, creatinine 0.53 mg/dl, uric acid 5.66 mg/dl, and elevated LDH (669 U/l) without hepatic, renal, or electrolyte disorders. Arterial blood gas analysis showed severe metabolic acidosis with an elevated anion gap secondary to type B hyperlactatemia. Despite initial invasive mechanical ventilation and bicarbonate infusion, serum bicarbonate levels did not improve, prompting hemodialysis.

The diagnosis of the Warburg effect was made after excluding other metabolic disorders such as sepsis, insulinoma, and intoxications. Chemotherapy induction with R-CVP regimen (rituximab 593 mg, cyclophosphamide 1185 mg, vincristine 2 mg, and dexamethasone 16 mg) was initiated in collaboration with the hematology service. Improvement in gasometric parameters was observed, with the patient weaned off mechanical ventilation on the sixth day of ICU hospitalization and tumor size reduction confirmed on the tenth day (Figure 1). The patient continued to have a favorable evolution while hospitalized in the hematology department, following the chemotherapy induction regimen (Figure 2).

Discussion

In 1920, Otto Warburg demonstrated that tumor tissues metabolize glucose ten times more than normal tissues under non-hypoxic conditions, producing lactic acid, initially considered a physiological mitochondrial failure [3]; Critics such as Sonveaux [4] later analyzed this phenomenon, recognizing it as a metabolic reprogramming of malignant neoplastic cells aimed at ac-

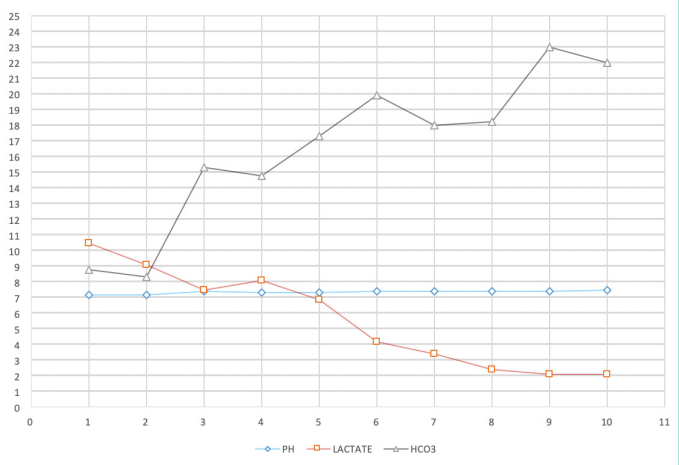

Figure 2: Evolution of lactate levels, pH, PCO2, HCO3 after chemotherapy.

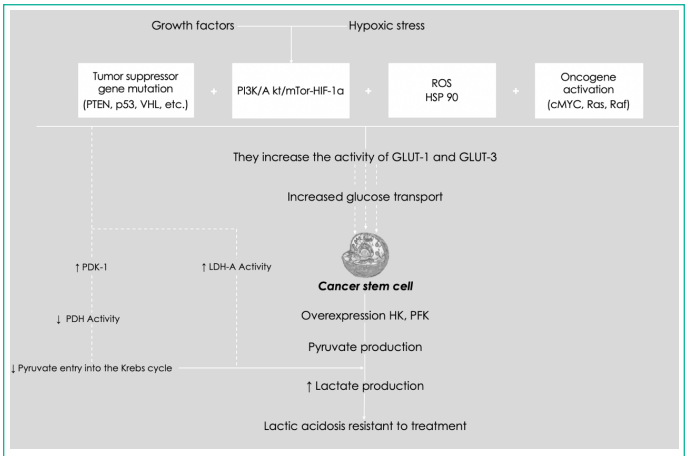

Figure 3: Pathophysiology of the Warburg effect.

celerating glycolytic and glutaminolytic fluxes to sustain rapid and continuous growth.

Physiopathologically, several factors contribute to the reprogramming of malignant neoplastic stem cells. Stimulation of growth factors and hypoxic stress alter master regulators (PI3K/Akt/mTor-, HIF-1a), suppressing genes and activating oncogenes (cMYC, Ras, Raf). This hostile tumor microenvironment increases GLUT-1 and GLUT-3 activity, enhancing glucose influx into the cytoplasm. Consequently, there's overexpression of glycolytic enzymes (hexokinase, phosphofructokinase), leading to increased pyruvate production. Activation of HIF-1a and cMYC further elevate PDK-1 and LDH-A levels. PDK-1 inhibits PDH, reducing pyruvate entry into the Krebs cycle, while LDH-A metabolizes pyruvate into lactic acid, causing treatment-resistant metabolic acidosis, a hallmark of malignant progression (Figure 3) [5].

The clinical presentation is nonspecific, and typically manifests as hypoglycemia [6], hyperlactatemic metabolic acidosis, or both. Initial support involves intravenous administration of HCO3, Kim et al [7] performed a retrospective analysis demonstrating increased mortality when lactic acidosis is treated with HCO3 if the underlying cause of lactic acid production is not addressed. The BICAR-ICU [8] did not find improvement in any aspect between the intervention and control groups, except in patients with Acute Kidney Injury (AKI), where an improvement in mortality at 28 days and a reduction in the need for of renal replacement therapy. Furthermore, Fujii et al [9] found improvement and maintenance of higher mean arterial pressure values in vasopressor-dependent patients. Therefore, the decision to infuse HCO3 depends on the condition associated with the Warburg effect. Hemodialysis improves plasma HCO3 levels and helps eliminate lactate, but hypoglycemia must be corrected, because neurons use lactate as an energy source. Other therapeutic approaches, such as the use of dichloroacetate to switch the metabolism of malignant neoplastic cells from glycolytic phosphorylation to oxidative phosphorylation, have been studied since 1992 [10,11]; however, strong evidence supporting its use is lacking.

Conclusions

In the field of critical oncology, patients presenting with severe metabolic acidosis associated with type B hyperlactatemia and hypoglycemia, along with a hematologic neoplasm such as lymphoma, should be directed towards a diagnosis of the Warburg effect. Only tumor burden reduction will definitively resolve this condition, as other therapeutic options serve as palliative measures and temporarily support critically ill pa-

tients. Furthermore, none of these options have strong scientific evidence supporting their use, emphasizing the imperative for early administration of specific chemotherapy regimens, regardless of the patient's condition.

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