

The Trilogy: Warburg's effect on Non-Hodgkin's Lymphoma in a Patient Infected with the Human Immunodeficiency Virus

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ABSTRACT

According to the Warburg Effect, or aerobic glycolysis, tumor cells prefer, in the presence of oxygen, to metabolize glucose through glycolysis, to the detriment of oxidative phosphorylation, producing high levels of lactate. This metabolic reprogramming, in which lactate is transported to the extracellular environment, promotes an acidic microenvironment, supporting the high rate of proliferation. The aerobic glycolytic phenomenon is present in several tumors, namely in hematological tumors such as Non-Hodgkin's Lymphoma (NHL).

The risk of developing NHL in the context of Human Immunodeficiency Virus (HIV) infection is approximately 60 to 100 times higher than that of the HIV-negative population.

This clinical case describes a patient hospitalized for a condition presumably compatible with gastrointestinal opportunistic infection, in an immunosuppressed patient with a recent diagnosis of HIV. It added, analytically, high hyperlactacidemia and marked hypoglycemia, not compatible with the clinical status of the patient, given that the patient was practically asymptomatic throughout the hospital stay.

Keywords

Warburg effect, Non-Hodgkin's Lymphoma, HIV, Lactate, Hypoglycemia, Asymptomatic.

Introduction

Lactacidemia increases, among other causes, in tissue hypoperfusion. Persistent hyperlactacidemia without hypoxia should condition the exhaustive screening of other diseases, namely metabolic ones. The Warburg Effect, or aerobic glycolysis, was first described in 1924 by the German biochemist, Nobel Prize in Physiology and Medicine, Otto Warburg. He demonstrated that tumor cells prefer to metabolize glucose through glycolysis rather than oxidative phosphorylation, producing lactate even in the presence of oxygen [1]. Thus, in contrast to what happens in healthy cells, most tumor cells produce high lactate levels regardless of oxygen availability, and this form of metabolism is

often referred to as “aerobic glycolysis” [2].

The most common malignancy in HIV-infected patients in developed countries is NHL, particularly those derived from B lymphocytes [3]. HIV creates an environment in which chronic antigen stimulation, cytokine dysregulation and co-infection with oncogenic viruses, in the context of genetic abnormalities and interrupted immune surveillance for tumor antigens, can lead to the appearance of monoclonal B cells [4].

Clinical Case

A 71-year-old man with a relevant personal history of arterial hypertension, insulin-treated type 2 diabetes mellitus and stage 4 chronic kidney disease. He was regularly medicated with insulin, antihypertensives, cyclosporine and low-dose corticosteroid therapy. He had a recent diagnosis of HIV without instituted

treatment. The patient had several recurrences at the emergency department in the months prior to hospitalization due to vomiting and diarrhea, culminating in hospitalization. In the physical exam, he did not present relevant alterations. Analytically, normocytic and normochromic anemia, hypoglycemia (55mg/dL) and increased inflammatory parameters were highlighted. The presence of metabolic acidosis and hyperlactacidemia of 10 mmol/L. In the remaining study the following stand out: Hepatitis A: IgG+IgM Positive; Hepatitis B: antibodies HBs > 1000.00, antibodies HBc total Positive; HIV 1+2 antigens and antibodies P24 Positive; Fasting insulin: decreased; Negative blood cultures; parasitological and bacteriological examination of the feces and negative clostridium research. The patient also underwent a colonoscopy, which revealed: "Nonspecific colitis". During hospitalization, the patient maintained mild abdominal discomfort with persistence of hypoglycemia (minimum 30mg/dL) despite twice-daily fixed therapy with glucose solution. Added hyperlactacidemia with values of approximately 21 mmol/L in a practically asymptomatic patient. He started broad-spectrum antibiotic therapy due to persistently increased inflammatory parameters, assuming a gastrointestinal infectious focus, having completed seven days of piperacillin and tazobactam and seven days of meropenem. During hospitalization, he was hemodynamically stable. Despite this, there was clinical and analytical worsening and the patient died.

The histological result of the colonoscopy, post mortem, revealed: "Colic infiltration by cells of a high-grade non-Hodgkin's Lymphoma B."

Discussion

In this clinical case, the most likely diagnostic hypothesis initially would be a gastrointestinal opportunistic infection, which was excluded after septic screening. He maintained hypoglycemia and hyperlactacidemia throughout the hospital stay. In cases of persistent hyperlactacidemia without hypoxia, exhaustive

screening for other diseases, namely metabolic diseases, should be started, as well as investigation with imaging and histological examinations. This case was only unraveled after the histological result, after the death of the patient, concluding that it was a non-Hodgkin B Lymphoma with a high degree of malignancy in a patient with HIV, with a recent diagnosis. After excluding other causes, and in the aforementioned clinical context, hypoglycemia and hyperlactacidemia were thus attributed to the Warburg effect (aerobic glycolysis). However, an unresolved question remains: Why do tumor cells prefer a less efficient energy production method in terms of Adenosine Triphosphate (ATP) production? One possible explanation is that lower ATP production per glucose molecule metabolized is only a problem when resources are scarce. This is not the case for proliferating cells, which are exposed to a continuous supply of glucose through neogenesis. In addition, this type of metabolism allows the survival of tumor cells in adverse conditions, such as hypoxia, while promoting an increase in the acidity of the extracellular environment (due to the high production of lactate), which conditions the death of normal cells. Adjacent to the tumor facilitating its growth and invasiveness. Finally, it appears that the Warburg phenomenon is due to irreversible changes in oxidative phosphorylation in tumor cells, ultimately leading to exaggerated lactate production [4].

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