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Basics of Oncologic Type B Lactic Acidosis: Increased Awareness for Better Outcomes?

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Introduction

The most common and best known form of lactic acidosis, Type A, presents in the environment of tissue hypoxia. The lesser known form, Type B, does not involve tissue hypoxia, is not well understood, and very often results in death. No randomized controlled trials (RCTs) comparing treatment modalities currently exist (Ruiz, Singh, & Hart, 2011). Increased recognition by medical and nursing disciplines may result in quicker diagnosis, opportunity to implement treatment, possibility for RCTs, and better outcomes.

Clinical Presentation

- History of leukemia or lymphoma, less often solid tumors. See Table 1
- Signs of relapse or worsening oncologic conditions: pancytopenia, lymphandopathy
- Associated diffuse symptoms including (not exhaustive): fatigue, bleeding, myalagias, edema
- Non-oncologic etiologies: medications, other disease processes, hereditary or metabolic disorders, and thiamine deficiencies related to alcohol use or chemotherapy administration. See Table 2
- Presentation with lactic acidosis, an anion gap, and normal blood pressure
- Acute respiratory distress and no identifiable pulmonary source (Friedenberg, Douglas, Brandoff, & Schiffman, 2007).

Table 1. Summary of Case Reports of Type B Lactic Acidosis from 2000 to 2010

	Number of cases	Percent of Total Cases
Hematologic Malignancies	27	87
Lymphoma	18	58
Non-Hodgkin's Lymphoma	17	55
Hodgkin's Lymphoma	1	3
Leukemias	8	26
Acute Lymphoblastic Leukemia	5	16
Acute Myeloid Leukemia	2	6
Chronic Lymphocytic Leukemia	1	3
Multiple Myeloma	1	3
Solid Malignancies	4	13

Adapted from Tang, Perry, and Akhtari (2013)

Table 2. Non-oncologic Etiologies of Type B Lactic Acidosis

Other medical diseases	Liver failure Renal failure HIV Diabetes mellitus
Medications or toxins	Metformin Historically phenformin Nucleoside reverse transcriptase inhibitors Salicylates Linezolid Propofol Isoniazid Alcohol Cyanide
Hereditary disorders	Glucose 6-phosphate deficiency Frutose-1,6-diphosphate deficiency Pyruvate carboxylate deficiency Oxidative phosphorylation deficiencies

Adapted from Friendenberg, et al. (2007)

Underlying Pathophysiology

Figure 1. Metabolism of Glucose in Normal Conditions

Normal aerobic conditions: glucose → pyruvate + oxygen + thiamin → ATP + carbon dioxide + water

Normal anaerobic conditions: glucose → pyruvate → ATP + lactic acid

In normal anaerobic conditions, glucose degradation produces lactic acid, in normal aerobic conditions, it does not, see Figure 1. Lactic acid is continually produced and broken down. Lactic acidosis occurs when this balance is disturbed; causes include overproduction, underutilization, or both. Lactic acidosis is defined as whole blood level lactic acid > 5 mmol/L and a pH < 7.30 (Sia, Plumb, & Filaus, 2013).

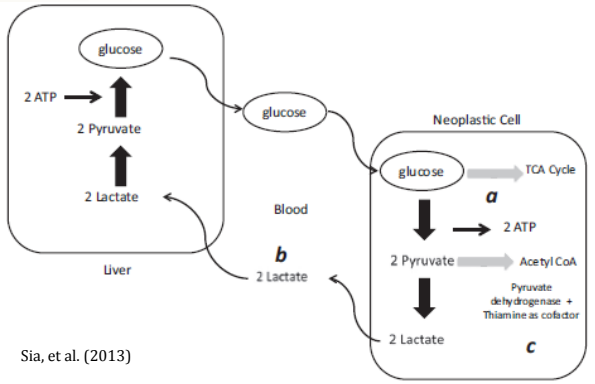
Discovered by Otto Van Warburg, in 1924, and named the Warburg Effect, cancer cells will sometimes take an anaerobic pathway even in the presence of oxygen, see Figure 2, a. It is not known why this effect occurs, but it is theorized that the process might improve tumor proliferation (Ruiz et al., 2011). Alternatively, quickly growing tumors might overgrow their blood and thus oxygen supply (Kumar & Raina, 2014). Regardless, the Warburg effect results in the overproduction lactate.

Other potential causes of the over-production of lactic acid include increased viscosity of blood in the case of leukemias potentiating microvascular aggregates, in fact producing a Type A hypoxic lactic acidosis (Ustin et al., 2002).

Vitamin deficiency, in particular thiamin, is associated with the increased production of lactate. As can be seen below in Figure 2, c, the absence of thiamin pushes metabolism toward the anaerobic pathway. Another theory posits that tumor necrosis factor may alter enzymatic levels which push pyruvate toward the aerobic process (Hae et al., 2010). In yet another theorized cause, tumor tissue may overproduce insulin-like growth factor, altering mitochondrial respiration (Kumar and Raina, 2014).

Related to problems of decreased lactic acid degradation or removal, normally the liver either converts lactate back to glucose or oxidizes lactate to carbon dioxide and water (Ustun et al., 2002). The liver manages 80-90% of lactate clearance, the kidneys manage the remainder. As the liver and kidney contribute to gluconeogenesis and lactate clearance, dysfunction in these organs can result in lactate underutilization, see Figure 2, b. Often this dysfunction involves tumor involvement (Kuo, Yeh, & Lin, 2014). However, there may be another, non-structural process at work in the liver (Ruiz et al, 2011).

Figure 2. Changes in Glucose Metabolism Contributing to Type B Lactic Acidosis



Sia, et al. (2013)

Significance of Pathophysiology

- In-depth knowledge of this pathophysiology remains speculative
- Type B lactic acidosis potentially has multiple contributing factors
- Mortality rates are markedly high, 81%, per Ruiz et al., 2011
- Type B lactic acidosis is usually a diagnosis by exception, ruling out common causes of hypoxia in oncologic patients (sepsis, cardiomyopathy, hypovolemia) (Ustin et al, 2002).
- Non-oncologic causes of Type B lactic acidosis, could produce a synergistic effect with oncologic causes
- The current poor outcomes of this condition could be related to delays in diagnosis and treatment (Sia, et al., 2013).

Implications for Nursing Care

- Awareness that treatment involves addressing the underlying cause, often with chemotherapy, occasionally with thiamine supplementation.
- Supportive treatments include: renal replacement therapy, bicarbonate administration, and respiratory support (Tang, et al., 2013).
- As presently patients with this diagnosis tend to have poor outcomes, often death, (Kumar & Raina, 2014), in addition to high-acuity care, nursing interventions might lean toward supportive end-of-life psychosocial interventions.

Conclusions

It is possible many cases of Type B lactic acidosis are missed or caught later than necessary. It is possible that with early differential diagnosis and recognition, RCTs might be instituted to identify more efficacious treatment modalities improving mortality rates with this disease process. Although this is a basic review of Type B lactic acidosis for the purpose of increased awareness, theory and research point to more specific biochemical mechanisms, and readers are encouraged to explore this topic to a desired level of interest and comfort.

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