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Case Presentation

Type B Lactic Acidosis Associated with High Risk Refractory Multiple Myeloma

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Abstract

Lactic Acidosis (LA) is a frequent cause of metabolic acidosis in hospitalized patients. Traditionally, LA has been divided into type A (hypoxic) and type B (non-hypoxic) with the latter being associated with malignancies. The exact mechanism of type B LA in malignancy is unknown, although several hypotheses have been proposed. To date most cases of type B LA have been described in patients living with solid tumors, leukemias, or lymphomas. We report the sixth known case of type B LA associated with refractory Multiple Myeloma (MM). This case report highlights well-described diagnostic challenges experienced by clinicians when approaching severe LA in patients with MM, as evidenced by frequent overtreatment of these patients with aggressive resuscitative measures without any gain in survival. The aim of our report is to facilitate earlier clinician recognition of type B LA secondary to MM through a review of the pathogenesis and approach to LA.

Keywords: Multiple myeloma; Refractory; Lactic acidosis; Type B; Approach

Introduction

Lactic Acidosis (LA) is a frequent cause of metabolic acidosis in hospitalized patients [1,2]. Most commonly, hyperlactatemia results from tissue hypoxia (type A LA), although it can be caused by other metabolic derangements in the absence of hypoxia (type B LA) [1-3]. Treatment in either case is prompt recognition and management of the triggering condition(s) [1,2,4]. The link between type B LA and malignancy is well established; however, with respect to hematologic malignancies, it is best documented in leukemia and lymphoma [5]. The existence of type B LA in Multiple Myeloma (MM), a malignancy of plasma cells, has been described only in five case reports to date [5,11-14]. Failure to recognize progressive MM as a cause of a patient's LA often leads to patient overtreatment with aggressive therapies and interventions, which are unlikely to alter the overall outcome and may increase suffering [5]. Thus, we describe a case of severe type B LA in a patient with refractory MM, focusing on the pathogenesis of LA and an approach to type B LA, in order to improve clinicians' ability to promptly recognize this entity. Of note, our review is limited to L-LA, the isomer most commonly produced in humans; reviews of D-LA can be found elsewhere [6].

Case Presentation

A 63-year-old female with progressive back pain was diagnosed with lambda light chain MM in the spring of 2018. Initial diagnostic evaluation revealed the presence of end-organ damage, 60% plasma cells in the bone marrow, beta-2 microglobulin of 9.2mg/L, Lactate Dehydrogenase (LDH) of 293, as well as t(4;14) translocation and 17p deletion. According to the revised International Staging System for MM, this patient had high-risk disease. Interestingly, at the time of her diagnosis she was noted to have LA, which subsequently paralleled her disease course (Figure 1).

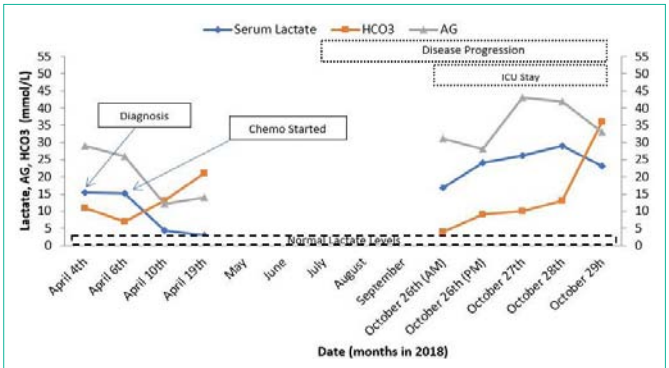

Figure 1: Multiple myeloma course and serum lactate levels.
AG – anion gap, HCO_3 – serum bicarbonate.

The patient received induction chemotherapy consisting of cyclophosphamide, bortezomib, and dexamethasone with an excellent response until the end of cycle 4, at which point her disease progressed with the emergence of multiple plasmacytomas and rising serum lambda light chains (Figure 2). Second-line chemotherapy with lenalidomide and dexamethasone was initiated. Again, the patient had an initial response but subsequently progressed at the beginning of cycle 3. Ixazomib was added with a hope of achieving disease control. However, within a month the patient deteriorated further (Figure 2). In the late October, the patient was admitted to a local hospital with confusion and profound LA, culminating in a transfer to the Intensive Care Unit (ICU) (Figures 1 and 2).

On admission to the ICU, the patient's vital signs were: T 36.7, P 119, RR 26, BP 131/58, O2 97% on room air. There was no evidence of regional ischemia, seizures, hepatic dysfunction, toxic ingestions, or severe anemia (hemoglobin 89g/L) to account for the critically high lactate level. The patient was given intravenous fluids, broad-spectrum antibiotics, and stress doses of steroids for suspected occult sepsis. Sodium bicarbonate infusion was started for severe acidosis on presentation and continued for the duration of the patient's ICU

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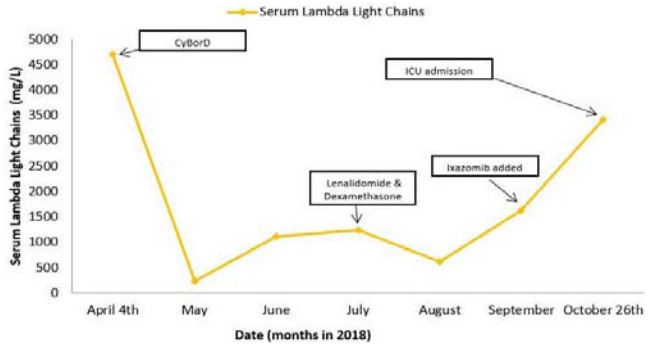

Figure 2: The patient's multiple myeloma course punctuated by various chemotherapeutic regimens.
CyBorD - Cyclophosphamide, Bortezomib, Dexamethasone.

stay. Within 24-hours her tachycardia resolved, and she remained hemodynamically stable without any vasopressor support. Cultures of the blood, urine, and stool were negative. The patient never required mechanical ventilation. On October 28th of 2018, the patient was transfused two units of packed red blood cells for a hemoglobin of 74g/L and given intravenous thiamine, as the treating physicians attempted to address all possible causes of type A LA. Later that day, the Hematology service discussed the patient's poor prognosis - given her refractory MM and current unsuitability for further chemotherapy - with the family, who then chose to proceed with palliative care measures. Finally, the diagnosis of type B LA secondary to rapidly progressive refractory MM was made in the absence of any evidence of tissue hypoxia and other culprit etiologies for type A LA. The patient died the following day.

Discussion

We describe a case of severe LA in a well-oxygenated and hemodynamically stable patient with refractory MM, which posed a diagnostic challenge to this patient's treating team. Although type A LA is the most common cause of LA in patients with cancer [7], the different types of LA often co-exist within a given patient [1-2,4]. Hence, it is important to understand the various conditions that lead to hyperlactatemia, as described below:

Type A LA:

Hypoxia (Figure 3H): When sufficient oxygen is not available, Krebs cycle cannot metabolize pyruvate, which then must be converted to lactate by the action of LDH [8].

Type B LA:

1. Thiamine deficiency (Figure 3T): Thiamine is a necessary co-factor for pyruvate dehydrogenase, which allows the entry of pyruvate into the Krebs cycle by converting it to Acetyl-CoA [8]. In the absence of thiamine, pyruvate cannot undergo oxidative phosphorylation and instead is converted to lactate [8]. Conditions such as beri beri, alcoholism, and malignancy place patients at increased risk of thiamine deficiency [1].

2. Ingestions/Poisonings (Figure 3I): The conversion of pyruvate to lactate requires NADH and H+. Conditions which result in elevated NADH, such as ethanol ingestion and ketoacidosis, promote production of lactate independent of tissue oxygenation

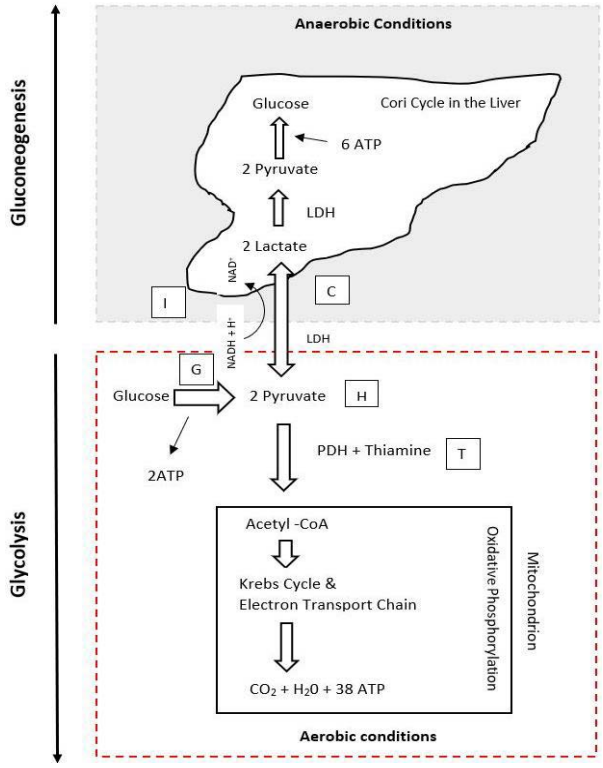

Figure 3: Glucose metabolism and lifecycle of lactate with illustrations of critical steps in the development of hyperlactatemia. Adapted from Suetrong and Walley (2015).
ATP: Adenosine Triphosphate; C: Clearance; G: Glycolysis; H: Hypoxia; I: Ingestions; LDH: Lactate Dehydrogenase; NAD^+/NADH: Nicotinamide Adenine Dinucleotide (oxidized and reduced forms, respectively), PDH: Pyruvate Dehydrogenase; T: Thiamine Deficiency

[1,8].

3. Decreased clearance (Figure 3C): A decreased rate of lactate clearance, as a result of liver dysfunction and/or kidney injury, is another cause of increased serum lactate [8].

4. Type A & B LA

5. Increased glycolysis (Figure 3G): Beta-2 receptor stimulation leads to increased aerobic glycolysis in conditions such as shock, sepsis, pheochromocytoma, cocaine ingestion, and vasopressor use [1-2,8]. Once Krebs cycle becomes saturated with pyruvate, as a result of this increased glycolytic flux, additional pyruvate is converted to lactate [8].

The diagnosis of type B LA is made when there is no evidence of tissue hypoxia despite an exhaustive search (Figure 4) [2,9]. Patients are usually hemodynamically stable and may be well-appearing despite significant acidosis [7]. We conceptualize type B LA as being caused by certain medical conditions, medications, or inborn errors of metabolism: [3].

1. The presence of conditions that are commonly associated with type B LA in a patient's past medical history should alert clinicians to the possibility of this entity. Treatment is individualized to each condition. For example, chemotherapy has been used to control both hematologic and solid malignancies thereby decreasing

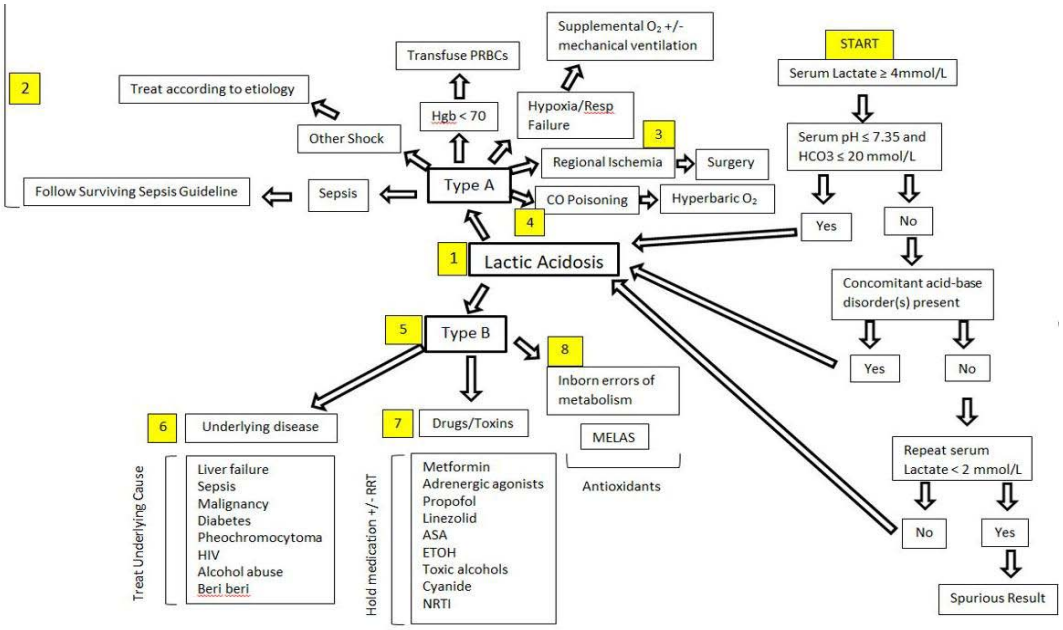

Figure 4: Approach to lactic acidosis.
CO: Carbon Monoxide; HCO_3: Serum Bicarbonate; Hgb: Hemoglobin; MELAS: Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-Like Episodes; NRTI: Nucleoside Reverse Transcriptase Inhibitors; RRT: Renal Replacement Therapy

the amount of lactate generated by the tumor cells [7]. Also, thiamine is an effective therapy for individuals who are thiamine deficient as in those with beri beri [1,7].

2. Medications that cause type B LA usually do so *via* interference with oxidative phosphorylation and/or stimulation of aerobic glycolysis *via* beta-2 adrenergic receptors [1,7]. In some cases, withholding the culprit medication may be enough to resolve the condition. In others, such as poisoning with ethylene glycol, administration of antidotes is required as well as initiation of dialysis to remove toxic metabolites and preserve kidney function [1,7].

3. Patients with inborn errors of metabolism, causing mitochondrial dysfunction, usually present with chronic LA [10]. Treatment of mitochondrial disorders may include antioxidants (coenzyme Q10) and amino acids (l-arginine) [7].

The pathogenesis of LA in malignancy is multifactorial, including: liver and kidney injury, mitochondrial dysfunction, thiamine deficiency, tumor necrosis factor alpha activity, and chemotherapy [5,7,11-14]. Furthermore, malignant cells overproduce lactate even under aerobic conditions by increasing the rates of glycolysis until the capacity of Krebs cycle is exceeded, leading to shunting of pyruvate to lactate, which is known as the Warburg effect [15].

Type B LA was described first in patients with leukemia and lymphoma [5]. The first case of type B LA secondary to MM was described by Mizock and Glass (1994) in a 60-year-old female with relapsed-refractory disease [12]. Since that time, four other case reports of type B LA associated with MM have been described in the literature. The described patients varied from each other in terms of gender, myeloma subtype and stage, chemotherapeutic regimens, and median survival [5,11,13,14]. The only similarities among them and our patient included the presence of refractory MM and utilization of aggressive resuscitative measures to manage the LA.

Conclusion

In summary, refractory MM carries a poor prognosis [11]. After type A LA has been ruled out, physicians should suspect type B LA in this patient population. Chemotherapy represents the only effective treatment, which may also improve survival [11]. Other abovementioned treatments can be considered; however, none of them have been shown to affect mortality [5,11,13]. Furthermore, type B LA secondary to malignancy might itself serve as an indicator of poor prognosis and prompt a discussion of advance care plans in the appropriate patient context [5,11]. Although more research is needed in this area.

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