D-lactic acidosis mediated neuronal encephalopathy in acute lymphoblastic leukemia patient: An under diagnosis

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Background: D-lactic acidosis, also referred as D-lactate encephalopathy, has been reported in patients with short bowel syndrome (SBS).
Case report: The neurologic symptoms include altered mental status, slurred speech, and ataxia. Onset of neurological symptoms is accompanied by metabolic acidosis and high anion gap. We present here a case of D-lactic acidosis in a patient with acute lymphoblastic leukemia (ALL) who developed severe neurological symptoms and metabolic acidosis due to vancomycin-resistant enterococci (VRE) infection, and elevated D-lactic acid.

1. Introduction

Lactic acid has L (+) and D (−) isomers. L-lactate is the major physiological enantiomer of lactate in the human body. L-lactate acidosis is relatively common, occurring primarily as a result of tissue hypoxia, but also due to drugs, toxins and inborn errors of metabolism [1]. Under normal physiologic metabolism L-lactate is a product of anaerobic glycolysis, whereas D-lactate is a product of methylglyoxal (MG) metabolism through glyoxalase pathway [2]. The role of glyoxalases has been reported in several types of human cancer, including colon, renal and prostate cancers, and also in leukemic cells [3,4]. However, in rapid tumorigenesis population, MG can be markedly increased due to extensive glycolysis and infections. Even slightly high concentration of D-lactate can induce severe metabolic acidosis [5] and elevated anion gap and is associated with neurological symptoms and encephalopathy. D-lactate acidosis is a rare event often clinically associated with a neurological syndrome that can be unrecognized in chemotherapeutic cancer population and can respond to appropriate treatment. Most of the cases described in adults have occurred in the context of a jejunoileal bypass surgery. However, no case reports were published in the absence of short bowel syndrome (SBS) with VRE infection in hematological malignancy population.

2. Case report

A 66-y old woman with fever and abdominal pain visited a local hospital emergency care and was found to be leukopenic. The patient's complete blood count was found to be 67% blasts and was referred to oncology clinic at Wisconsin. A bone marrow biopsy showed 70% cellularity with 50% blasts; stains for CD19, human leukocyte antigen (HLA) Class II antigens (HLA-DR), CD34 and CD30 were positive, suggestive of precursor B-cell lineage leukemia. The initial work up was consistent with acute lymphoblastic leukemia (ALL). The patient was treated with a total of six cycles of chemotherapy (R-hyper-CVAD). A month following discharge, the patient started experiencing fever, myalgias, sporadic episodes of dizziness with gait instability, and slurred speech, and was admitted to the nearest hospital. During this hospitalization period she was transfusion dependent and blood cultures were positive for VRE infection for which the patient was treated with cefepime, methotrexate, and linezolid. Prior to discharge, a bone marrow biopsy revealed 90% of blasts (indicative of disease refractory to the prior salvage treatment) and she was referred to Memorial Sloan-Kettering Cancer Center (MSKCC) urgent care center, with the symptoms of tachypnea, an altered mental status and neuropathy (unable to button her shirt), and fatigue suspicious for leptomeningeal disease. A subsequent magnetic resonance imaging (MRI) showed no evidence of leptomeningeal involvement. Routine laboratory testing revealed elevated D-lactic acidosis (pH 7.45, pCO2 24.2 mm Hg, bicarbonate 18 mmol/l, L-lactate 8 mmol/l) with an increased anion gap (26 mEq/l), base excess (−10.8 mmol/l) and no ketonuria (Table 1). D-lactic acid was elevated, so further clinical evaluation ensued. Also...

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altered mental status and neuropathy are not commonly seen in L-lactic acidosis.

Given the clinical laboratory data, a potential diagnosis of D-lactic acidosis was considered and a urine sample was tested for D-lactic acid. The patient’s D-lactic acid was 0.36 mmol/l, which was moderately elevated (normal: 0–0.25 mmol/l) thus making the diagnosis of D-lactic acidosis probable.

The compensated metabolic acidosis (as evidenced by increased pH) might be due to several causes, such as L-lactate, aspirin overdose, methanol or ethylene glycol overdose, diabetic ketoacidosis and D-lactate. Lactic acidosis is characterized by L-lactate levels > 5 mmol/l with serum pH < 7.35; however, the patient’s L-lactic acid was elevated with a pH of 7.45 and these data substantiated the L-lactic acid mediated acidosis. The patient was not on metformin, aspirin, salicylate, isoniazid or other agents that cause metabolic acidosis.

On the basis of the data presented above the compensated metabolic acidosis, wide anion gap, negative base excess and neuronal encephalopathy D-lactic acidosis were likely. The pathological causes for the production of D-lactate in this patient are extensive glycolysis, VRE. The abnormal activity or expression of glyoxalase-1 has been reported in several types of human cancer, including colon, renal and prostate cancers, and also in leukemic cells [3,4]. Due to extensive glycolysis in tumor cells and low serum phosphorous (1.7 mg/dl) a high rate of methyl glyoxal (MG) is produced [6]. This increase in MG favors the production of D-lactic acid through glyoxalase enzymes. Abnormal physiological levels of D-lactate can be due to either increased production, decreased renal clearance or a combination of both.

The mechanism for vancomycin resistance used by VRE involves at least 9 genes, one of which is vanH. D-Hydroxy acid dehydrogenase is the protein product of the vanH gene, and its action creates a pool of D-lactate, which has been described as a mechanism for vancomycin resistance [7].

### 3. Discussion

D-lactic acidosis or D-lactate encephalopathy is a rare neurological syndrome [8] that most commonly occurs in humans with SBS following surgical removal or by-passing of a large portion of the small intestine. The clinical presentation of a D-lactate acidosis is characterized by episodes of encephalopathic and metabolic acidosis [9]. This is a rare clinical observation of symptomatic D-lactic acidosis in an ALL patient. However there may be a degree of under-diagnosis as it is not routinely considered and its incidence has been never reported in the literature. The limited success in treating D-lactic-acidosis in the leukemia/lymphoma population demands further work dedicated to identify the cause of the disorder and also highlights the value of a D-lactate test. Nevertheless, because of inflammation, infection and rapid tumorigenesis in liquid tumors necessitate to investigate the role of D-lactate in cancer patients. Therefore, the number of patients at risk for D-lactic acidosis is also increasing and there are no reports that described D-lactate associated neurological syndromes in ALL population.

The neurologic episodes in SBS can last from hours to days during which plasma D-lactate levels are increased. Although, there is not complete consensus, a plasma D-lactate concentration of >3 mmol/l is frequently used in defining D-lactic acidosis in SBS [7]; however, no clear cut-off levels for D-lactic acidosis were established/defined in the malignant/metastatic populations. The renal reabsorption of D-lactic acid is complete when plasma levels of D-lactate are lower than <2 mmol/l [10]. Fluctuations of D-lactic acid levels in the urine are dependent on the time of specimen collection, treatment conditions (antibiotics for VRE, D-lactate producing microbiome, and chemotherapy) and glucose levels in the diabetic patients. Mihir et al. in 2007 [5] reported D-lactate associated neuropathy at a level of 0.36 mmol/l in SBS patient. D-lactic acidosis should be considered in patient’s preliminary diagnosis in hematological malignancies. It should also be emphasized that D-lactic acidosis occurs more commonly in hematological malignancies than is generally recognized. Therefore, in these types of patients, the possibility of a D-lactic-acidosis needs to be considered in cases of metabolic acidosis with an elevated anion gap in which the identity of the acid is not readily apparent or the symptoms of the patient are consistent with this diagnosis.

### References