Fatal Lactic Acidosis Associated with Lymphoma, Interferon and Ribavirin[§]

Vidula T. Vachharajani[1] and Tushar J. Vachharajani[*,1,2]

[1]*Louisiana State University Health Sciences Center, and* [2]*Overton Brooks Veterans Affairs Medical Center Shreveport, LA, USA*

Abstract: Severe lactic acidosis in malignancies is a rare and fatal complication. We report a 51-yr male who presented with fever, fatigue and syncopal episodes and with past medical history of non-Hodgkin's lymphoma in remission for 3 years, and hepatitis C. He developed severe lactic acidosis and eventually succumbed despite adequate and timely interventions. The clinical presentation resulting from the recurrence of non-Hodgkin's lymphoma was evident from the initial dramatic response to steroid therapy and confirmed subsequently on histopathology. Mitochondrial toxicity from recent use of peg-interferon and ribavirin possibly contributed to the severity of lactic acidosis.

Keywords: Lactic acidosis, lymphoma, peg-interferon.

INTRODUCTION

Hyperlactemia is defined as serum lactate levels greater than 2 mmol/L and is considered severe when the levels are greater than 5 mmol/L. Based on the underlying pathophysiology, two different types of lactic acidosis have been described: type A and type B [1].

Type A lactic acidosis is seen in clinical conditions associated with tissue hypoxia as with septic or cardiogenic shock.

Type B lactic acidosis is less common and refers to the conditions in which there is no clinical evidence of reduction in tissue oxygen delivery. There is overproduction of lactic acid from a variety of reasons. Depending on the etiology and associated disease, it is further sub classified as:

- B1: Ketoacidosis, leukemia, lymphoma, AIDS.
- B2: Medications like phenformin, anti-retrovirals, nitroprusside, ribavirin and toxins like cyanide, methanol.
- B3: Pyruvate dehydrogenase deficiency.

Severe lactic acidosis in malignancies is a rare complication, which is often fatal. The underlying pathogenesis is poorly understood.

CASE REPORT

A 51-year old male was admitted to the Overton Brooks Veterans Affairs Medical Center, Shreveport for evaluation of fever, fatigue and pre-syncopal episodes for 2 weeks. He had lost 20 lbs over the last month and had noticed progressive generalized weakness. His past medical history was significant for hepatitis C and non-Hodgkin's lymphoma, which had been in remission for 3 years. He had received 11 months therapy with peg-interferon and ribavirin for hepatitis C that were discontinued 2 weeks before presentation because of symptomatic anemia.

On physical examination, he was cachectic, lethargic with a respiratory rate of 26/min, tachycardic, blood pressure 80/50 mmHg and a palpable 2x3 cm, firm, non-tender supraclavicular lymph node along with hepato-splenomegaly. Cardiac, lung and neurological examinations were unremarkable.

Laboratory data showed a hemoglobin 7.5 g/dL, hematocrit 21.8%, MCV 81fl, WBC 22K/mm^3 (Neutrophils 55%, bands 20% and metamyelocytes 3%), reticulocyte count 0.5%, platelets 98K/mm^3, SGPT 209U/L, SGOT 1417U/L, total bilirubin 11.5mg/dL, albumin 2.6mg/dL, alkaline phosphatase 193U/L, LDH 1195U/L, uric acid 8.6 mg/dL, Na^+ 130 mmol/L, K^+ 3.6 mmol/L, Cl^- 101 mmol/L, CO_2 12mMol/L, anion gap 31, glucose 46mg/dL, BUN 41mg/dL and creatinine 2.7mg/dL. Arterial blood gas at room air showed: pH 7.1, pCO_2 26mmHg, pO_2 82mmHg and serum lactate 13.4mMol/L. Urine drug screen, alcohol levels and repeated pan-cultures were negative. CT scan of abdomen revealed hepatosplenomegaly, hypodense areas in spleen and liver, enlarged pelvic and inguinal lymph nodes.

Patient was transferred to the intensive care unit with acute respiratory failure and severe metabolic acidosis along with worsening of liver and renal functions. The development of acute renal failure and worsening lactic acidosis required continuous renal replacement therapy. He was also empirically treated with intravenous steroids with a clinical diagnosis of recurrence of non-Hodgkin's lymphoma, while awaiting lymph node histopathology before initiating chemotherapy. Hypotension, lactic acidosis, and liver function significantly improved, following steroid therapy. He was switched from continuous renal replacement therapy to intermittent dialysis therapy for his acute renal failure following significant improvement in his hemodynamic status. Lymph node histopathology was consistent with high-grade B cell lymphoma. Subsequently, due to nosocomial lung infection on the 38th hospital day, steroids were tapered off

*Address correspondence to this author at the Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, USA; Tel: 336 716 8341; Fax: 336 716 4318;
E-mail: tvachhar@wfubmc.edu

[§]This scientific abstract was presented at the Southern Regional meeting of AFMR in New Orleans, LA, USA.

1874-303X/08 2008 Bentham Open

with recurrence of severe lactic acidosis (20.6mMol/L), hypoglycemia, fever, anemia, and thrombocytopenia. His clinical condition never improved to attempt a standard chemotherapy trial. Patient died within 48 hours despite resuscitative measures and reintroduction of aggressive continuous renal replacement therapy.

DISCUSSION

The pathogenesis of lactic acidosis in malignancy remains unknown. Lactic acidosis is a grave and frequently a fatal complication of hematological malignancies [2-5]. Lactic acidosis is derived from the reduction of pyruvic acid and is the end product of the anerobic metabolism of glucose as represented by the following equations [6]:

1- Glucose + 2 ADP + 2 NAD^+ + 2 P_i -----> 2 Pyruvate + 2 ATP + 2 NADH + 2 H^+

2- Pyruvate + NADH + H^+ <==> Lactate + NAD^+

Hydrogen ions generated by the hydrolysis of adenosine triphosphate (ATP) converts lactate to lactic acid. Under normal conditions, the liver and kidney rapidly convert these minimal amounts of lactic acid to pyruvic acid, which is then metabolized to carbon dioxide and water. Under conditions of oxygen deprivation and decreased oxygen delivery to the tissues, anerobic metabolism takes place, resulting in excessive production of lactic acid. Most disease processes that result in decreased oxygen delivery also frequently lead to diminished hepatic function, further compounding lactic acid accumulation.

Cancer cells can produce excessive lactate because of their high rate of glycolysis [3-5]. Lactic acidosis and hypoglycemia have been known to be associated with acute leukemia [7, 8]. The association of refractory lactic acidosis with lymphoma is rare and has been seldom reported. The pathophysiologic mechanism is the overproduction of lactic acid as well as impaired hepatic gluconeogenesis in the presence of hematological malignancy.

Patients who develop severe sepsis can demonstrate lactic acidosis. Lactic acidosis can be a marker of severe stress in the setting of sepsis and is believed to be due to increased production from tissue hypoxia and anaerobic metabolism as well as decreased lactate clearance. The development of nosocomial pneumonia and sepsis in our patient complicated the clinical situation further. Severe metabolic acidosis with arterial pH of less than 7.2 is associated with impaired cardiac contractility and suboptimal response to exogenous catecholamines. Elevation of serum lactate concentration may have negative inotropic effects independent of serum pH. The associated liver and renal failure prevented the use of standard chemotherapeutic drugs in our patient. Trial of steroid therapy was the only possible option, which resulted in rapid resolution of lactic acidosis and significant improvement in renal and liver failure. Further aggressive therapy of non-Hodgkin's lymphoma was prevented by the development of nosocomial infection necessitating withdrawal of steroid therapy, which in turn resulted in recurrence of lactic acidosis, hypoglycemia, fever, anemia and thrombocytopenia. Patient died within 48 hours despite all interventions.

Anti-retroviral drugs used in human immunodeficiency virus (HIV) infected patients along with ribavirin have been reported to cause mitochondrial toxicity that can account for type B lactic acidosis. Nucleoside reverse transcriptase inhibitors (NRTIs) inhibit mitochondrial DNA replication, resulting in liver damage and impaired gluconeogenesis [9-12]. We hypothesize that the recent treatment in our patient with ribavirin and peg-interferon possibly contributed further to the mitochondrial dysfunction and worsening of lactic acidosis. As yet, there is no reported case of lactic acidosis in non-HIV patients treated with ribavirin or interferon.

Lactic acidosis in association with hematological malignancies carries an extremely poor prognosis. Early recognition and prompt institution of chemotherapy may lead to effective correction of lactic acidosis, but not necessarily change the ultimate outcome.

REFERENCES

[1] Cohen R, Woods H. Clinical and Biochemical Aspects of Lactic Acidosis. Blackwell Scientific Publications 1976.

[2] Field M, Block JB, Levin R, Rall DP. Significance of blood lactate elevations among patients with acute leukemia and other neoplastic proliferative disorders. Am J Med 1996; 40: 528-47.

[3] Doolittle GC, Wurster MW, Rosenfeld CS. Malignancy induced lactic acidosis. South Med J 1988; 81(4): 533-6

[4] Osorio S, Bernis C, Cámara R. Lactic acidosis in Non-Hodgkin's lymphoma and response to chemotherapy. Haematologica 2002; 87: (02) ELT05.

[5] Sillos EM, Shenep JL, Burghen GA, Pui C, Behm FG, Sandlund JT. Lactic acidosis: a metabolic complication of hematologic malignancies. Case report and review of the literature. Cancer 2001; 92(9): 2237-46.

[6] Robergs RA. Exercise-Induced Metabolic Acidosis: Where do the Protons come from? Sportscience 2001; 5(2). Available from: http://www.sportsci.org/jour/0102/rar.html (accessed November 25, 2008).

[7] Makino H, Nodak K, Inagaki Y. Lactic acidosis and hypoglycemia associated with acute leukemia. Jap J Int Med 1985; 24(3): 257-62.

[8] Durig J, Fiedler W, de Wit M, Steffen M, Hossfeld DK. Lactic acidosis and hypoglycemia in a patient with high-grade non-Hodgkin's lymphoma and elevated circulating TNF-alpha. Ann Hemato 1996; 72(2): 97-9.

[9] Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 2001; 357(9252): 280-1.

[10] Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. AIDS Read 2003; 13(7): 344-8.

[11] Guyader D, Poinsignon Y, Cano Y, Saout L. Fatal lactic acidosis in a HIV-positive patient treated with interferon and ribavirin for chronic hepatitis C. J Hepatol 2002; 37(2): 289-91.

[12] Moreno A, Quereda C, Moreno L, *et al*. High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin. Antivir Ther 2004; 9(1): 133-8.

Received: August 13, 2008 Revised: October 7, 2008 Accepted: November 12, 2008