Lactic Acidosis: A Rare Oncological Emergency in Solid Tumors at Presentation.

Ranjit R. Nair MD
Lehigh Valley Health Network, Ranjit_R.Nair@lvhn.org

Usman Shah MD
Lehigh Valley Health Network, Usman.Shah@lvhn.org

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Lactic Acidosis: A Rare Oncological Emergency in Solid Tumors at Presentation

Ranjit Nair, MD and Usman Shah, MD

ABSTRACT

Lactic acidosis is a potentially life-threatening complication characterized by accumulation of blood lactate resulting in low arterial pH. The majority of lactic acidosis in malignancies are reported in association with hematologic malignancies. It may result from an imbalance between lactate production and hepatic lactate utilization, but the exact pathophysiology is far more complex than what we can fathom from current micromolecular studies. We report a case of a 71-year-old male with metastatic lung cancer presenting with fatal lactic acidosis in the absence of liver involvement. Review of the literature reveals only 27 reported cases of solid tumors presenting with lactic acidosis, of which nearly all of them had extensive liver metastasis. Patients were treated with aggressive fluid resuscitation, bicarbonate administration and hemodialysis, but the only effective treatment modality was early aggressive chemotherapy initiation.

Key Indexing Terms: Lactic acidosis; Solid tumors; Chemotherapy; Liver; Tumor burden. **[Am J Med Sci 2017;353(4):402–406.]**

BACKGROUND

Our understanding of lactic acidosis and its association with malignancies has been evolving since it was first described by Field et al.[1] Luft et al[2] defined lactic acidosis with the criteria of pH $\leq$ 7.35 and serum lactate $\geq$ 5 mEq/L. Approximately more than 80 cases of malignancies with lactic acidosis at presentation have been documented in literature; most are associated with hematologic malignancies.[3-7] However, an exhaustive review of the literature reveals only 27 reported cases of solid tumors presenting with lactic acidosis. These patients, all but 4 of whom had extensive liver metastasis, were treated with aggressive fluid resuscitation, bicarbonate administration and hemodialysis, but the only effective treatment modality was early aggressive chemotherapy initiation. Chemotherapy works by cytoreducing the tumor and the hepatic involvement, but the exact pathophysiology is far more complex than what we can fathom from current micromolecular studies. We report a case of solid tumor presenting with fatal lactic acidosis in the absence of liver involvement.

CASE

A 71-year-old white male presented with a 1-week history of chest discomfort, shortness of breath and unintentional weight loss. During the work-up, which included a computed tomography chest scan, he was found to have a right upper lobe lung mass (Figure 1). He subsequently underwent biopsy of the mass. His routine blood work at that time showed hemoglobin 10.5 g/dL, white blood cell count 6,700/μL and normal renal and liver function tests. On the day following the biopsy, the patient sustained a fall from generalized weakness, further suffering subarachnoid and subdural hemorrhage. He was admitted to the neurosurgery intensive care unit. Work-up on the day of hospitalization showed the patient in severe metabolic acidosis with high anion gap (AG) and elevated creatinine (Cr). His significant medical comorbidities included a remote history of myocardial infarction with percutaneous intervention, systolic dysfunction with an ejection fraction of 45%, peripheral vascular disease, hypertension, dyslipidemia and hypothyroidism. He had a remote history of tobacco abuse of 40 pack-years. At presentation, the patient was alert and oriented with stable vital signs and normal physical examination.

A complete blood count showed hemoglobin of 10.2 g/dL, white blood cell count of 6,300/mm^3 and a stable thrombocytopenia at 133,000/μL. His significant laboratory abnormalities included Cr 2.1 mg/dL, potassium 5.9 mEq/L, AG 22 and lactate 15 mmol/L, which worsened to Cr 3.1 mg/dL, potassium 6.5 mEq/L, AG 38 and lactate $>$25 mmol/L on day 2. The patient's liver enzymes were within normal limits, bicarbonate level was 11 mEq/L and arterial blood gas showed a pH of 7.11. He had no signs of sepsis, shock or ischemia and multiple blood cultures drawn were negative. A computed tomography scan of the abdomen and pelvis showed normal liver with no abnormal intra-abdominal findings. The patient was initially treated with sodium bicarbonate and further started on emergent hemodialysis.

On day 2, a transient improvement in the metabolic acidosis was noted, despite lactate levels trending up (Figure 2). During days 6-9, metabolic acidosis started to deteriorate, by which time the lung biopsy result showed a high-grade neuroendocrine tumor with mixed large-cell and small-cell features. Immune histochemical stain was positive for the markers CD56, CAM 5.2, AE1/AE3 and

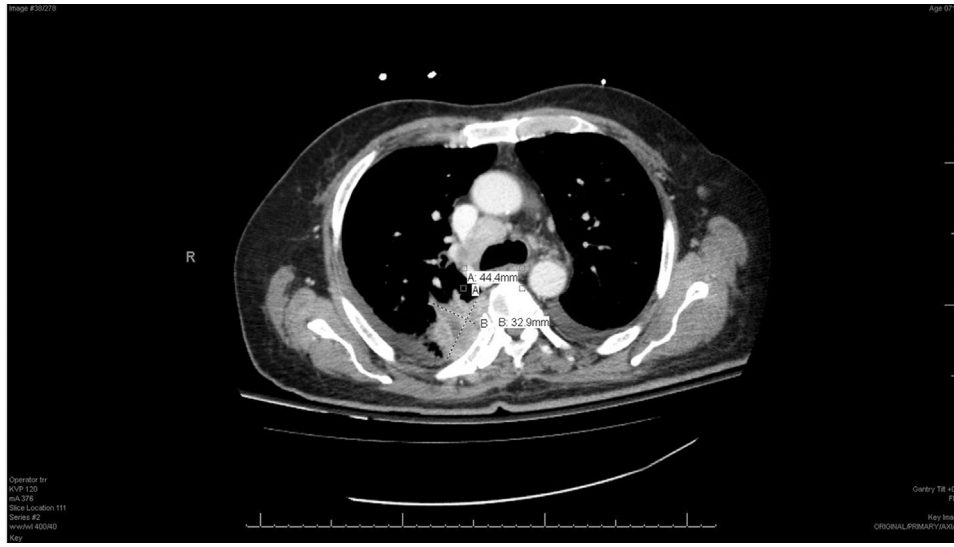

FIGURE 1. Computed tomography scan of the chest with contrast showing the lung mass.

ck7 and negative for p63, ck5/6, TTF1, ck20 and CD3 with Ki-67 staining showing more than 50% positivity. These findings confirmed the diagnosis of neuroendocrine carcinoma. Owing to the presence of nucleated red blood cells, myelocytes and thrombocytopenia, a bone marrow biopsy was performed, which showed extensive infiltration with immunohistochemical evidence of neuroendocrine differentiation.

The patient was started on chemotherapy from day 8 of hospitalization with dose-adjusted cisplatin, etoposide, concomitant dexamethasone and Neupogen. With initiation of chemotherapy, lactate started to trend down. On day 11, he developed febrile neutropenia and was started on broad-spectrum antibiotics; however, the next day he went into severe respiratory failure and required mechanical ventilation. The patient continued to deteriorate, was placed on comfort care on day 18, and died soon after extubation.

DISSCUSSION

Lactic acidosis is often described as a rare and an ominous complication of hematologic malignancies with significant tumor burden or extensive liver involvement. There are only a few cases reported for solid tumors presenting with lactic acidosis, nearly all of which had extensive hepatic involvement. Conversely, our patient had a poorly differentiated lung carcinoma and lactic

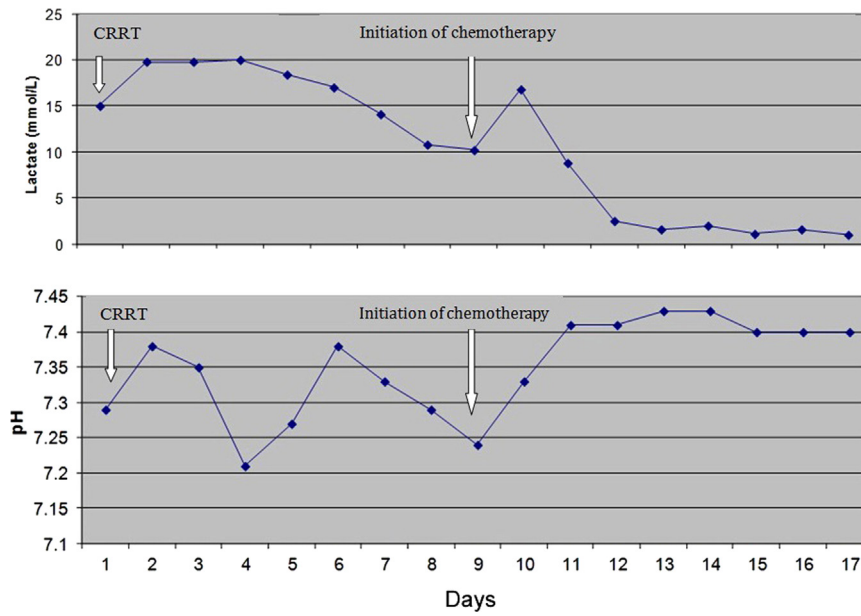

FIGURE 2. Trend of lactate levels following chemotherapy.

TABLE. Case reports of lactic acidosis associated with solid malignancies.

Type of cancer (reference), age and sex of patient	Lactate, (mEq/L)	pH at onset	Liver involvement	Treatment	Outcome in the acute setting
Unknown primary (8), 25 years and female	18.9	7.08	Extensive	Hemodialysis, sodium bicarbonate	Fatal outcome in 8 days
Small cell lung (9), 55 years and male	26	7.17	Extensive	Chemotherapy, radiation	Fatal outcome on day 5
Small cell lung (9), 57 years and male	25.5	7.18	Extensive	Antibiotics	Fatal in a few days. Not specified
Squamous cell lung. Poorly differentiated (10), 84 years and female	14	7.13	No liver involvement	Sodium bicarbonate	Fatal in 2 days
Squamous cell lung. Poorly differentiated (11), 66 years and male	24	7.27	Extensive	Sodium bicarbonate	Fatal in 10 hours
Epidermoid lung (11), 63 years and male	11.4	-	Extensive	Chemotherapy, sodium bicarbonate	Fatal in 4 days
Small cell lung (12), 57 years and male	26.6	7.17	Extensive	Antibiotics, sodium bicarbonate	Fatal in 14 hours
Small cell lung (12), 52y M	25	7.18	Extensive	Antibiotics, sodium bicarbonate	Fatal in 5 days
Breast adenocarcinoma (13), 61 years and female	17.2	-	Extensive	-	Fatal in days
Metastatic cholangiocarcinoma (14), 70 years and male	12.5	7.11	Extensive	Hemodialysis, sodium bicarbonate	Fatal outcome on day 6
Colon cancer (15), 64 years and female	>11	7.24	Extensive	Thiamine, chemotherapy	Lactic acidosis improved with chemotherapy and patient survived the acute episode
Osteogenic sarcoma (16), 16 years and male	19	7.15	No liver involvement	Antibiotics, sodium bicarbonate	Fatal in 3 days
Small cell lung (17), 45 years and male	20	7.11	Extensive	Chemotherapy, sodium bicarbonate	Survived and was discharged from hospital
Breast adenocarcinoma (18), 36 years and female	11.8	7.34	Extensive	-	Fatal in 6 days
Breast adenocarcinoma (19), 67 years and female	17.2	-	Extensive	-	Fatal in days
Undifferentiated large cell metastatic neoplasm of presumed lung origin (20), 81 years and male	12	7.24	No liver involvement	Sodium bicarbonate	Fatal
Metastatic breast adenocarcinoma (21), 31 years and female	16	-	Extensive	Antibiotics	Fatal
Metastatic breast adenocarcinoma (22), 36 years and female	5	7.27	Unknown	Chemotherapy, sodium bicarbonate	Survived with complete remission at 14 months
Small cell lung (23), 79 years and male	5	7.26	Extensive	Sodium bicarbonate	Fatal
Prostate adenocarcinoma (24), 71 years and male	22	7.07	Extensive	Chemotherapy, sodium bicarbonate	Fatal within days
Breast adenocarcinoma (25), 86 years and female	7.5	-	Extensive	Thiamine, Sodium bicarbonate	Fatal in few weeks
Small cell lung (26), 64 years and male	15.8	7.18	Extensive	Hemodialysis, sodium bicarbonate	Fatal

(continued on next page)

TABLE. *(continued)*

Type of cancer (reference), age and sex of patient	Lactate, (mEq/L)	pH at onset	Liver involvement	Treatment	Outcome in the acute setting
Small cell carcinoma of the lung (27), 70 years and male	15	7.29	No liver involvement	Supportive bicarbonate chemotherapy	Survived the acute event but died after 3 months
Reticulum cell sarcoma (28), 53 years and female	15.9	7.13	Extensive	Supportive bicarbonate chemotherapy	Fatal in 1 week
Moderately differentiated adenocarcinoma of unknown primary origin (29), 76 years and male	7.7	7.34	Extensive	Supportive bicarbonate hemodialysis	Fatal on day 15
Metastatic small cell carcinoma (30), 73 years and male	>10	7.37	Extensive	Supportive	Fatal on day 33
Small cell carcinoma of the lung (31), 56 years and male	12.8	7.32	Extensive	Bicarbonate chemotherapy	Survived and was discharged from hospital

acidosis with absent hepatic involvement. A thorough review of the reported cases of solid tumors presenting with lactic acidosis yielded a total of 27 cases (Table).[8-31] Of these, 14 (>50%) were lung malignancies and, with the exception of 4 cases,[10,16,20,27] all had metastatic liver disease. Several theories, postulated to explain the mechanism of lactic acidosis in solid malignancy, include the high tumor burden with associated hypoxic microenvironment, increased lactate production by tumor cells and decreased lactate utilization due to hepatic involvement. The pivotal importance of the liver in all forms of lactic acidosis has been emphasized by Berry and others.[32,33] Although a peripheral increase in lactate production may be the initiating event in lactic acidosis, it is a defect in the liver's ability to metabolize lactate that results in onset of clinical acidosis. In our patient, there was no significant liver involvement throughout the hospital course, leading us to believe that the lactic acidosis was due to aggressive tumor activity. Research during the past decade has identified the role of the microvascular and microenvironmental stress surrounding a tumor cell, which explains this phenomenon.[34-36]

Lactic acidosis in the setting of solid tumors is a poor prognosticator and in all cases warrants the immediate initiation of aggressive chemotherapy. In our patient, despite an initial improvement in metabolic acidosis with hemodialysis, the results were only transient. Immediately after the administration of chemotherapy, a spike in lactate level was noticed, followed by a rapid improvement of pH and lactate levels in 3 days.

Of the 27 cases reviewed here, only 5 patients survived the acute episode of lactic acidosis with documented improvement in the metabolic acidosis. Of the 5 patients, 3 patients were <60 years of age with no significant comorbidities and all 5 patients were newly initiated on chemotherapy after the onset of lactic acidosis. In patients with significant liver involvement, an improvement in the lactate level was noticed even days before improvement in the liver function supporting the concept of an alternate pathway for significant lactate production. Lactic acidosis with an absence of hepatic involvement was reported in only 4 solid tumor cases; of these, 3 patients unfortunately did not survive long enough to receive chemotherapy.

With intent to avoid deleterious effects of acidosis to the cardiovascular system, aggressive bicarbonate administrations were reported in most cases. Among 18 of these cases, in which sodium bicarbonate therapy was administered without initiation of hemodialysis, 14 had either no response or worsening of the lactic acidosis soon after administration and 3 cases reported an improvement in the acidosis; however, the response was transient and the patient deteriorated within 24-48 hours.[12,20] In the case reported by Fraley et al,[20] administration of bicarbonate improved the pH but not the serum bicarbonate level. There was a net increase in acid excretion in urine and increased calculated acid pool, suggesting that the bicarbonate corrected the extracellular pH but did not affect the significant intracellular acid production due to high tumor cell turnover. Owing to paradoxical increases in lactate and carbon dioxide production, use of sodium bicarbonate is not favored in these patient groups.[20,37-40]

None of the cases reported herein, with the exception of 3 cases[8,14,26] and the patient at our hospital, were initiated on renal replacement therapy due to rapid deterioration, early death or in a few cases, unclear reasons. Prikis et al[40] reported a case of a patient with undiagnosed B-cell lymphoma and severe lactic acidosis. Large amounts of bicarbonate were administered concomitant with sustained low-efficiency dialysis, which helped to stabilize the patient until chemotherapy was initiated and helped to avoid mechanical ventilation.[40] Until more studies on solid tumors are available, hemodialysis could be considered to act as a bridge until more definitive cytoreductive chemotherapy can be instituted.

Type B lactic acidosis is a rare and potentially fatal complication of aggressive tumors and should be considered in the differential of solid tumors with aggressive tumor burden. Despite timely treatment initiation, patients with lactic acidosis can deteriorate rapidly due to cardiorespiratory failure. Though anecdotal, the literature is provocative enough to suggest early and aggressive chemotherapy initiation in this patient group. The prognostic factors that can possibly affect the outcome are patient's age, comorbidities, type of tumor and the rapidity of chemotherapy initiation. Currently, there is a lot of interest in identification of tumor microenvironmental stress and genetic factors to delineate the pathophysiology of lactate generation in aggressive tumors.[34-36] Understanding this complex web of relationships and the consequential ability to untangle the role of each of these factors may lead to novel therapeutic strategies to modify tumor progression and complications.

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From the Department of Hematology and Oncology (RN, US), Lehigh Valley Health Network, John and Dorothy Morgan Cancer Center, Allentown, Pennsylvania.

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Correspondence: Ranjit Nair, MD, Department of Hematology and Oncology, Lehigh Valley Health Network, John and Dorothy Morgan Cancer Center, 1240 South Cedar Crest Boulevard, Suite 401, Allentown, PA 18103 (E-mail: ranjit_r.nair@lvhn.org).