

Malignancy Associated Type B Lactic Acidosis: A Rare, yet Fascinating Oncological Emergency

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ABSTRACT

Type B lactic acidosis has been described infrequently in hematologic malignancies, but even less often in solid tumors. Since 1978, there have been only 58 cases of solid tumor associated Type B lactic acidosis described in the literature. Lung cancer (neuroendocrine) is the most common tumor; others frequently have a poorly/undifferentiated histology. The prognosis is dismal. Malignancy associated type B lactic acidosis is not associated with hypoxemia. The most highlighted pathogenetic mechanism is the Warburg effect (aerobic glycolysis of tumor cells causing excess lactate). We describe a patient with metastatic GI neuroendocrine carcinoma with profound lactic acidosis, who died within 24 hours. When extremely ill cancer patients present with lactic acidosis, sepsis is usually a primary concern. This case highlights the need for providers to consider malignancy associated lactic acidosis (MA-LA) in the differential diagnosis, particularly in patients with advanced malignancies, of lung origin, of neuroendocrine or poorly/undifferentiated histologic subtypes. The implications and approach are distinct from Type A/D lactic acidosis, and would involve treatment of the underlying malignancy at the earliest.

KEYWORDS: Lactic Acidosis, Type B Lactic Acidosis, Solid Tumor Malignancy, Warburg Effect, Neuroendocrine Tumors

INTRODUCTION

Lactic acidosis is a common occurrence in critically ill patients and stands as the most prevalent cause of metabolic acidosis. It is characterized by a pH of ≤ 7.35 and a serum lactate level of ≥ 5 mEq/L.¹ The condition is categorized into three subtypes based on its underlying pathophysiology. Type A lactic acidosis is associated with sepsis, tissue hypoperfusion, and hypoxemia. Type B lactic acidosis occurs in oxygen-rich conditions, the causes of which may involve exposure to toxins, medications (e.g., metformin, HIV antiretroviral therapy), diabetic ketoacidosis, thiamine deficiency, liver disease, and, though rare, malignancies (hematologic, and even less commonly, solid tumors).² Type D lactic

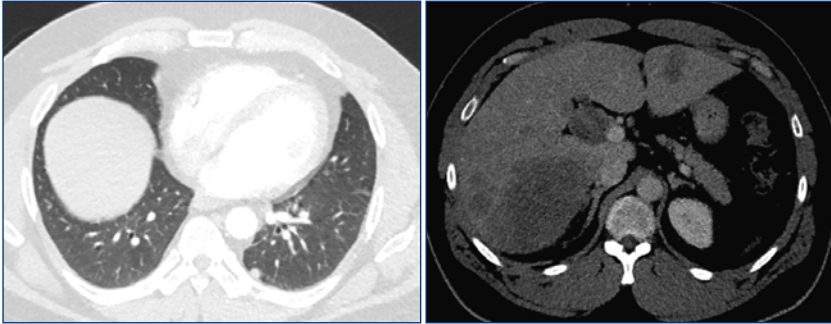
acidosis is characterized by excessive D-lactic acid production stemming from the proliferation of intestinal bacteria.

We present a patient who developed Type B lactic acidosis in the context of a widely metastatic aggressive neuroendocrine carcinoma of GI origin.

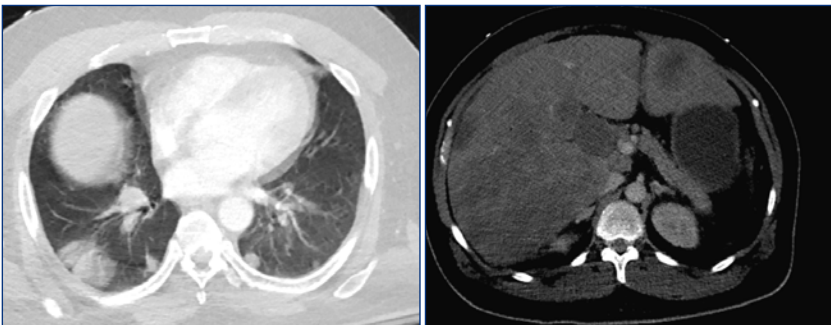
CASE PRESENTATION

A 51-year-old African American male, previously healthy, presented with right shoulder pain. Imaging studies revealed a 3.4cm soft tissue mass within the common bile duct area, multiple liver hypodensities, bilateral lung nodules measuring up to 7 mm, and a 1.7cm lymph node near the right hilum; brain imaging was negative. The right shoulder pain was attributed to referred pain from the liver. Laboratory findings revealed a markedly elevated lactate dehydrogenase (LDH) of 1440 Units/L (125–243), an INR of 1.5, and liver enzymes which were mildly/minimally elevated. A liver biopsy was done and the immunohistochemical stains were positive for synaptophysin, equivocal for chromogranin and CD56, negative for keratin 7, keratin 20, TTF-1, p40, CA19-9 and GATA-3. Overall, the findings were consistent with large cell neuroendocrine carcinoma, likely originating from the gastrointestinal tract. He was started on treatment with etoposide (VP-16) and carboplatin. Next generation sequencing testing was unremarkable; PDL1 was 0, and tumor mutational burden (TMB) was 4. Following two cycles of chemotherapy, the patient developed a cough, dyspnea, diffuse pain, and weakness. A chest CT scan confirmed the presence of a pulmonary embolus and demonstrated disease progression in the periportal and aortocaval nodes, along with the emergence of a new pulmonary nodule in the left lung. Notably, hepatic metastases and the lymph nodes near the right hilum remained stable (**Figures 1,2**). He was treated for possible pneumonia with outpatient antibiotics. However, his condition continued to deteriorate over the next 10 days, resulting in confusion, anorexia, a persistent cough with clear sputum, and increased dyspnea. On exam, vital signs revealed tachycardia (129 bpm), tachypnea (respiratory rate 28), and an oxygen saturation level of 95% on room air. Physical examination was notable for a significantly enlarged liver, at least five fingerbreadths below the margin. Laboratory studies displayed a white blood cell count of 44.7 K/cmm (4.5–11), platelet count 447 K/cmm

Figures 1 and 2. Cross sectional images of CT chest and abdomen showing left lower lobe pulmonary nodule and multiple hypodensities in the liver.



Figures 3 and 4. Cross sectional images of CT chest and abdomen showing mass like consolidation in the right lower lobe, increased size of left lower lung nodule, increased hepatic metastases at the time of presentation with lactic acidosis.



(140-360), serum creatinine 1.3 mg/dL (0.5-1.5), potassium 5.8 mMOL/L (3.5-5.0), anion gap 33 (8-12), CO₂ 7 mMOL/L (20-30), Bilirubin 4.1mg/dL (0.2-1.2) mostly direct, gamma glutamyl transferase 555 (10-65), aspartate transferase 351 Units/L (5-34), alanine transferase 132 Units/L (7-52), and glucose 80mg/dL (65-100). Lactate levels were alarmingly high at >11.95 (0.5-1.8). A urinalysis detected the presence of blood, but was negative for leukocyte esterase, nitrite or pyuria. Blood cultures were negative. Peripheral blood smear, which revealed dacrocytes, nucleated red blood cells, and early white cells, was consistent with a leucoerythroblastic picture, suggestive of bone marrow involvement by tumor. While a CT of the head was unremarkable, CT scans of the chest, abdomen, and pelvis confirmed further disease progression, particularly in the liver and chest, without evidence of ductal dilatation (**Figures 3,4**). Reevaluation of the previously suspected "pneumonia" was more consistent with disease progression, based on the appearance of an enlarging consolidative mass. In the absence of any apparent infection, the possibility of MA-LA was considered the most likely diagnosis. The patient's family opted against hospital admission, and he was discharged home with hospice services. Unfortunately, the patient died 24 later.

DISCUSSION

Lactic acidosis can arise due to an increased production of lactate, decreased metabolism, or a combination of both factors. Type A lactic acidosis is primarily associated with tissue hypoperfusion, while Type D lactic acidosis is attributed to the excessive production of D-lactic acid resulting from small intestinal bacterial overgrowth. In contrast, Type B lactic acidosis occurs in the absence of tissue hypoperfusion.

Malignancy associated type B lactic acidosis is a rare but life-threatening oncological emergency. It was first documented in 1963 in a patient with leukemia³ and has since been reported in both hematological malignancies and, much less commonly, in solid tumors.⁴ Upon literature review on PubMed from the year 1978 (first case associated with a solid tumor) to 2023, we identified 58 reported cases of Type B lactic acidosis in patients with solid tumors.

The exact pathophysiology of MA-LA remains unclear; however, there are several proposed mechanisms. One prominent hypothesis, known as the Warburg effect, is a phenomenon in which tumor cells switch their metabolic machinery towards a glycolytic state even in the presence of normal oxygen concentration, leading to excess lactate production.⁵ Another hypothesis suggests that altered lactate metabolism due to liver and kidney dysfunction plays a role; the liver metabolizes 80% of lactic acid through gluconeogenesis to produce glucose, while the kidneys are responsible for metabolizing the remainder. This observation corresponds to the fact that most solid tumor cases associated with lactic acidosis have liver metastases. However, this relationship is not vice versa, and the presence of liver metastasis does not suggest the patient will develop lactic acidosis. Thirdly, severe thiamine depletion has been linked to lactic acidosis especially in the context of rapidly proliferating tumors, and patients who get total parenteral nutrition. Thiamine acts as a cofactor for pyruvate dehydrogenase, an enzyme critical for the conversion of pyruvate to acetyl CoA. In the absence of thiamine, excess pyruvate is converted to lactic acid by lactate dehydrogenase.⁶ Finally, the role of tumor necrosis factor alpha (TNF-alpha) in inhibiting pyruvate dehydrogenase and increasing lactic acid production has also been proposed, but remains unclear in solid tumors. Some solid tumors express other growth factors such as insulin-like growth factor that induces overexpression of the enzyme type II hexokinase, which is responsible for catalyzing the first step in glycolysis which can lead to increased glycolysis and pyruvate production.⁷

Effective management strategies for lactic acidosis in the context of solid tumors have not been definitively established. Thiamine supplementation is often employed (but is not a standard of care, and the benefit unclear), as thiamine serves as a cofactor in the conversion of pyruvate to acetyl CoA, potentially diverting pyruvate away from lactic acid production. Intravenous bicarbonate and renal replacement therapy have been utilized as temporary measures, although their efficacy is limited as they do not directly target the mechanisms driving lactic acid overproduction.⁴ In general, chemotherapy is considered the most effective treatment as it reduces tumor burden and addresses malignant liver involvement. However, many patients at this stage have aggressive disease and poor performance status which may preclude them from getting prompt antineoplastic therapy.

To date, there have been a total of 59 cases of MA-LA reported in solid tumors (including our present case). Twenty-five (42%) of the cases were of neuroendocrine origin, and the majority of the other cases appeared to be undifferentiated or poorly differentiated. Most patients had lung cancer (30%), followed by gastrointestinal (24%), and breast (18%) malignancies. Of the 59 cases, 66% cases had liver metastases. Most patients died within 10 weeks (80%), with 55% died within a week.

A comprehensive workup for lactic acidosis is imperative in critically ill patients who have cancer; given the severity of MA-LA, lack of good treatment options, and dismal prognosis overall, this phenomenon should be considered particularly in cancer patients who have a high tumor burden, extensive liver metastases, and a neuroendocrine or poorly/undifferentiated histology. The implications and approach are different from that of other forms of lactic acidosis. The overall prognosis for MA-LA is exceedingly poor, with survival typically measured in days to weeks.⁸

CONCLUSION

This case underscores the critical role that malignancy can play in Type B lactic acidosis, and emphasizes the importance of considering it as a potential cause of lactic acidosis in patients who do not exhibit clear signs of tissue hypoperfusion, sepsis, and hypoxemia. MA-LA is associated with few effective treatment options, and an extremely grim prognosis.

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