Type B Lactic Acidosis in a Solid Tumor Malignancy without Liver Metastases: A Rare Case of Refractory Acidosis

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Abstract

Malignancy-induced type B lactic acidosis is a rare, yet fascinating, cause of refractory acidosis in patients with cancer, often unresponsive to usual medical treatments. Case reports usually discuss the paraneoplastic phenomenon in hematologic malignancies; however, we present the case of a 72-year-old woman with metastatic breast cancer, who initially presented to hospital with an elevated lactate in the absence of acidosis. She appeared to improve with fluids; however, she then represented 2 weeks later with a severe metabolic acidosis and undetectable high lactate level. Ultimately, the patient did not respond well to supportive care, and the decision was made to pursue comfort-directed therapy.

Résumé

L'acidose lactique de type B induite par une tumeur est une cause rare, mais extrêmement intéressante, d'acidose réfractaire chez les patients cancéreux et qui, souvent, ne répond pas aux traitements médicaux habituels. Les études de cas traitent généralement du phénomène paranéoplasique des tumeurs malignes hématologiques; toutefois, nous présentons le cas d'une femme de 72 ans atteinte d'un cancer du sein métastatique, qui s'est d'abord présentée à l'hôpital pour un taux élevé de lactate dans le sang, mais sans acidose. Son état a semblé s'améliorer grâce à un apport de liquides; toutefois, elle s'est présentée de nouveau à l'hôpital deux semaines plus tard pour une acidose métabolique grave et un taux élevé de lactate indétectable. Au bout du compte, la patiente n'a pas bien répondu aux soins de soutien, et il a été décidé d'appliquer les soins de confort.

Case Presentation

A 72-year-old woman was admitted to hospital with a 2-day history of weakness, malaise, nausea, and decreased oral intake, as well as a 1-day history of expressive aphasia and word-finding difficulties. She had a similar recent presentation to hospital 2 weeks prior, during which she was diagnosed with hypercalcemia and treated with intravenous pamidronate. The patient also reported 2 months of gradual functional decline and a 20-pound unintentional weight loss. On review of systems, she had no infectious symptoms, including cough, shortness of breath, fever or chills, abdominal pain, diarrhea, lower urinary symptoms, mouth sores, or other neurological symptoms.

Her past medical history was significant for metastatic, triple-negative, invasive ductal carcinoma of the left breast, T3N1, status post-mastectomy, and adjuvant radiation, with metastases to the left chest wall and pancreatic tail found

during her previous hospital admission. Her most recent CA 15-3-K was 512 kU/L (normal 0–31); CEA was 3.3 ug/L (normal 0–5). She also had a previous history of triple-positive breast cancer in the left breast, depression, and severe compression fractures of the lumbar spine. Her home medications consisted of long-acting morphine for pain and trazodone for insomnia. During her prior hospital admission, she was hemodynamically stable, but had been found to have an elevated anion gap with a compensated metabolic acidosis on a venous blood gas (pH 7.35, pCO_2 32mmHg, HCO_3 18mmol/L). She had elevated beta-hydroxybutyrate at 1.14mmol/L, thought to be related to malnutrition ketosis in the setting of her cancer. Her lactate was also significantly elevated (15.3mmol/L), which improved moderately with intravenous fluids to 11.6mmol/L.

Upon representation to hospital, the patient was tachycardic, with a heart rate of 105 beats per minute, blood pressure of 127/73, respiratory rate of 16, oxygen saturation of 96% on room air, and temperature of 36.6° Celsius. She appeared comfortable and was sitting up reading. She was mildly cachectic, and physical exam was consistent with hypovolemia: dry axilla, dry mucus membranes, and flat jugular venous pressure. Otherwise, her cardiac, respiratory, and abdominal exams were noncontributory. Neurologically, she was alert and oriented but had noticeable word finding difficulties and self-reported confusion; however, the remainder of her neurological exam was normal. She had a small, stage two sacral ulcer with no discharge or surrounding erythema.

The full panel of her laboratory investigations is listed in Table 1. Notably, laboratory results again demonstrated hypercalcemia and a high anion gap metabolic acidosis with significantly elevated lactate (>17 mmol/L). A chest X-ray showed new compression fractures. A bone scan showed no clear metastasis. A CT of the chest, abdomen, and pelvis showed no liver lesions but did show new metastasis in left chest wall and pancreatic tail.

Her hypercalcemia was treated with 2 L of intravenous (IV) normal saline bolus and IV zoledronic acid. Her constipation, confusion, and word-finding difficulties resolved by the following morning, leaving only mild residual nausea. She was started on a bicarbonate infusion in an attempt to treat the persistent acidosis. Despite continuing the bicarbonate infusion for several days, however, the patient's lactate remained undetectably high, and the blood pH remained acidotic. She still appeared clinically well, and was thus transitioned to oral bicarbonate.

A number of causes for lactic acidosis, including thiamine deficiency, sepsis, renal dysfunction, hepatic dysfunction, and hypoxia, were ruled out (Table 1). She had no history of toxic alcohol ingestions or any pharmaceutical culprits. Ultimately, it was determined her lactic acidosis was malignancy-induced. She was treated for type B lactic acidosis associated with malignancy supportively, and treatment for the underlying malignancy was considered. Hence, medical oncology was consulted, and she was offered palliative systemic chemotherapy. However, the patient and her family decided to focus on symptom-directed care only. She died in hospital 2 weeks later.

Discussion

Lactic acidosis is defined as a serum pH less than 7.35 coupled with a serum lactate greater than 5 mmol/L.[1] There are three types of lactic acidosis described in the literature: Type A, Type B, and Type D.[2] Type A represents lactate overproduction secondary to hypoperfusion and tissue hypoxia. Type D lactic acidosis is an uncommon subtype, occurring mainly in the setting of gastrointestinal malabsorption and short bowel syndrome.[2]

This case presentation shows an example of Type B lactic acidosis, defined as nonhypoxia-induced lactic acidosis. Causes of Type B lactic acidosis include medications (such as metformin and propofol), alcohol intoxication, and, rarely, malignancy.[3]

Malignancy-induced Type B lactic acidosis was first described in 1963, observed in a patient with leukemia.[4] Since then, there have been case reports of lactic acidosis in patients with both hematologic and, less commonly, solid tumor malignancies. In the realm of solid tumors, metastatic small cell carcinoma and undifferentiated carcinoma represent the leading causes identified in the literature.[2] We performed a literature search in MEDLINE and PUBMED with search strategy of terms "lactic acidosis," "solid tumors," and MeSH terms for "neoplasms" and "acidosis, lactic," respectively, from 1970 to 2018. Most cases of solid-tumor Type B lactic acidosis in the literature (90% +) are associated with liver metastases; indeed, there are only an isolated number reported in the literature in recent years (Table 2). A 1992 review article of malignancy-induced Type B lactic acidosis reported three cases of solid-tumor-induced lactic acidosis without liver metastases, one of which was a sarcoma, which rarely spreads to the liver.[5] A 2011 literature review subsequently found no cases of solid-tumor-induced lactic acidosis without liver metastases in a 10-year period.[6] We report a case of a rare cause of lactic acidosis arising in a breast cancer without known liver metastases; a similar case does not appear to be reported in the literature.

The mechanism by which malignancy leads to Type B lactic acidosis is not fully understood. However, popular speculation suggests a form of aerobic glycolysis, termed the "Warburg Effect."[3] As tumors expand, cancer cells frequently outgrow their original blood supply. Survival of the fittest preferentially selects those cells with maximal capacity for anaerobic (lactic-acid-producing) glycolysis. However, via the Warburg Effect, some of these same cancer cells have developed the ability to engage in anaerobic glycolysis even in the presence of oxygen (hence, "aerobic glycolysis").[1] This leads to an overproduction of lactic

Table 1. Laboratory Values

Lab variable	Normal reference range	Prior admission blood work	Prior admission day 10 blood work	Current admission blood work	Current admission day 3 blood work
White cell count	4.0–10.5 × 10^9/L	9.1	5.7	6.0	4.2
Hemoglobin	3.7–5.1 × 10^{12}/L	**104**	**95**	**87**	**69**
Platelets	150–400 × 10^9/L	**102**	**60**	**59**	**43**
Calcium	2.25–2.80 mmol/L	**3.09**	2.62	**2.82**	
Ionized calcium	1.15–1.32 mmol/L	**1.45**		**1.41**	
Phosphate	0.74–1.52 mmol/L	1.07		1.26	
Magnesium	0.66–1.07 mmol/L	0.86		0.91	
Sodium	133–145 mmol/L	138	140	138	
Potassium	3.7–5.5 mmol/L	4.5	4.3	4.4	
Chloride	97–110 mmol/L	97	94	101	
Urea	4–8 mmol/L	**10.4**			
Glucose, random	3.5–11.1 mmol/L	**4**.8			
Total CO_2	19–27 mmol/L	**17**	22	**8**	
Anion Gap	8–12	**24**	**24**	**29**	
Creatinine	0–85 umol/L	69		50	
LDH	120–315 U/L	**472**			
Uric acid	155–365 umol/L	**349**			
Albumin	35–38 g/L	35		35	
AST	10–35 U/L	32	**76**	28	
ALT	8–40 U/L	17	46	22	
ALP	61–157 U/L	126	132	**328**	
GGT	3–45 U/L			34	
Bilirubin (total)	0–17 umol/L	9	14	10	
INR	0.9–1.1			**1.4**	
Lipase	0–79 U/L			23	
BOHB	0.00–0.37 mmol/L	**1.12**		**1.14**	
Lactate	0.5–2.2 mmol/L	**15.3**		**>17**	**>17**
VBG (pH)	7.32–7.43	7.35		**7.08**	**7.22**
VBG (pCO_2)	40–50	**32**		**27**	**27**
VBG (pO2)		37		18	15
VBG (HCO3)	22–29	**18**		**8**	**11**
PTHrP	14–27 pg/mL	11			
PTH	2.0–9.4 pmol/L	1			
Thiamine	75–225 nmol/L			162	
Serum osmolality	281–297 mmol/kg			309	
Acetaminophen	54–112 umol/L			<20	
Blood cultures				No growth	
TSH	0.40–4.50 mIU/L			1.16	
B12	140–650 pmol/L			196	
Reticulocytes	30–120 × 10^9/L			72	
Ferritin	4–205 ug/L			356	
Folate	7–45 nmol/L			26	

Table 2. Reported Cases of Solid-Tumor-Induced Lactic Acidosis without Liver Metastases

Case	Year	Tumor
Nair R, Shah U	2017	Lung primary
Rao KS, Mehta R, Ferlinz J	1988	Lung primary, Squamous cell carcinoma
Stacpoole PW, Lichtenstein ML Polk JR et al.	1981	Sarcoma
Fraley DS, Adler S, Bruns FJ, Zett B	1980	Lung primary

acid, which may ultimately lead to lactic acidosis. It has been hypothesized that the ability to engage in aerobic glycolysis lends cancer cells an advantage in cell proliferation.[7] Specifically, the acidic environment created by lactate around cells may contribute to genomic instability, local invasion, progression to metastatic disease, and resistance to treatment.[8] This process is more likely to occur in the setting of liver metastases (and consequent functional impairment) as roughly 80% of the body's lactate is metabolized in the liver.

Of course, not all malignancies lead to lactic acidosis. Risk factors identified in the literature include nutritional deficiencies (such as thiamine deficiency), hepatic or renal impairment (e.g., from liver metastases or chronic conditions), and a high rate of tumor cell proliferation.[3] Clinical examination is typically nonspecific but may include Kussmaul respirations (tachypnoea without hypoxia) and refractory hypoglycemia despite intravenous dextrose administration.[1]

Treatment of malignancy-induced Type B lactic acidosis is mainly supportive and the diagnosis itself conveys a poor prognosis.[4] Most patients diagnosed with malignancy-related lactic acidosis will die within hours to months.[7] The best-known treatment is chemotherapy or systemic treatment of the underlying malignancy.[3] Supportive treatment with thiamine supplementation has been shown to have no risk in the acute setting, albeit the degree of potential benefit being unclear. Renal replacement[3] and bicarbonate drips[3,7] have not been shown to have any improvement or change in outcome.

Conclusion

Solid tumor malignancies without liver metastases represent a rare cause of Type B lactic acidosis. However, malignancy is an important cause of lactic acidosis and should be considered in patients presenting with elevated serum lactate in the setting of acidosis without clear hypoperfusion and tissue hypoxia, particularly when routine measures such as antibiotics and intravenous bicarbonate infusions do not induce improvement. Finally, malignancy-associated lactic acidosis suggests a poor overall prognosis.

Key Points

1. The causes for lactic acidosis expand beyond the typical culprits for shock.
2. Risk factors for malignancy-associated lactic acidosis include nutritional deficiencies, hepatic impairment, renal impairment, and a high rate of cell proliferation.
3. Treatment for malignancy-associated lactic acidosis is focused on treating the underlying malignancy.
4. Malignancy-associated lactic acidosis suggests a poor overall prognosis.

Competing Interests

None.

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