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REVIEW

Type B lactic acidosis in solid malignancies

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ABSTRACT

Background: Type B lactic acidosis is thought to be a rare complication of malignancy. It was first described in patients with acute leukaemia by Field *et al.* in 1963. Since then, it has been observed more often, in particular in haematological malignancies and rarely in solid tumours.
Methods: Previously reported cases of lactic acidosis in solid malignancy are reviewed. In addition, we report a case of type B lactic acidosis in a woman with metastatic breast cancer. Afterwards, we speculate on the elusive pathophysiology of this oncological emergency.
Results: 14 cases of lactic acidosis due to solid malignancies, without prior chemotherapy, were identified. The cases were published from the year 1978 to 2006.
Discussion: Several theories concerning the mechanism for type B lactic acidosis in solid malignancy have been postulated. During the last decade, more and more evidence supports the role of overproduction of lactic acid due to ischaemia in the neoplastic tissue bed and with cancer cells having an aberrant energy production.

Keywords: Lactic acidosis, malignancy, solid tumour

INTRODUCTION

Lactate is a tricarbonic anion which can be viewed as a metabolic dead-end in that it is initially produced from pyruvate and later re-converted into pyruvate. The major factors determining lactate production are the pyruvate concentration and to a lesser extent the redox state of the cytosol. These in turn are influenced by glycolytic flux, the transamination from alkaline and mitochondrial function.[1] One molecule of lactate combines with one positive hydrogen ion to form lactic acid.[2] Normal subjects produce 15 to 20 mmol/kg of lactic acid per day. Virtually all tissues can produce lactic acid, the major contributors being skin, erythrocytes, brain and skeletal muscle.[3] In normal conditions, lactate is metabolised mainly in the liver and to a lesser extent in the kidneys to form glucose, a process known as gluconeogenesis. Furthermore, lactate utilisation is determined by the flow of pyruvate into the Krebs cycle.[1,2]

Hyperlactataemia and subsequent lactic acidosis develops in cases of increased production and/or diminished utilisation of lactate. It should be noted that hyperlactataemia is not necessarily accompanied by acidosis and can occur due to peripheral hypoxia, leading to dysfunction of the mitochondrial respiratory chain, causing a switch to anaerobic metabolism. This occurs in states such as sepsis, burns or trauma.[1] Current diagnostic criteria for lactic acidosis are a pH less than 7.35 and a plasma lactate concentration greater than 5 to 6 mmol/l.[1,4] Symptoms of lactic acidosis are variable and can include increased respiratory rate, tachycardia, abdominal pain, and hepatomegaly.[2]

There are several types of lactic acidosis. Those most commonly described and seen in clinical practice are type A and B. Type A lactic acidosis is due to tissue hypoperfusion or acute severe hypoxaemia. In type B lactic acidosis several mechanisms may be involved, such as toxin-induced impairment of cellular metabolism, or regional areas of ischaemia.[5] The aetiologies of type B lactic acidosis consist of hereditary metabolic diseases, drugs / toxins (for example biguanides, salicylates, nucleoside reverse transcriptase inhibitors,[6] and methanol) and systemic disorders. Underlying diseases associated with type B lactic acidosis are diabetes, thiamine deficiency, pheochromocytoma, sepsis, liver disorders and malignancy.[1,5]

Type B lactic acidosis is also thought to be a rare complication of malignancy. It was first described in patients with acute leukaemia by Field *et al.* in 1963.[7] Since then, it has been observed more often especially in haematological malignancies,[8] but has also been noticed in solid nonhaematological tumours such as small cell lung cancer, cholangiocarcinoma, breast cancer, gynaecological cancers and metastasis from unknown primary carcinoma.[9-15]

We have reviewed previously reported cases of lactic acidosis in solid malignancy. In addition, a new case of lactic acidosis in a patient with metastatic breast cancer is presented. Finally, we speculate on the elusive pathophysiology of this oncological emergency.[2]

METHODS

We searched MEDLINE and PubMed in English, Dutch and German language publications, with the search strategy: "lactic acidosis AND tumours" and "solid tumours AND acidosis". We also used the reference list of all reviews and relevant papers that we retrieved. We identified cases of lactic acidosis associated with solid malignancies that satisfied the criteria of Luft and associates[4] (pH ≤7.35 and plasma lactate concentration ≥5 mmol/l) and in which the malignancy was the primary cause of the lactic acidosis. Patients who had previously received chemotherapy or had another cause of lactic acidosis beside malignancy were excluded. In addition, we report one additional case not previously published.

RESULTS/REVIEWS OF CASES REPORTED IN THE LITERATURE

Fourteen cases of lactic acidosis due to solid malignancies (1978-2006) were identified, in patients not previously undergoing chemotherapy (*table 1*). Most of the cases were seen in the USA, but there were also single reports from hospitals in the UK, India and Japan.

CASE REPORT

An 86-year-old white female was sent to the emergency department of our hospital in August 2008 because of two weeks of fever, nausea, anorexia, non-productive cough and generalised malaise.

Her past medical history included a colon carcinoma cured after a hemicolectomy in 1981, type 2 diabetes mellitus, hypertension and two myocardial infarctions. She was currently taking glimepiride, atorvastatin and perindopril. She did not use metformin for her diabetes. She was a non-smoker and drank no alcohol.

On the day of admission, she had a normal mental status, was normotensive, had a pulse of 100 beats/min, a body temperature of 38 °C, a respiratory rate of 25/min, and was in mild respiratory distress.

On physical examination, she had nipple retraction with a firm, nontender mass in the right breast, abdominal tenderness on deep palpation and hepatomegaly.

Laboratory investigations showed a noticeable elevated lactic acid of 7.5 mmol/l. In addition, haematology and electrolytes were normal, plasma creatinine was 120 µmol/l. Liver enzymes were elevated but liver function tests appeared normal.

Arterial blood pH was 7.35, pCO_2 was 3.3 kPa, PO_2 was 12.5 kPa and bicarbonate (HCO_3) was 13 mmol/l. An increased anion gap of 26 mmol/l was calculated. Computed tomography of the thorax and abdomen showed diffuse liver metastasis and a mass in her right breast. Biopsies of the lesions revealed a high-grade infiltrating ductal adenocarcinoma of the breast and metastasis to the liver.

Furthermore, as our patient had a normal glucose level, no signs of intestinal ischaemia or tissue hypoxia, and was not taking any lactic acidosis-inducing drugs, we concluded the lactic acidosis was due to malignancy. Determination of thiamine and riboflavin revealed a mild vitamin B1 deficiency (69 nmol/l, reference value 100 to 200 nmol/l). Treatment was initiated with 100 mg per day of intravenous thiamine, but had no effect on her lactic acidosis. Sodium bicarbonate ($NaHCO_3$, 100 mmol/24 hour, intravenously) was administered to relieve symptoms, such as her 'Kussmaul' breathing. Lactate level remained 12 mmol/l.

Because of her age and suboptimal performance score only capecitabine monotherapy was started. Despite this treatment, the patient deteriorated and died a few weeks after discharge from our hospital.

Table 1. *Cases of lactic acidosis due to solid tumours, without previously given chemotherapy*

Tumour	# patients	Range age (years)	Liver metastasis	Survival after presentation	Range lactate mmol/l	pH	Reference
Small cell carcinoma lung	9	45-70	+ and -	5 days - 16 weeks	11.3-26.6	7.11-7.29	9-11,16-21
Large cell carcinoma lung	1	80	-	NA	13.1	NA	22
Endometrial carcinosarcoma	1	72	-	4 weeks	9.2	7.20	14
Cholangiocarcinoma	1	70	+	2 weeks	12.5	7.11	12
Breast adenocarcinoma	2	36-61	+	Unknown-remission	5.0-17.2	7.27- 7.31	13,23

NA = not analysed.

DISCUSSION

Type B lactic acidosis seems to be a well-recognised problem in patients with uncontrolled leukaemia. Reviewing the literature and reports of nonhaematological solid tumours, type B lactic acidosis seems more common then previously believed and may well be an under-recognised problem.

The aetiology of type B lactic acidosis in solid malignancy remains elusive. Studying the pathogenesis of type B lactic acidosis is difficult and looking into the behaviour of tumour cells one can see why. Solid tumours present with great cellular heterogeneity, and often consist of variable proportions of malignant cells, stromal regions, infiltrated defence cells, and necrotic areas. Furthermore, the tumour cells themselves exhibit variable biological properties with regard to proliferation, differentiation, metabolic activity and viability as a consequence of both genetic instability and of heterogeneous microenvironmental conditions.[24] Some of these characteristics may well contribute in the pathogenesis of type B lactic acidosis in malignancy.

Several theories concerning the mechanism for type B lactic acidosis in solid malignancy have been postulated. Hypotheses include liver dysfunction due to massive liver metastasis leading to lactate underutilisation and subsequently lactic acidosis. Indeed, most of the reported cases of solid tumours and lactic acidosis, including our case, were accompanied by extensive liver metastases.

It should be noted, however, that neoplasm-associated lactic acidosis has been reported without liver metastasis, and in most cases parameters of hepatic function (bilirubin, albumin and prothrombin time) were normal. Furthermore, lactic acidosis is uncommon in severe liver diseases such as hepatitis, cirrhosis and fulminant hepatic failure. Liver involvement alone cannot fully explain the syndrome, and its exact role is not completely understood.[1,2,25]

During the last decade more and more evidence has emerged supporting the role of overproduction of lactic acid due to ischaemia in the neoplastic tissue bed and cancer cells having an aberrant energy production.[1,26] It has been suggested that large tumours or tightly packed bone marrow may limit blood supply and oxygenation, leading to a hypoxic microenvironment and a subsequent production of lactic acid.[1,17] In sharp contrast to most normal tissues, it was shown by the German biochemist Otto Warburg in the early part of the 20th century that cancer cells frequently develop a modified glucose metabolism, whereby a significant portion of the blood glucose consumed by the tumour cells is converted one step beyond pyruvate, i.e., to lactic acid, even when oxygen is plentiful.[26] Nowadays numerous studies have demonstrated that the majority of tumour cells *in vivo* exhibit elevated levels of glucose transport and elevated rates of glycolysis that result in an increase in the production of lactate.[26] Although glucose is the major source of lactate in most solid tumours, glutamine and serine can also contribute to the formation of this tricarbonic anion.[24,27]

The last few years major discoveries concerning the high rate of glycolysis in cancer cells have been published.

Recently, hypoxia-inducible factor (HIF) was identified as an important factor in the upregulation of glycolytic enzymes. HIF activation not only stimulates glycolysis but also actively attenuates mitochondrial respiration, making HIF a key regulator of cancer cell metabolism.[28] HIF leads to overexpression or aberrant expression of mitochondrially bound glycolytic enzymes such as hexokinase. Hexokinase is the first rate-limiting enzyme in the glycolytic pathway. The high affinity of hexokinase for glucose can help cancer cells maintain a high rate of glycolysis in the presence of oxygen, allowing tumour cells to proliferate rapidly and survive for prolonged periods. Insulin regulates the activity of this enzyme; however, many cancer cells overexpress insulin-like growth factors and their receptors that can mimic many activities of insulin.

The activity of pyruvate dehydrogenase (PDH), which catalyses the rate-limiting reaction of converting pyruvate to acetyl-CoA, is primarily regulated by pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase phosphatase (PDP). In the glucose metabolic pathway, PDK inhibits the conversion of pyruvate to acetyl-CoA thus blocks the entry to Krebs cycle by phosphorylation and inactivation of PDH. Such action of PDK inhibits mitochondrial respiration and shifts the cellular biogenesis to cytoplasmic glycolysis.

As no single theory gives a universal explanation, experts believe the aetiology of type B lactic acidosis associated with (solid) malignancy is multifactorial.[1,25,29]

Consistent with the theory of overproduction are clinical data in which succesful treatment of the underlying malignancy resolved the lactic acidosis and recurrence of the neoplasm was associated with relapse of acidosis.[1,10,17,25,30-33]

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