Eur J Cancer Clin Oncol, Vol. 19, No. 5, pp. 597–601, 1983.
Printed in Great Britain.

0277-5379/83/050597-05$03.00/0

Lactic Acidosis: a Metabolic Complication of Extensive Metastatic Cancer

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Abstract—*Lactic acidosis is a rare metabolic complication of cancer. An analysis of the cases reported in the English and French literature shows that all the patients have extensive neoplastic disease. Metastatic hepatic lesions are present in the large majority of cases, suggesting that alteration of liver function is part of the clinical picture. Chemotherapy against the neoplastic disease is the only effective treatment of this type of lactic acidosis.*

INTRODUCTION

LACTIC acidosis was first described in 1961 by Huckabee [1]. Since then many other observations have been reported and Cohen and Woods have recently proposed a new classification for this clinical picture [2]. Table 1 shows the common causes of lactic acidosis.

Our purpose is to review the cases of lactic acidosis related to cancer that are available in the English and French medical literature and to analyze the role of lactate production by the tumor and that of hepatic lesions in the outcome of this complication.

Table 1. Classification of lactic acidosis

Type A
Tissue hypoperfusion, hypoxemia
Type B
1. Various common disorders
Diabetes
Renal failure
Liver disease
Infection
Leukemia and neoplasia
2. Drugs and toxins
Biguanides (phenformin)
Ethanol
Fructose
3. Hereditary forms
Glucose-6-phosphatase deficiency
Fructose-1-6-diphosphatase deficiency
Others

Accepted 22 November 1982.

REPORTED CASES OF LACTIC ACIDOSIS ATTRIBUTED TO CANCER

In the present review we have excluded reports of lactic acidosis not directly related to cancer such as those caused by tissue hypoperfusion or hypoxemia. Table 2 presents the cases of lactic acidosis in connection with neoplastic diseases which we have found in the English and French literature. They are classified in three main categories according to their association with leukemias, lymphomas or solid tumors. We have added one personal observation of a woman with a breast metastatic cancer.

Case report

A 36-yr-old woman was admitted to the hospital because of cervical pain. X-rays revealed a metastasis in the cervical spine and radiotherapy was commenced.

Eight months previously a mastectomy had been performed for a right breast adenocarcinoma; all the axillary nodes were invaded. She received 3 courses of adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil.

At the time of admission respiration was normal and there was no hepatomegaly. Laboratory tests showed marked alterations of hepatic function: alkaline phosphatases: 185 U (normal value <85 U); SGOT: 66 U (<20 U); SGPT: 71 U (<20 U); and LDH: 302 U (<240 U). Bilirubin, ionogram and renal function were normal. Hepatic echography was not contributory.

Three weeks after admission she developed unexplained hyperventilation. At that time Na

Table 2. Cases of lactic acidosis in connection with cancer

Case No.	Neoplasia	Neoplastic liver lesions	Other complications	Anticancer chemotherapy administered	Blood lactate changes (mEq/l)	Correction of lactic acidosis	Reference
I. Leukemias							
1.	ALL*	+	-	+	20 → 4	+	[4]
2.	AML	?	-	+	16 → 8	+	[4]
3.	ALL	?	-	+	14 → 6	+	[4]
4.	AML	+	-	-	12 → 18	-	[4]
5.	AML	+	-	+	14.6 → 3.0	+	[20]
6.	ANLL	+	-	+	42 → 5	+	[24]
7.	ANLL	+	-	-	15.8	-	[17]
8.	AMoL	+	-	-	8.2	-	[12]
9.	AMoL	+	-	-	10.5	-	[12]
10.	Acute crisis CML	+	-	-	11.5	-	[12]
II. Lymphomas							
11.	Hodgkin's disease	+	-	+	8.8 → 3.6	+	[21]
12.	Burkitt-type lymphoma	-	-	+	3.5 → 0.9	+	[9]
13.	Reticulum cell sarcoma	+	-	+	15.9	-	[16]
14.	Diffuse histiocytic lymphoma	+	-	+	21.8 → 39.9	-	[18]
15.	Diffuse histiocytic lymphoma	+	-	+	14.2 → 18.0	-	[18]
16.	Diffuse histiocytic lymphoma	+	-	+	5.9 → 1.1	+	[18]
17.	Diffuse histiocytic lymphoma	+	-	+	12.4 → 1.6	+	[18]
18.	Reticulum cell sarcoma	-	hypoglycemia	-	11.6	-	[5]
19.	Hodgkin's disease	+	-	+	14 → 3.5	+	[19]
III. Solid tumors							
20.	Lung oat cell ca	+	-	-	26.6	-	[22]
21.	Lung oat cell ca	+	-	-	25.0	-	[22]
22.	Lung anaplastic large-cell ca	-	-	-	12	-	[11]
23.	Colon ca	+	-	-	15	-	[14]
24.	Breast ca	+	-	+	15	?	[23]
25.	Breast ca	+	-	+	11.8 → 13	-	See text

*ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; ANLL: acute non-lymphocytic leukemia; AMoL: acute monoblastic leukemia; CML: chronic myelogenic leukemia.

was 132 mEq/l; K: 4.7 mEq/l; Cl: 97 mEq/l; and bicarbonate: 12 mEq/l. Glucose was 148 mg/100 ml; pH: 7.34; and lactate: 11.8 mEq/l. Hepatomegaly was present and liver function tests showed a further increase of the enzyme levels: alkaline phosphatases: 252 U; SGOT: 208 U; SGPT: 78 U; and LDH: 570 U. Bilirubin and blood ammonium remained normal. Lactic acidosis was attributed to the metastatic liver involvement by breast cancer. Bicarbonate was given at the dose of 250–400 mEq per day and chemotherapy with adriamycin (75 mg/m^2) and vincristine (2 mg) was administered. The evolution was rapidly pejorative with no clear correction of the lactic acidosis but aggravation of hepatic failure and appearance of coagulation disorders. The patient died six days later.

At autopsy there was a massive metastatic infiltration of the liver with destruction of almost all the normal parenchyma. Ovarian and osseous metastases were also present.

Cases of the literature

As indicated in Table 2, we found 24 cases of lactic acidosis attributed to cancer (25 with our patient): 10 leukemias, 9 lymphomas and 5 solid tumors (6 with our report). All had symptomatic lactic acidosis and biological tests confirming the diagnosis according to the criteria reported by Oliva (blood lactate concentration greater than 2.0 mEq/l in association with an arterial pH below 7.37, in the absence of the other causes of acidosis) [3].

In the first group we have summarized data pertaining to the patients with acute leukemia, lymphoblastic or non-lymphoblastic lymphoma. From the paper of Field *et al.* [4] we have only retained the patients with evolutive leukemias and we have excluded the three reported cases with minimal disease or remission and fatty metamorphosis of the liver or extensive hepatic necrosis. All but two had some evidence of metastatic liver lesion. In patients 2 and 3 there is no information about liver function before chemotherapy; however, at autopsy there was in patient 2 extensive leukemic infiltrates involving almost all organs and in patient 3 marked fatty metamorphosis of the liver but no evidence of active leukemia. Five of the 10 patients received chemotherapy and all the patients who had regression of the lactic acidosis were also those who responded to chemotherapy. When patient 5 relapsed lactic acidosis reappeared; administration of chemotherapy induced a second remission and correction of the acidosis.

In the group of lymphomas are two patients with Hodgkin's disease and seven with non-Hodgkin's lymphomas, usually of the aggressive histologic types. All but two had evidence of neoplastic liver lesions. Patient 18 had severe lactic acidosis associated with hypoglycemia without alteration of liver function and without evidence of liver involvement at autopsy [5]. In this case hypoglycemia attributed to a huge retroperitoneal reticulum cell sarcoma could have been an important factor in the development of lactic acidosis. Of the eight patients who were treated with cytotoxic drugs five showed tumor regression with partial or complete regression of the lactic acidosis. When patient 12 relapsed lactic acidosis reappeared and was subsequently controlled again with chemotherapy. Patient 16 also relapsed but the lactic acidosis was not corrected since the tumor did not respond to chemotherapy.

In the group of solid tumors are two patients with oat-cell carcinomas of the lung, one with anaplastic large-cell carcinoma of the lung, one with colon carcinoma and two with breast adenocarcinomas. Five of these patients had extensive metastatic hepatic lesions. None of those cases responded to symptomatic treatment of lactic acidosis. One patient received chemotherapy without any effect on the tumor or on the acidosis. Patient 24 was lost to follow-up.

DISCUSSION

Lactate is produced from pyruvate by lactic dehydrogenase as an end product of anaerobic glycolysis. Its concentration depends on the pyruvate cytoplasmic concentration, the intracellular pH and the NADH/NAD$^+$ cytoplasmic ratio that reflects the redox state of the cytoplasm. Skin, muscles, brain and red cells are the main producers of lactate which is taken by the liver and the kidneys to be transformed into glucose via gluconeogenesis. The maximal rate of production of lactate is not known but the minimal estimate is in the range of 1290 mmol/day. The liver plays an essential role in lactate homeostasis. Its maximal capacity to extract lactate from the circulation is about 3400 mmol/day. The kidneys are also important in that respect and utilize 30% of the lactate production [6, 7]. Physiopathology of lactic acidosis associated with cancer is complex because it depends on multiple factors that regulate the balance between production and utilization of lactate. Several explanations of that syndrome can be given but all remain hypothetical.

In cancer cells there might exist an imbalance of glycolysis over gluconeogenesis [8]. *In vitro* experiences have demonstrated that under hypoxic conditions leukemic and lymphomatous cells are able to produce sufficient amounts of lactate to explain lactic acidosis *in vivo* [4, 9, 10]. The

formation of lactate depends on the type of tumor and is also variable from one tumor to another of the same histologic type; for example, acute leukemic cells produce more lactate than cells of chronic myelogenous leukemia. This might explain why lactic acidosis has been reported in acute leukemias only. Clinical data suggest that solid tumors are also able to produce lactate [11].

Another source for lactate formation could be a disturbance of tissue oxygenation by leukostasis [10, 12]. Microvascular aggregates of leukemic cells resulting from their poor deformability could be responsible for hypoxia and anaerobic metabolism in otherwise normal tissues. This phenomenon might induce lactate production by anaerobic glycolysis and contribute to the development of lactic acidosis.

Underutilization of lactate by the liver and, to a lesser extent, by the kidneys seems to be an important factor in the pathogenesis of lactic acidosis. In our analysis of the literature, of 25 described cases 20 had evidence of neoplastic involvement of the liver. In all solid tumors but one there was an extensive metastatic liver disease often with signs of hepatic failure. In leukemias the liver damage and hepatic dysfunction resulted from massive blastic infiltration.

In one case [5] of lymphoma the liver was normal as demonstrated at autopsy but lactic acidosis was associated with hypoglycemia which is a factor known to predispose to or to produce lactic acidosis. There are many cases of such an association described in the literature [1]; in these patients acidosis can be controlled by correction of the hypoglycemia [13].

According to our review the only effective therapy against lactic acidosis associated with cancer is therapy of cancer itself with chemotherapy. All the patients who did not receive cytotoxic drugs or did not respond to chemotherapy died. Symptomatic treatment of lactic acidosis was often unsuccessful to control the situation. Bicarbonate is usually administered as a treatment for lactic acidosis but in cancer patients it seems to increase lactate production [11, 14]; it should thus be used cautiously and be added only if acidosis is very severe.

Hypertonic glucose administration should also be prescribed carefully. One case report [15] of a patient with a bulky undifferentiated tumor suggested that it could rather induce lactic acidosis since it was reversible with discontinuation of the glucose infusion.

There is no experience in the literature about other types of symptomatic treatments of lactic acidosis in cancer patients such as dichloroacetate, vasodilator agents or dialysis.

To conclude, lactic acidosis is a rare but life-threatening metabolic complication in cancer patients and can be seen with any type of tumor. Its pathogenesis remains unclear; it may result from an imbalance between production and utilization of lactate but there are experimental data suggesting that overproduction of lactate occurs in the cancer cells themselves.

From our review it appears that a large majority of patients have evidence of major neoplastic involvement of the liver. This suggests that hepatic function integrity might be an important factor in avoiding lactate accumulation; perhaps alteration of the liver function is the key mechanism for the development of lactic acidosis.

The only effective therapy against this complication is the destruction of the tumor by cytostatic drugs. Bicarbonate and glucose infusion must be used carefully because they can induce formation of lactate and further aggravate the clinical symptoms.

REFERENCES

1. Huckabee WE. Abnormal resting blood lactate. I. The significance of hyperlactatemia in hospitalized patients. *Am J Med* 1961, **30**, 833–839.
2. Cohen RD, Woods HF. *Clinical and Biochemical Aspects of Lactic Acidosis*. Oxford, Blackwell Scientific Publications, 1976.
3. Oliva PB. Lactis acidosis. *Am J Med* 1970, **48**, 209–215.
4. 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* 1966, **40**, 528–547.
5. Lee JW, Rosenberg N, Konigsberg SF, Finkelstein NM. Severe lactic acidosis in reticulum cell sarcoma. *J Med Soc NJ* 1979, **76**, 917–919.
6. Kreisberg RA. Lactate homeostasis and lactic acidosis. *Ann Intern Med* 1980, **92**, 227–237.
7. Park R, Arrieff AI. Lactic acidosis. *Adv Intern Med* 1980, **25**, 33–68.
8. Weber G. Enzymology of cancer cells. *N Engl J Med* 1977, **296**, 541–551.
9. Block JB, Bronson NR, Bell WR. Metabolic abnormalities of lactic acid in Burkitt-type lymphoma with malignant effusions. *Ann Intern Med* 1966, **65**, 101–108.

10. BLOCK JB. Lactic acidosis in malignancy and observations on its possible pathogenesis. *Ann NY Acad Sci* 1974, **230**, 94–102.
11. FRALEY DS, ADLER R, BRUNS FJ, ZETT B. Stimulation of lactate production by administration of bicarbonate in a patient with a solid neoplasm and lactic acidosis. *N Engl J Med* 1980, **303**, 1100–1102.
12. LECLERCQ B, LEPORRIER M, CAMUS F *et al.* Acidose lactique au cours des leucémies aiguës. Problèmes physiopathologiques et conséquences thérapeutiques. *Ann Méd Interne (Paris)* 1978, **129**, 523–526.
13. MAGUIRE LC, SHERMAN BM, WHALEN JE. Glucose therapy of recurrent lactic acidosis. *Am J Med Sci* 1978, **276**, 305–310.
14. FIELDS ALA, WOLMAN SL, HALPERIN ML. Chronic lactic acidosis in a patient with cancer: therapy and metabolic consequences. *Cancer* 1981, **47**, 2026–2029.
15. GOODGAME JT, PIZZO P, BRENNAN MF. Iatrogenic lactic acidosis. Association with hypertonic glucose administration in a patient with cancer. *Cancer* 1978, **42**, 800–803.
16. KACHEL RG. Metastatic reticulum cell sarcoma and lactic acidosis. *Cancer* 1975, **36**, 2056–2059.
17. MARTY M, VERNANT JP, ROCHANT H, TULLIEZ M, BRUN B, DREYFUS B. Acidose lactique au cours d'une leucémie aiguë. *Ann Méd Interne (Paris)* 1975, **126**, 115–120.
18. MINTZ U, SWEET DL, BITRAN JD, ULTMANN JE. Lactic acidosis and diffuse histiocytic lymphoma. *Am J Hematol* 1978, **4**, 359–365.
19. NADIMINTI Y, WANG JC, CHOU SY, PINELES E, TOLIN MS. Lactic acidosis associated with Hodgkin's disease. *N Engl J Med* 1980, **303**, 15–17.
20. ROTH GJ, PORTE D. Chronic lactic acidosis and acute leukemia. *Arch Intern Med* 1970, **125**, 317–321.
21. SCHEERER PP, PIERRE RV, SCHWARTZ DL, LINMAN JN. Red-Sternberg cell leukemia and lactic acidosis. *N Eng J Med* 1964, **270**, 274–278.
22. SPECHLER SJ, ESPOSITO AL, KOFF RS, HONG WK. Lactic acidosis in oat cell carcinoma with extensive hepatic metastases. *Arch Intern Med* 1978, **138**, 1663–1664.
23. VARANASI UR, CARR B, SIMPSON DP. Lactic acidosis associated with metastatic breast cancer. *Cancer Treat Rep* 1980, **64**, 1283–1285.
24. WAINER RA, WIERNIK PH, THOMPSON WL. Metabolic and therapeutic studies of a patient with acute leukemia and severe lactic acidosis of prolonged duration. *Am J Med* 1973, **55**, 255–260.