Aggressive Undifferentiated Carcinoma of Unknown Primary Site Complicated by Lactic Acidosis After Bleeding: a Case Report

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Undifferentiated carcinoma of unknown primary site complicated by lactic acidosis has not been documented. We describe a young female with undifferentiated carcinoma of unknown primary site manifested by widespread lymph node and hepatic infiltration, hyperuricemia and very high levels of lactate dehydrogenase. She developed lactic acidosis suddenly after an episode of bleeding following nasal biopsy. The bleeding episode is likely to have caused subclinical hepatic hypoperfusion and hypoxemia, thereby aggravating lactate overproduction by tumor cells and clearance impairment due to diffuse hepatic infiltration to result in rapidly fatal acidosis before cytotoxic agents could be instituted. Although uncommon, when a critical event occurs in aggressive malignancies with massive hepatic involvement, the clinician should be alert for the development of lactic acidosis because the life-threatening metabolic complication is best avoided by prompt and effective cytoreduction therapy.

Key words: undifferentiated carcinoma – cancer of unknown primary origin – liver metastasis – hemorrhage – lactic acidosis

INTRODUCTION

Lactic acidosis is uncommon in patients with cancer even when it is a rapid growing tumor (1). It often develops suddenly, may become profound in a few hours (2) and is frequently life-threatening, with ~50% of patients dying of the complication (3,4) unless an effective cytoreduction therapy for the underlying malignancy is available and administered early (3,5,6). Previous reviews have shown that lactic acidosis occurred most often in rapidly growing malignancies with extensive hepatic metastasis (3,6). To the best of our knowledge, among the wide variety of tumor types associated with lactic acidosis, undifferentiated carcinoma of unknown primary site has not been reported before. We describe a case of aggressive undifferentiated carcinoma of unknown primary site with diffuse hepatic infiltration who rapidly developed fatal lactic acidosis after an episode of nasal bleeding.

CASE REPORT

A 25-year-old female was admitted to the Hematology Division of the Taipei Veterans General Hospital in February 2001 for generalized lymphadenopathy. She was previously in general good health and had had no recent febrile illness, but dull epigastric pain and dyspepsia developed 4 weeks prior to this admission. One week before admission she entered a district hospital where upper gastrointestinal endoscopic examination revealed antral gastritis. Abdominal sonography disclosed liver infiltration and retroperitoneal adenopathy, so she was referred to our hospital for further evaluation and management.

At the time of admission, the patient looked comfortable and was markedly obese. Her blood pressure was 120/80 mmHg, pulse 94/min and respiratory rate 18/min. Physical examination revealed diffuse hepatic infiltration and retroperitoneal adenopathy, so she was referred to our hospital for further evaluation and management.

A chest X-ray showed a mass with increased density measuring about 7–8 cm in diameter in the right hilar region. Computed tomography of the chest and whole abdomen disclosed hepatomegaly with diffuse hypodense confluent nodular lesions in both hepatic lobes (Fig. 1) and enlarged lymph nodes in the right anterior mediastinum, lower paraesophageal, subdiaphragmatic, perigastric, celiac axis, superior mesenteric artery, paraaortic, aortocaval, portocaval and hepatic hilar regions (Fig. 2). There was mini-
mal ascites but no splenomegaly and no definite focal tumor growth in bowel loops or bilateral adnexal regions could be identified. Other laboratory tests including blood and urine routine, plasma sugar, serum albumin, bilirubin, creatinine and electrolyte values were all within normal limits. Anti-HCV EIA test was negative but HBsAg was positive. The hemoglobin (Hb) level was 12.5 g/dl and platelet count was \(320 \times 10^3/\mu l\). Biopsy of the left supraclavicular lymph node was performed on the third hospital day. Histopathology disclosed a metastatic undifferentiated carcinoma (Fig. 3) which was positive for cytokeratin (Fig. 4) but negative for common leukocyte antigen by immunostaining. Tumor marker studies showed an elevated CA-125 value of 2329 U/ml (normal: <35) but normal CA15-3, CEA, \(\beta\)-HCG and AFP levels. A metastasis of epithelial origin was presumed from the results of the above studies. After checking the routine preoperative coagulation tests which showed PT INR 1.24 (normal ratio: 1–1.25) and APTT 40.1 s (control: 34.7), a detailed nasopharyngeal endoscopic examination and biopsy from multiple sites were performed on the sixth hospital day. Results of the examination and the subsequent pathology report were negative.

Unfortunately, the night following nasal biopsy there was continuous blood oozing from the biopsy site. After local treatment with cold compression and vasoconstrictive agent, bleeding was stopped in the early morning of the next day. However, passage of tarry stool, tachycardia (pulse rate 120/min), tachypnea (respiratory rate 24/min), Hb level 8.1 g/dl and platelet count \(307 \times 10^3/\mu l\) were noted, so packed RBCs were transfused for symptomatic anemia. Follow-up of the Hb level at noon showed an elevation to 10.2 g/dl. Tarry stool which was probably due to swallowed blood was not observed thereafter. Throughout the bleeding episode, the blood pressure ranged

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**Figure 1.** Contrast-enhanced computed tomography of the upper abdomen shows diffuse enlargement of the liver and multiple hypodense confluent hepatic nodules involving both hepatic lobes (arrows).

**Figure 2.** Contrast-enhanced CT scan: apparent retroperitoneal lymph node enlargement is also evident (large arrows). The renal vein and inferior vena cava (small arrows) are anteriorly displaced by the nodes.

**Figure 3.** Lymph node biopsy reveals sheets and nests of metastatic undifferentiated carcinoma cells which bear a hyperchromatic nucleus with prominent nucleoli and indistinct cell border (H&E, \(\times100\)).

**Figure 4.** Most of the tumor cells are positive for cytokeratin by immunohistochemistry staining (CKER, \(\times100\)).
Table 1. Significant clinical data related to nasal bleeding

<table>
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<tr>
<th>In hospital</th>
<th>Day 1</th>
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<td>9AM</td>
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| BP (mmHg)   | 120/80 | 142/88 | 140/86 | 123/75 | 115/52 | 127/76 | 122/75 | 117/63 | 125/73 |
| PR/R (l/min)| 94/18  | 115/20 | 105/22 | 112/20 | 122/24 | 118/22 | 120/24 | 156/30 | 150/36 |
| Hb (g/dl)   | 12.5   | 11.5   | 8.1    | 10.2   | 8      |        |        |        |        |
| Platelets (x10^9/l) | 320   | 348    | 307    | 296    | 274    |        |        |        |        |
| PT INR      | 1.24   |        |        |        |        |        |        |        |        |
| APTT P/C (s)| 40.1/34.7 | 40.5/31.9 |        |        |        |        |        |        |        |
| Fibrinogen (mg/dl) | 0.9    |        |        |        |        |        |        |        |        |
| T Bil (mg/dl)| 0.7    |        |        |        |        |        |        |        |        |
| Cr (mg/dl)  |        |        |        |        |        |        |        |        |        |
| Lactate (mg/dl)|        |        |        |        |        |        |        |        |        |

BT = blood transfusion; P/C = patient/control; T Bil = total bilirubin.

from 140/86 to 115/52 mmHg and the patient was well orientated. However, hyperventilation persisted and Kussmaul’s respiration developed in the afternoon with an increase of respiratory rate up to 36/min and pulse up to 150 beats per minute. The patient was lethargic and confused. The follow-up Hb value was 8.0 g/dl, platelet count 274 × 10^9/µl, PT INR 2.59 and APTT 40.5 s (control: 31.9). The test for fibrinogen was 150 mg/dl, that for FDP 40 µg/ml (normal <10) and D-dimer was positive. A specimen for arterial blood gas analysis taken while the patient breathed on room air disclosed pH 7.08, \( P_{\text{aO}} \_2 \) 133 mmHg, \( P_{\text{aCO}} \_2 \) 12 mmHg and actual bicarbonate 5.01 mequiv./l. The electrolyte values were sodium 135, potassium 5.1 and chloride 92 mequiv./l. Further investigation revealed blood lactic acid value 171.5 mg/dl (normal: 5–15), but creatinine 1.4 mg/dl, glucose 91 mg/dl and ketones negative. These studies confirmed a diagnosis of lactic acidosis (some of the significant clinical data related to period of nasal bleeding are indicated in Table 1). Packed RBCs and fresh frozen plasma were administered for possible occult bleeding and coagulopathy. Hemodialysis was performed and intravenous sodium bicarbonate was given in an attempt to correct the severe acidosis which was associated with extreme hyperventilation and tachycardia. Although the blood pH had been elevated to above 7.22 after treatment, her condition deteriorated over the next 3 h to stupor and circulatory collapse so that hemodialysis had to be discontinued. The metabolic complication progressed with multiple organ failure, recurrence of noticeable frank nasal bleeding and passage of large amounts of tarry stool. Subsequent resuscitation efforts were unsuccessful and the patient died on the morning of the eighth hospitalization day.

**DISCUSSION**

This patient presented with widespread lymphadenopathy and extensive hepatic infiltration with which lymphoma and primary hepatic carcinoma are most connected in differential diagnosis. It is unusual to find the lymphoma cells clustering in sheets and nests and separated by stromals of normal lymphoid cells in the lymph node (Fig. 3) but the feature of cohesive growth pattern in addition to some pleomorphic cells alerted us to the probability of anaplastic large cell lymphoma (ALCL). However, positive cytokeratin immunostaining (Fig. 4) and the absence of the general diagnostic features of ALCL such as hallmark cells (detectable in all variants of ALCL) with horse-shoe- or kidney-shaped nuclei that have a prominent clear or more eosinophilic zone of Golgi area surrounded by the nuclear lobes, sheets of large, pleomorphic tumor cells with an abundant gray–blue cytoplasm that is characteristic of the common type of ALCL and the usually admixed inflammatory elements among the tumor cells make the diagnosis of ALCL very unlikely (7). On the other hand, diffuse involvement of both hepatic lobes by multiple hypodense confluent nodules as shown by CT scan (Fig. 1) with the absence of known primary malignancy at another site raised the diagnostic possibility of primary hepatic malignancy. However, in the lymph node examined, we found no trabecular or acinar growing pattern or hepatocyte-like tumor cells with eosinophilic cytoplasm that is typical of well or moderately differentiated hepatocellular carcinoma (HCC). The characteristic features of poorly differentiated or undifferentiated HCC such as solid or compact growth pattern, tumor cells with scanty or basophilic cytoplasm, mononucleated and/or multinucleated giant cells or tumor cells with short spindle-shaped and/or round nuclei were not observed (8). We also did not find any stigmata of cholangiocarcinoma. Furthermore, in a retrospective study of 660 autopsy cases with HCC, only 1.8% (12/660) of the patients...
had supraclavicular lymph node metastasis (9). In view of the pathological and clinical features, the diagnosis of primary hepatic carcinoma can be excluded. In our patient, the lymph node architecture was replaced by a relatively uniform population of metastatic tumor cells without readily identifiable differentiation. Although positive cytokeratin immunostaining of the tumor cells (Fig. 4) and elevated blood CA-125, which may be found in a variety of epithelial malignancies, had prompted us to examine her nasopharynx more thoroughly, the results of the nasopharyngoscopic examination and biopsies were negative. Image studies including computed tomography of the chest and abdomen had failed to disclose the primary site of neoplasm. These findings favor the diagnosis of undifferentiated carcinoma with unknown primary site, especially when lymphoma and primary hepatic malignancy are excluded.

The invasive procedure employed to investigate the primary site of malignancy in our patient led to nasal bleeding. The complication was primarily a consequence of local injury from multiple biopsies because the pre-operation PT and APTT were normal and bleeding was manageable by local treatment. Coagulopathy (elevated FDPs and prolonged PT) associated with deteriorating liver function because of progressive tumor infiltration, haemodynamic instability and severe acidosis is probably an additional cause of recurrent hemorrhage. Bleeding due to decompensated disseminated intravascular coagulation was unlikely because there was no abnormal bleeding from venous puncture sites and the platelet count was normal without a prominent decrease in number during hospitalization.

Patients with lactic acidosis often present typically with hyperventilation and sometimes hypotension and nonspecifically with tachycardia, weakness, stupor, etc. (1). In our patient, hyperventilation and tachycardia which developed on the morning of the seventh hospital day were assumed to be associated with anemia due to nasal bleeding. The metabolic complication was apparent until the afternoon of the same day when she had increasing respiratory rate with Kussmaul’s breathing pattern and extreme tachycardia despite the fact that the hemoglobin had been raised from 8.1 to 10.2 g/dl after transfusion and the nasal bleeding had ceased. The results of elevated blood lactate, metabolic acidosis with widened anion gap, normal serum creatinine and negative test for serum ketones confirmed the diagnosis of lactic acidosis (10).

The common causes of the development of lactic acidosis in cancer patients due to peripheral tissue hypoxia (type A lactic acidosis), such as circulatory insufficiency, sepsis and shock, were ruled out by the medical history and laboratory data in our patient. Similarly, a variety of disorders such as infection, diabetes mellitus and renal failure or the offending drug and toxin causing type B lactic acidosis were also excluded (1,5). Excessive tumor cell production and impaired hepatic utilization of lactic acid have been implicated because the majority of cancers associated lactic acidosis are rapid growing with a large tumor burden and extensive liver metastasis (2,3,6,11–13). Lactate overproduction, which may be due to accelerated (14–20) or altered (21,22) metabolism of the cancer cells in a hypoxic environment (4,15,20) or possibly to elevated TNF-α (14), have been shown by several in vitro or in vivo studies (14–22). As the liver plays an essential role in lactate homeostasis, excessive hepatic infiltration can cause compromised metabolism or impaired elimination of lactate and even decreased gluconeogenesis of normal liver cells (2,10–12,23–26). However, either lactate overproduction or impaired elimination alone is insufficient to explain the development of lactic acidosis, because the liver has a large capacity to eliminate lactate via gluconeogenesis and oxidation, some patients with lactic acidosis have minimal or no liver metastasis, many with widespread liver metastasis or serious liver disease rarely develop lactic acidosis, the kidney is able to excrete about one third of lactic acid (27,28) and, moreover, in one study, lactate overproduction by tumor cells was not demonstrated (29).

At presentation, our patient showed no evidence of lactic acidosis despite a large tumor burden with extensive liver infiltration and rapid cell turnover, as indicated by the markedly elevated LDH and uric acid. Moderate anemia alone, which is commonly encountered in cancer patients, has not been reported to cause lactic acidosis. Recently, a marked disparity between the whole body and liver oxygenation was demonstrated by hepatic venous catheterization in a patient with extensive metastatic melanoma of the liver. Following a critical event of sepsis, a further increase in tumor cell metabolic activity as a cause of regional hypermetabolism with enhanced splanchnic oxygen utilization was thus detected. The unmatched proportional increase in regional oxygen delivery thereby worsened hepatic hypoxia to exacerbate lactic acidosis (30). A similar discrepancy of oxygenation due to unmatched oxygen delivery was also reported in a case of cholangiocarcinoma with liver metastasis who had intermittent atrial fibrillation with rapid ventricular response. Extensive areas of acute necrosis within the large hepatic metastasis disclosed by autopsy suggested local tissue ischemia precipitated by subtle splanchnic blood flow alteration due to cardiac arrhythmias. Enhanced anaerobic glycolysis of the ischemic and rapid growing tumor cells, coupled with impaired hepatic clearance, were likely to cause hyperlactatemia without clinical detectable hypoxia or shock (31). In our patient, it is likely that the onset of lactic acidosis after the critical event of nasal bleeding is related to the moderate degree of anemia with limited oxygen delivery capability and the subtle change of blood pressure (Table 1) that is associated with bleeding. These may induce subclinical hepatic hypoxia as a consequence of unmatched oxygen delivery for the increased oxygen consumption by a large tumor burden with rapid cell turnover and splanchnic hypoperfusion due to unstable hemodynamics. In a patient who has a marginal reserve of the liver function due to massive tumor infiltration, hepatic hypoxemia and hypoperfusion further exacerbate lactate overproduction and clearance impairment, resulting in very severe lactic acidosis.

Prolonged and severe acidosis may decrease cardiovascular function and splanchnic blood flow, causing hypotension further to enhance lactate overproduction and utilization impairment, thus forming a vicious cycle of refractory lactic acidosis.
In order to avoid the deleterious effects of severe lactic acidosis, sodium bicarbonate was administered in an attempt to titrate the excessive and uncontrolled hydrogen ion production. In one case, bicarbonate therapy partially corrected the extracellular acidosis. However, in our patient, the metabolic complication progressed rapidly to shock in about 6 hours and she died 20 h after the diagnosis of lactic acidosis even though the blood pH was increased to above 7.22 by vigorous sodium bicarbonate infusion. In fact, most authors argued for the use of sodium bicarbonate as it may further increase lactate and carbon dioxide production and impair oxygen delivery (16,35–37). Furthermore, other alkali therapy has not shown a survival benefit in comparative studies (38).

Although uncommon, the clinician should be alert to the development of life-threatening lactic acidosis especially when a critical event occurs in a rapidly growing malignancy with massive hepatic involvement. The fatal metabolic complication can be avoided or reversed only by prompt institution of effective cytoreductive agents for the underlying malignancy because all patients who did not respond to chemotherapy died (3,6).

References