American Journal of Case Reports

ISSN 1507-6164
© Am J Case Rep, 2013; 14: 518-525
DOI: 10.12659/AJCR.889580

Received: 2013.07.18
Accepted: 2013.08.02
Published: 2013.12.02

Diffuse large B-cell lymphoma: A metabolic disorder?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Georges Tanios
ADE 1 Ines M. Aranguren
ADE 1,2 Jack S. Goldstein
ABDEF 1 Chirag B. Patel

1 Department of Internal Medicine, East Tennessee State University James H. Quillen College of Medicine, Johnson City, TN, U.S.A.
2 Department of Internal Medicine, Mountain Home VA Medical Center, Johnson City, TN, U.S.A.

Corresponding Author: Chirag B. Patel, e-mail: cbpatel@mednet.ucla.edu

Patient: Male, 81
Final Diagnosis: Non-Hodgkin lymphoma
Symptoms: General weakness • hypoglycemia • metabolic acidosis
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Challenging differential diagnosis

Background: B cell lymphoma constitutes 80–85% of cases of Non Hodgkin's lymphoma in the Untied States. Metabolic complications may arise from the disease itself or through its end organ involvement.

Case Report: We describe a case of a diffuse large B cell lymphoma diagnosed by abdominal computed tomography after it initially presented as hypoglycemia not correctable by dextrose infusion that instead resulted in increased anion gap metabolic acidosis with elevated lactate levels.

Conclusions: The case illustrates how lymphomas can present unusually with hypoglycemia and lactic acidosis, the latter being an ominous sign that can occur without liver involvement. In this regard, the case demonstrates the metabolic sequelae of lymphoma that should raise suspicion for an underlying process. This has implications for diagnosis, treatment, and patient survival. Attention should be paid especially in the primary care setting in order to minimize delays in diagnosis.

Key words: B-cell lymphoma • hypoglycemia • Non Hodgkin's lymphoma • lactic acidosis • Warburg effect

Full-text PDF: http://www.amjcaserep.com/download/index/idArt/889580

1911 1 2 35

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

Background

Diagnostic errors in medicine are on the rise and the incidence of post-mortem findings of undiagnosed malignancy at autopsy have been reported as high as 11% [1]. B cell lymphoma constitutes 80–85% of cases of Non Hodgkin's lymphoma (NHL) in the Untied States, most of which are diffuse large B cell lymphomas (DLBCL, 32%), and is the seventh leading cancer in both male and female patients [2]. Patients with B cell lymphoma commonly present with nodal disease, and additional symptoms may include fever, night sweats, and weight loss.

This disease has widespread manifestations resulting in systemic signs, focal signs, and metabolic complications that may arise from the disease itself or through its organ involvement. Major uncommon complications include renal infiltration (34% post-mortem) [3], glomerulonephritis [4], membranous nephropathy [4], cryoglobulinemia [5], and renal failure; adrenal abnormalities, whether primary [6] or metastatic disease [7]; calcium disorders in human T-lymphotropic virus type I-associated lymphomas [8]; and metabolic acidosis without renal disease with/without liver involvement with/without hypoglycemia. The unusual manifestations themselves can be an ominous sign, altering the course of the disease and its management, which highlights the need for familiarity with the uncommon manifestations of common diseases in order to reach the correct diagnosis earlier and ultimately improve treatment outcomes.

We present a case of a newly diagnosed DLBCL initially presenting as hypoglycemia not correctable by dextrose infusion that instead resulted in increased anion gap metabolic acidosis with elevated lactate, leading to a final diagnosis of NHL lymphoma manifesting as infiltrative abdominal masses. A literature review of similar cases is also presented.

Case Report

An 81-year-old man with worsening generalized weakness presented to the emergency room after experiencing a fall. Past medical history was significant for atrial fibrillation, coronary artery disease, ischemic cardiomyopathy, congestive heart failure, hypertension, myelodysplastic syndrome, and senile dementia. Review of symptoms was positive for multiple falls and negative for fever and weight loss. He quit smoking at the age of 50 years.

Home medications included galantamine, quetiapine, citalopram, finasteride, aspirin, metoprolol, lisinopril, simvastatin, omeprazole, and sublingual nitroglycerin as needed. On admission, the patient's vital signs were pulse 109 beats per minute, blood pressure 118/81 mmHg, and temperature 97.8 F. Physical exam was remarkable for irregularly irregular rate and rhythm, tachycardia with an aortic systolic ejection murmur, and trace edema in both lower extremities. No lymphadenopathy was appreciated.

Laboratory values on admission were Na^+ 136 mEq/L (reference: 135–145 mEq/L), K^+ 5.0 mEq/L (reference: 3.6–5.0 mEq/L), Cl^- 97 mEq/L(reference: 101–111 mEq/L), CO_2 24 mEq/L (reference: 21–31 mEq/L), glucose 106 mg/dL (reference: 75–110 mg/dL), creatinine 1.6 mg/dL (reference: 0.7–1.3 mg/dL), blood urea nitrogen 41 mg/dL (reference: 9–21 mg/dL), total protein 5.8 g/dL (reference: 6.4–8.3 g/dL), albumin 2.7 g/dL (reference: 3.5–5.0 g/dL), total bilirubin 0.7 mg/dL (reference: 0.2–1.0 mg/dL), alkaline phosphatase 179 U/L (reference: 38–126 U/L), aspartate transaminase 150 U/L (reference: 15–46 U/L), alanine aminotransferase 35 U/L (reference: 7–56 U/L), white blood cells 3.7×10^9/L (reference: $4.8–10.5\times10^9$/L), monocytes 24% (reference: 4.5–13%) lymphocytes 17% (reference: 20–49%), hemoglobin 12.5 g/dL (reference: 13.6–17.3 g/dL), platelets 80×10^9/L (reference: $166–383\times10^9$/L). Chest x-ray was clear with no active infiltrates or consolidations. Electrocardiogram showed atrial fibrillation, heart rate of 110 beats per minute, without acute ischemic changes. Head computed tomography was negative for any acute intracranial process.

During the first night, the patient was agitated and found to have a blood glucose level of 37 mg/dL. Intravenous D10W bolus was given followed by D5NS maintenance. The next day, D5NS was stopped and shortly thereafter the patient was again hypoglycemic (blood glucose 60–70 mg/dL), at which time D5NS was resumed. Blood glucose remained in the hypoglycemic range while the patient was off of D5NS. Further labs were ordered and revealed insulin level 0.6 µU/mL (reference: 6–27 µU/mL), C-peptide 1.0 ng/mL (reference 1.1–4.4 ng/mL), cortisol 17 µg/dL (reference: 3.1–22.4 µg/dL), adrenocorticotropic hormone 5.6 pmol/L (reference: 0–10.0 pmol/L), and IGF-I <25 ng/mL (reference: 55–166 ng/mL). On the third day, the patient was kept on intravenous D5NS and blood glucose ranged from 70 mg/dL to 75 mg/dL. The underlying cause of the protracted hypoglycemia remained unresolved. On day 4, labs included K^+ 5.2 mEq/L, CO_2 17 mEq/L, lactate 13.4 mmol/L (reference: 0.5–2.2 mmol/L), arterial blood gas pH 7.29 (reference: 7.35–7.45)/pCO_2 36 mmHg (reference: 35–45 mmHg)/pO_2 85 mmHg (reference: 80–95 mmHg)/HCO3 – 17.3 mEq/L (reference: 22–26 mEq/L), with an anion gap of 20 mEq/L.

Blood cultures remained negative and kidney function was normalized after IV hydration. CT abdomen showed a mass-like infiltration of the left renal pelvis and retroperitoneal structures suspicious for malignancy. On day 5, CT-guided biopsy indicated non-Hodgkin lymphoma, diffuse large B cell type that was confirmed with flow cytometry. Because chemotherapy was declined by the patient and his family, systemic corticosteroids

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

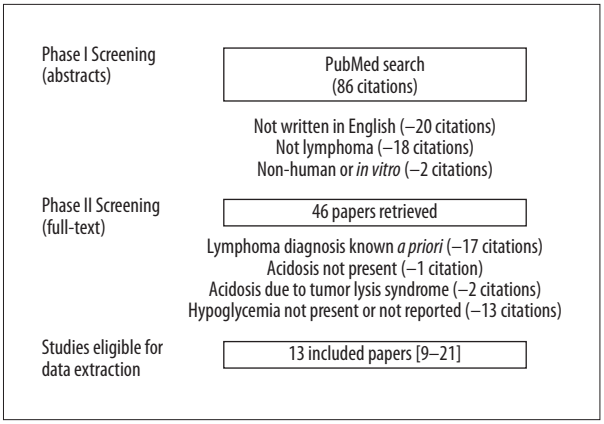

Figure 1. Flowchart of literature review.

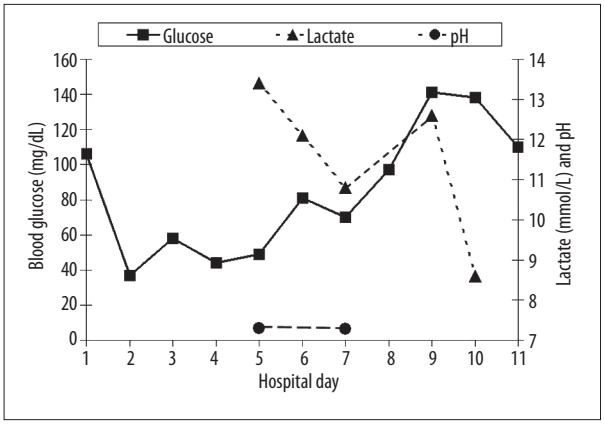

Figure 2. Blood glucose, lactate, and pH during hospital course.

were initiated on day 6 as part of lymphoma palliative management, with the hope it would help to mitigate the hypoglycemic state. By day 9, blood glucose levels were normalized off D5NS with homeostasis achieved (140 mg/dL), and lactatemia also improved (8.6 mmol/L). Three days after discharge to hospice care, the patient expired.

Discussion

After facing the uncommon presentation described in this case, the literature was reviewed to identify similar cases of lymphoma initially presenting as hypoglycemia and lactic acidosis. PubMed search was performed with the following MESH terms: "lactic acidosis" and "lymphoma." Articles were discarded if they were not written in English, if a diagnosis of lymphoma had been determined prior to detecting the aberrant lab values, or if both hypoglycemia and lactic acidosis were not present prior to a diagnosis of lymphoma. Figure 1 summarizes the flowchart of the literature review. A total of 13 cases met the aforementioned search criteria and are summarized in Table 1 [9–21].

Because hypoglycemia was the driving sign in this patient, blood work was performed to exclude other causes such as insulinoma (normal insulin and peptide C levels), liver failure (normal international normalized ratio and bilirubin level), and adrenal insufficiency (normal blood pressure, cortisol, calcium, adrenocorticotropic hormone, and sodium with the exception of mild hyperkalemia most likely related to prerenal azotemia that was correctable with hydration). Moreover, many of this case's features (i.e., presence of an elevated anion gap, absence of pancreatic mass on imaging, persistent hypoglycemia rather than delayed postprandial hypoglycemia, advanced patient age, and male sex) reduced the likelihood of an insulinoma. The unexplained hypoglycemia, poor response to D10W infusion, and inability to maintain homeostasis are represented in Figure 2, which also shows a worsening lactatemia and increased anion gap following infusion of dextrose. Furthermore, neither the hypoglycemia nor the lactatemia could be explained by the patient's home medications. Normal bicarbonate levels upon presentation indicated that a new event was occurring during the hospitalization. Therefore, other possible causes, e.g., hypotension (blood pressure 118/81 mm Hg), hypoxemia (SpO2 94%), sepsis (afebrile with negative blood cultures), and tissue hypoperfusion (CT abdomen excluding mesenteric ischemia but identifying multiple large necrotic masses), were excluded.

Hypoglycemia and lactic acidosis have previously been reported in malignancies, with lactic acidosis being a rare complication [22]. While hypoglycemia can result from nonislet cell tumor hypoglycemia (NICTH), an uncommon but serious complication of malignancy [23], lactic acidosis could result from several other mechanisms. NICTH is mainly seen in solid [24], bulky tumors [25] consisting of the production of autoantibodies against insulin or insulin receptor. It also causes secretion of incompletely processed IGF-II and subsequently decreased IGF-I levels resulting in stimulation of the insulin receptors and increased glucose utilization noticed mainly in solid tumors, paraneoplastic manifestations, and lymphomas with extensive tumor burden. In the face of hypoinsulinemic hypoglycemia with low levels of IGF-I reflecting growth hormone suppression, we can safely conclude that our patient experienced hypoglycemia due to the large lymphoma burden in the abdomen, especially given its responsiveness to steroid treatment that is traditionally recommended in cases of NICTH when chemotherapy is not feasible [26], resulting in a steady blood glucose level (Figure 2).

Further review of the literature of severe lactic acidosis with B-cell lymphoma without mention of hypoglycemia demonstrated that the true incidence of lymphoma-induced lactic acidosis remains uncertain because most of the published cases met systemic inflammatory response syndrome criteria [27]. In our case, the patient was tachycardic and leukopenic

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

Table 1. Summary of literature review of lymphoma cases initially presenting with hypoglycemia and lactic acidosis.

Ref	Year	Sex	Age	Chief complaint	Reason for referral / transfer	Physical exam	Serum lactate (mmol/L)
Current case	2013	M	81	Generalized weakness	N/A	Pulse irregular rate and rhythm, systolic murmur in the aortic area, mild trace edema in both lower extremities	13.4 (d4)
[9]	2012	F	64	Generalized fatigue, poor appetite, weight loss (PMH: NR)	Pancytopenia and hypoglycemia	HSM, diffuse petechiae	28.5 (d1)
[10]	2011	F	55	2 months of bilateral lower extremity swelling, progressive shortness of breath, and decreased appetite (PMH: bronchial asthma and stage 3 chronic kidney disease of unknown etiology)	N/A	Nonpainful lymphadenopathy of the neck and lower extremity edema	12.7 (d5)
[11]	2010	M	45	nausea, vomiting, lethargy, upper abdominal and back pain (PMH: alcohol abuse)	Suspicion of worsening pancreatitis	Kussmaul breathing and bradycardia	16.05 (d1)
[12]	2010	M	53	HA and abdominal discomfort ×1 week. N/V/D ×2 days. Subjective fever, chills, diaphoresis, and dark urine ×1 week. (PMH: remote alcohol abuse, chronic untreated hepatitis C)	N/A	Cachexia, jaundice, bitemporal wasting. 2+ pitting edema from abdomen to feet. Significant HSM, mild abdominal tenderness.	13 (d1)
[13]	2010	M	79	Asthenia, weight loss, hypoglycemia (PMH: obese, DM, HTN, COPD, chronic heart failure)	(Transferred to ICU 2 wks after admission) generalized abdominal tenderness, acute respiratory failure, lactic acidosis, refractory hypoglycemia	(In ICU) HR 108, RR 50, GCS 12. Generalized abdominal tenderness, intra-abdominal pressure below 15 mmHg, no HSM	7.4 (d15)
[14]	2008	M	81	Refractory hypoglycemia, metabolic acidosis, unexplained lymphocytosis, and significant weight loss (PMH: non insulin-dependent DM, HTN, hypothyroidism)	N/A	No abnormalities noted	13.6 (d1)
[15]	2007	M	65	Myalgias, severe fatigue, abdominal pain with distention, confusion ×1 wk. Loss of appetite with 20 lb. weight loss (PMH: cardiac bypass surgery 10 years earlier)	Uncorrected lactic acidosis and s/p intubation for respiratory fatigue	Tachypnea	13 (d1)
[16]	2005	M	74	Progressive right upper and lower extremity swelling and pain ×2 wk (PMH: NR)	N/A	5×5 cm indurated mass overlying right shoulder with extension into right axilla. Several mobile, nontender right axillary LN present. 3 + right upper and lower extremity edema with massive scrotal swelling.	15.8 (d2)
[17]	2001	F	18	3-month h/o weakness, weight loss, low-grade fever (PMH: NR)	NR	NR	15.4 (d4)

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

Table 1 continued. Summary of literature review of lymphoma cases initially presenting with hypoglycemia and lactic acidosis.

Ref	Year	Sex	Age	Chief complaint	Reason for referral / transfer	Physical exam	Serum lactate (mmol/L)
[18]	1996	F	71	2 mo h/o palpable tumor of right thigh, night sweats, pollakiuria, general weakness (PMH: negative)	N/A	Tachypnea, tachycardia, obese, massive swelling of right inguinal and ventromedial femoral region with inflammatory skin infiltration	15.3 (d1)
[19]	1994	M	26	3 wk h/o generalized malaise, anorexia, subjective weight loss (PMH: HIV +)	N/A	Splenomegaly, epigastric mass, left basal coarse crepitations	7.9 (d1)
[20]	1991	F	74	10 mo h/o weight loss >10 kg, aphthous stomatitis, herpes zoster, fever (PMH: NR)	Temporary improvement of toxic epidermal necrolysis and iridocyclitis consistent with erythema multiforme exudativum, after 7 wk course of prednisone	Altered mental status, atrial fibrillation, erythema multiforme exudativum of skin and oral cavity	14.8 (d2)
[21]	2010	M	74	Generalized weakness, anorexia, 27 kg weight loss in 5 mo (PMH: bleeding duodenal ulcer and lactic acidosis 4 mo earlier)	Neurosurgical evaluation	Tachycardic, bilateral expiratory wheezes, not oriented to time	19.8 (d1)

Ref	pH	HCO3- (mmol/L)	BG (mg/dL)	Diagnostics	Pathology	Outcome
Current case	7.29 (d4)	17.3 (d4)	37 (d1)	CT abdomen, retroperitoneal bx	DLBCL	Patient refused chemo, steroids begun on d6, patient expired 3 days after discharge to hospice
[9]	7.24 (d1)	12 (d1)	26 (d1)	FDG-PET/CT	EBV+ DLBCL	Patient refused further chemo and died 1 wk after D/C
[10]	7.17 (d5)	8 (d5)	39 (d5)	BM bx	Large B-cell non-Hodgkin's lymphoma	Chemo begun. Pancytopenia. Neutropenic fever, secondary to VRE and coagulase-negative staphylococci bacteremia. Progressed to refractory septic shock and MOF. Expired on d30
[11]	"Lactic acidosis" (d1)	"Significantly decreased" (d1)	"Hypoglycemia" (d1)	FDG-PET/CT and BM bx	Primary osseous NKC NHL with possible splenic and hepatic involvement	Chemo initiated
[12]	"AG acidosis" (d1)	NR	50 (d1)	CT abdomen, MRI abdomen, liver bx, BM bx,	DLBCL	3 months after chemo began, CT showed near complete response with absence of splenic lesions and only mild HSM
[13]	7.29 (d15)	14 (d15)	"Refractory hypoglycemia" (d15)	CT abdomen, laparotomy, BM bx, liver bx	Stage IV DLBCL with hemophagocytosis	Expired on d17 (ICU d3)

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

Table 1 continued. Summary of literature review of lymphoma cases initially presenting with hypoglycemia and lactic acidosis.

Ref	pH	HCO3- (mmol/L)	BG (mg/dL)	Diagnostics	Pathology	Outcome
[14]	"AG metabolic acidosis" (d1)	19 (d1)	65 (d1)	BM bx, flow cytometry, cytogenetics	Mantle-cell lymphoma	Lactic acidosis and hypoglycemia resolved 2d after chemo was begun
[15]	7.23 (d1)	13.5 (d1)	86 (d1)	BM bx, liver bx	Large B-cell type (non-Hodgkin's) lymphoma with liver lymphoid infiltration	Dialysis on d2, chemo begun on d5, D/C to rehabilitation facility
[16]	7.29 (d2)	NR	27-60 (d2)	CT, thoracentesis, BM bx, autopsy	Stage IV Burkitt's lymphoma without liver involvement	Family refused chemo, patient expired on d13
[17]	7.32 (d4)	14 (d4)	44 (d4)	CT	Large cell malignant lymphoma (polymorphous immunoblastic T-cell subtype)	Chemo, brief complete remission, lymphoma recurred, patient refused further chemo, expired 7 mo after initial diagnosis
[18]	7.35 (d1)	10.1 (d1)	88 (d1)	Fine needle biopsy, BM bx, CT abdomen, MRI abdomen, FDG-PET	High-grade malignant non-Hodgkin's lymphoma	Chemo initiated. Expired on d15 due to recurrent GI bleed
[19]	7.23 (d1)	16.0 (d1)	63 (d1)	Abdominal U/S, BM bx	Burkitt's lymphoma	Chemo initiated, tumor lysis syndrome, expired on d7
[20]	7.34 (d1)	NR	36 (d2)	Abdominal U/S, BM bx, autopsy	Non-Hodgkin's T-cell lymphoma involving LN, spleen, liver, brain	Symptomatic therapy, expired on d5
[21]	7.07 (d1)	NR	47 (d1)	CXR, CT head, CT abdomen, electromyelogram, muscle bx, nerve bx, BM bx, cytogenetics, flow cytometry	Immature B-cell lymphoma/leukemia, myelodysplastic syndrome	Family opted for palliation, placed on steroids. Developed bacteremia and candidemia. Expired on d44

AG – anion gap, BG – blood glucose, BM – bone marrow, bx – biopsy, chemo – chemotherapy, COPD – chronic obstructive pulmonary disease, CT – computed tomography, CXR – chest radiograph, D/C – discharge, DLBCL – diffuse large B-cell lymphoma, DM – diabetes mellitus, EBV – Epstein-Barr virus, F – female, FOBT – fecal occult blood test, GCS – Glasgow coma scale, HA – headache, HIV – human immunodeficiency virus, h/o – history of, HR – heart rate (beats/minute), HSM – hepatosplenomegaly, HTN – hypertension, ICU – intensive care unit, lb – pound, LN – lymph node, LOS – length of stay, M – male, MOF – multi-organ failure, MRI – magnetic resonance imaging, N/A – not applicable, NHL – non-Hodgkin lymphoma, NK – natural killer cell, NR – not reported, N/V/D – nausea/vomiting/diarrhea, PMH – past medical history, RR – respiratory rate (breaths/minute), s/p – status-post, U/S – ultrasound, VRE – vancomycin-resistant enterococci.

(possibly due to myelodysplastic syndrome) but afebrile with negative blood cultures and without any identified source of infection, ruling out sepsis as the cause of lactic acidosis, which was also absent at initial presentation. A closer look at lactic acidosis in malignancies including lymphomas revealed other possible sources including anaerobic metabolism due to dense clusters of tumor cells [17], consistent with our patient's large bulky tumor masses in the abdomen leading to anaerobic metabolism.

The next challenge is to explain hypoglycemia and lactic acidosis as a single entity, as occurred in this case. The likely explanation is the Warburg effect, an intracellular physiologic process. It has been established that because cancer cells have higher rates of replication, and thus glycolysis, they cannot rely on normal oxidative phosphorylation that is the main source of energy in normal cells. Therefore, they shift to a glycolytic pathway at a higher rate (>200-fold) in aerobic conditions, resulting in lactic acid fermentation in the cytoplasm [28,29]. Another aberrantly expressed protein in highly dividing cells is

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

the pyruvate kinase inhibitor M2-PK that enables cancer cells to consume glucose at an accelerated rate, forcing the cells to switch to pyruvate kinase's splice variant, which is important for cancer metabolism and tumor growth and results in elevated lactate levels [30]. Additionally, p53 can promote glycolysis through activation of hexokinase II [31].

Additionally, lactic acidosis can occur with or without liver dysfunction [17,32,33]. A review of the literature demonstrates that NHL-induced lactic acidosis is associated with a mortality rate of 73% at 1 month and 92% overall; 90% of these cases had liver involvement [16]. Thus, lactic acidosis is a rare threatening sign when associated with lymphoid malignancies. Based on previous reports [12,14], one may conclude that only chemotherapy helps with treating the acidosis, which does not necessarily affect the outcome. Moreover, the strikingly high mortality associated with lactic acidosis has prompted some oncologists to consider this an oncologic emergency [34]. It is important to note that none of the patients in Table 1 were treated with bicarbonate, in contrast with what had been reviewed by Sillos and colleagues [17], since bicarbonate may increase lactic acid production [35] and is reserved only for control of acidosis along with dialysis awaiting chemotherapy.

In our patient, even though lactatemia and hypoglycemia started to correct after steroid treatment, poor prognostic markers based on the international prognostic index (IPI) and the patient's disposition precluded any further treatment. The patient died three days after discharge to hospice care.

Conclusions

This case illustrates how lymphomas can present unusually with hypoglycemia and lactic acidosis, the latter being an ominous sign that can occur without liver involvement. In this regard, presenting signs and symptoms of disease deserve special attention, in conjunction with clinical examination, to facilitate prompter accurate diagnosis and management of lymphoma, not only as an oncologic entity but also as a metabolic disorder.

Acknowledgments

We thank Lora Musich and Debbie Boone for their assistance in obtaining requested references.

Competing interests

The authors have no competing interests to disclose.

List of Abbreviations used

CT – computed tomography; **DLBCL** – diffuse large B-cell lymphoma; **IGF** – insulin-like growth factor; **NHL** – non-Hodgkin lymphoma; **NICTH** – nonislet cell tumor hypoglycemia.

References:

1. Karwinski B, Svendsen E, Hartveit F: Clinically undiagnosed malignant tumours found at autopsy. APMIS, 1990; 98(6): 496–500
2. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2012. CA Cancer J Clin, 2012; 62: 10–29
3. Richmond J, Sherman RS, Diamond HD, Craver LF: Renal lesions associated with malignant lymphomas. Am J Med, 1962; 32: 184–207
4. Da'as N, Polliack A, Cohen Y et al: Kidney involvement and renal manifestations in non-Hodgkin's lymphoma and lymphocytic leukemia: a retrospective study in 700 patients. Eur J Haematol, 2001; 67(3): 158–64
5. Martina MN, Solé M, Massó E et al: Mixed cryoglobulinaemia not related to hepatitis C virus, mesangiocapillary glomerulonephritis and lymphoplasmocytic lymphoma. Nefrologia, 2011; 31(6): 743–46
6. Holm J, Breum L, Stenfeldt K et al: Bilateral primary adrenal lymphoma presenting with adrenal insufficiency. Case Rep Endocrinol, 2012;2012:638298
7. Lam KY, Lo CY: Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. Clin Endocrinol (Oxf), 2002; 56(1): 95–101
8. Ejnisman B, de Figueiredo EA, Terra BB et al: Subacromial bursitis related to HIV infection: case report. Braz J Infect Dis, 2010; 14(6): 645–46
9. Elhomsy GC, Eranki V, Albert SG et al: "Hyper-Warburgism," a Cause of Asymptomatic Hypoglycemia with Lactic Acidosis in a Patient with Non-Hodgkin's Lymphoma. J Clin Endocrinol Metab, 2012; 97(12): 4311–16
10. Ruiz JP, Singh AK, Hart P: Type B lactic acidosis secondary to malignancy: case report, review of published cases, insights into pathogenesis, and prospects for therapy. Scientific World Journal, 2011; 11: 1316–24
11. Huo L, Luo Y, Zhang T et al: Unexpected primary osseous lymphoma as the cause of lactic acidosis in a patient suffering from pancreatitis. Clin Nucl Med, 2010; 35(10): 790–93
12. Keller BC, Nussensveig D, Dowell JE: Diffuse large B-cell lymphoma in a hepatitis C virus-infected patient presenting with lactic acidosis and hypoglycemia. Am J Med Sci, 2010; 339(2): 202–4
13. Jung B, Zoric L, Chanques G et al: Acute abdomen and severe lactic acidosis can lead to a surprising diagnosis. Intensive Care Med, 2010; 36(1): 169–70
14. Diab K, Knox KS, Hage CA: An 81-year-old man with lactic acidosis, refractory hypoglycemia, and lymphocytosis. Chest, 2008; 133(1): 306–10
15. Prikis M, Bhasin V, Young MP et al: Sustained low-efficiency dialysis as a treatment modality in a patient with lymphoma-associated lactic acidosis. Nephrol Dial Transplant, 2007; 22(8): 2383–85
16. Glasheen JJ, Sorensen MD: Burkitt's lymphoma presenting with lactic acidosis and hypoglycemia - a case presentation. Leuk Lymphoma, 2005; 46(2): 281–83
17. Sillos EM, Shenep JL, Burghen GA et al: Lactic acidosis: a metabolic complication of hematologic malignancies: case report and review of the literature. Cancer, 2001; 92(9): 2237–46
18. Durig J, Fiedler W, de Wit M et al: Lactic acidosis and hypoglycemia in a patient with high-grade non-Hodgkin's lymphoma and elevated circulating TNF-alpha. Ann Hematol, 1996; 72(2): 97–99
19. Bergin C, Pilkington R, McCreary C et al: Lactic acidosis, non-Hodgkins lymphoma and the acquired immunodeficiency syndrome. Genitourin Med, 1994; 70(2): 148–49
20. Caspar CB, Oelz O: Lactic acidosis in malignant lymphoma. Am J Med, 1991; 91(2): 197–98
21. Diaz J, Antoine J, Azad N: A case of hypoglycemia, lactic acidosis, and hematologic malignancy. Endocr Pract, 2010; 16(2): 241–43

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

22. Friedenberg AS, Brandoff DE, Schiffman FJ: Type B lactic acidosis as a severe metabolic complication in lymphoma and leukemia: a case series from a single institution and literature review. Medicine (Baltimore), 2007; 86(4): 225–32
23. Scott K: Non-islet cell tumor hypoglycemia. J Pain Symptom Manage, 2009; 37(4): e1–3
24. de Groot JW, Rikhof B, van Doorn J et al: Non-islet cell tumor-induced hypoglycemia: a review of the literature including two new cases. Endocr Relat Cancer, 2007; 14(4): 979–93
25. Fukuda I, Hizuka N, Ishikawa Y et al: Clinical features of insulin-like growth factor-II producing non-islet-cell tumor hypoglycemia. Growth Horm IGF Res, 2006; 16(4): 211–16
26. Teale JD, Marks V: Glucocorticoid therapy suppresses abnormal secretion of big IGF-II by non-islet cell tumors inducing hypoglycemia (NICTH). Clin Endocrinol, 1998; 49: 491–98
27. Chan FH, Carl D, Lyckholm LJ: Severe lactic acidosis in a patient with B-cell lymphoma: a case report and review of the literature. Case Rep Med, 2009; 2009: 534561
28. Gatenby RA, Gillies RJ: Why do cancers have high aerobic glycolysis? Nat Rev Cancer, 2004; 4(11): 891–99
29. Kim JW, Dang CV: Cancer's molecular sweet tooth and the Warburg effect. Cancer Res, 2006; 66(18): 8927–30
30. Christofk HR, Vander Heiden MG, Harris MH et al: The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature, 2008; 452(7184): 230–33
31. Maddocks OD, Vousden KH: Metabolic regulation by p53. J Mol Med (Berl), 2011; 89(3): 237–45
32. Rao KS, Mehta R, Ferlinz J: Unusual presentation of cancer-induced lactic acidosis. Postgrad Med J, 1988; 64(752): 475
33. Fujimura M, Shirasaki H, Kasahara K, Matsuda T: Small cell lung cancer accompanied by lactic acidosis and syndrome of inappropriate secretion of antidiuretic hormone. Lung Cancer, 1998; 22(3): 251–54
34. Jabr FI: Lactic acidosis in patients with neoplasms: an oncologic emergency. Mayo Clinic Proceedings, 2006; 81(11): 1505–6
35. Forsythe SM, Schmidt GA: Sodium bicarbonate for the treatment of lactic acidosis. Chest, 2000; 117(1): 260–67

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License