

Review began 02/19/2023  
Review ended 02/25/2023  
Published 02/27/2023

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# Atypical Presentation of Burkitt Lymphoma With Isolated Peritoneal Involvement and Association With Refractory Type B Lactic Acidosis and Hypoglycemia Secondary to the Warburg Effect

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## Abstract

Lactic acidosis is considered to be one of the most common causes of high anion gap metabolic acidosis in hospitalized patients. Warburg effect can present with type B lactic acidosis and is considered to be a rare but well-known complication of hematological malignancies. Here, we present the case of a 39-year-old male who had type B lactic acidosis and recurrent hypoglycemia secondary to newly diagnosed Burkitt lymphoma. This case highlights the importance of considering malignancy workup in any case of unexplained type B lactic acidosis with vague clinical presentation, which can aid in early diagnosis and management.

**Categories:** Internal Medicine, Oncology, Hematology

**Keywords:** non-hodgkin's lymphoma, unexplained ascites, burkitt lymphoma, warburg effect, lactic acidosis

## Introduction

Lactic acidosis is defined as a serum lactate concentration higher than 4 mmol/L and is considered to be one of the most common causes of high anion gap metabolic acidosis in hospitalized patients [1]. Etiology can be divided into reduced tissue oxygenation (type A) and conditions where hypoperfusion is not apparent (type B). Among many others, malignancy is a known rare cause of type B lactic acidosis [2]. Moreover, the Warburg effect is an uncommon but serious condition that happens when neoplastic cells shift to aerobic glycolysis and it is highly linked to many cancers, particularly B-cell lymphomas [3,4]. It is considered an oncological emergency and is associated with poor prognosis and a high mortality rate if untreated [4].

## Case Presentation

A previously healthy 39 years old Asian male presented to the emergency department with abdominal distension for a three months duration. Two weeks earlier, he was seen in another hospital where he had a normal colonoscopy and underwent ascitic fluid drainage of 2.7 liters without reaching a diagnosis. His abdominal distension was getting worse gradually after discharge, and he started to develop exertional dyspnea as well. It was associated with night sweats, loss of appetite, and significant weight loss.

On admission, the patient was afebrile, blood pressure was 135/101 mmHg, pulse rate of 114 beats/minute, respiratory rate of 26 breaths/minute, and oxygen saturation of 98% on room air. Physical examination showed a soft, non-tender moderately distended abdomen with a positive shifting dullness sign. There was no organomegaly, chronic liver disease, or coagulopathy signs. His cardiopulmonary examination was normal. Laboratory studies showed normal electrolytes, creatinine, urea, lipase, liver function test, and coagulation panel. His random serum glucose was 3.5 mmol, serum albumin was 28 g/L, and serum total protein was 64 g/L. White blood cell count of  $8.5 \times 10^9/L$ ; neutrophils, 68.9%; lymphocytes, 23.5%; hemoglobin of 148 g/L; and platelet count of  $391 \times 10^9/L$ . The C-reactive protein of 47.6 mg/L and negative COVID-19 PCR (coronavirus disease 2019 polymerase chain reaction) test. Venous blood gases showed Ph (potential hydrogen) of 7.36,  $HCO_3$  of 20 mmol/L, and lactic acid of 5.1 mmol/L. HIV (human immunodeficiency virus) and hepatitis panel negative.

Computed tomography (CT) of the abdomen/pelvis with contrast ruled out bowel ischemia but showed significant diffuse thickening of the omentum (omental cake) and the peritoneum (Figure 1). Along with a marked 10 cm segment of the distal ileum bowel wall thickening, in the right lower quadrant, with an increase in enhancement and surrounding large volume of free fluid that is extending to all quadrants (Figure 2). The adjacent terminal ileum shows a reactive inflammatory change and diffuses peritoneal enhancement. Multiple mesenteric reactive lymph nodes with no lymphadenopathy.

### How to cite this article

Abbas A K, Osman A Y (February 27, 2023) Atypical Presentation of Burkitt Lymphoma With Isolated Peritoneal Involvement and Association With Refractory Type B Lactic Acidosis and Hypoglycemia Secondary to the Warburg Effect. Cureus 15(2): e35521. DOI 10.7759/cureus.35521



**FIGURE 1: Computed tomography scan showing diffuse thickening of the omentum (omental caking)**



**FIGURE 2: Computed tomography scan showing distal ileum bowel wall thickening**

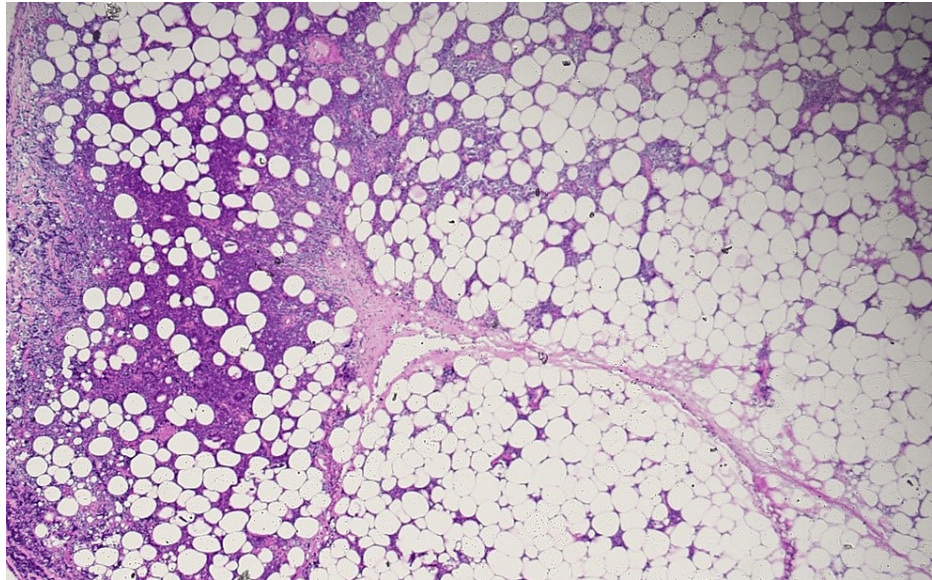
Abdominal fluid analysis revealed white-pinkish purulent fluid with Ph (potential hydrogen) of 8, nucleated cells  $104,239.00 \times 10^6/L$ , neutrophils 5%, lymphocytes 15%, monocyte 10%, mesothelial cells 70%. Albumin was 22 g/L, protein 37 g/L, glucose 0.2 mmol/L, LDH (lactate dehydrogenase) 9,867 IU/L, triglyceride 0.65 mmol/L, ADA (adenosine deaminase) 121 U/L, and peritoneal fluid cytology showed few atypical cells that are of uncertain clinical significance.

Initially was treated empirically as a case of peritoneal tuberculosis (as per infectious disease team advice) along with intravenous hydration. Despite that, the patient continued to deteriorate with his lactic acid reaching 20 mmol/L, bicarbonate of 4 mmol/L, persistent hypoglycemia, and positive serum ketones. The patient was shifted to the intensive care unit where he had cardiac arrest secondary to hyperkalemia ( $K^+$  of 8

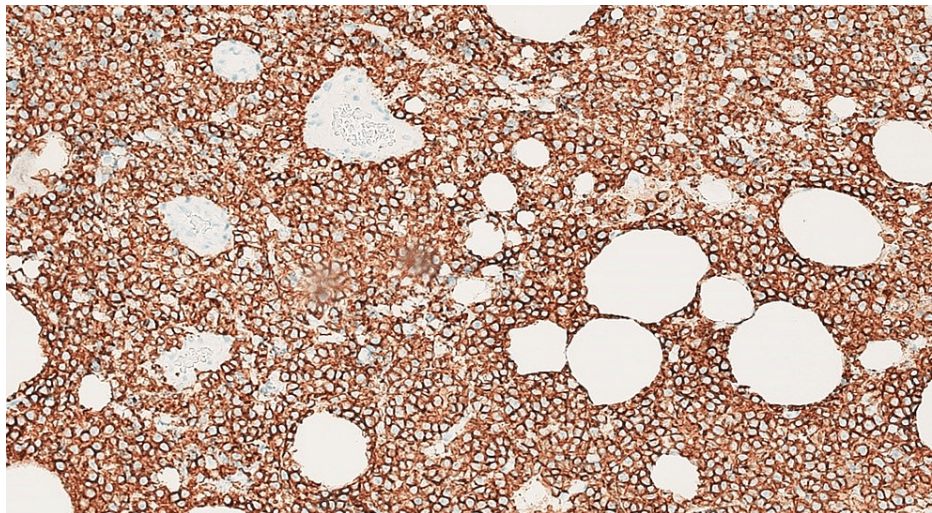


mmol/L) which was aborted after successful resuscitation.

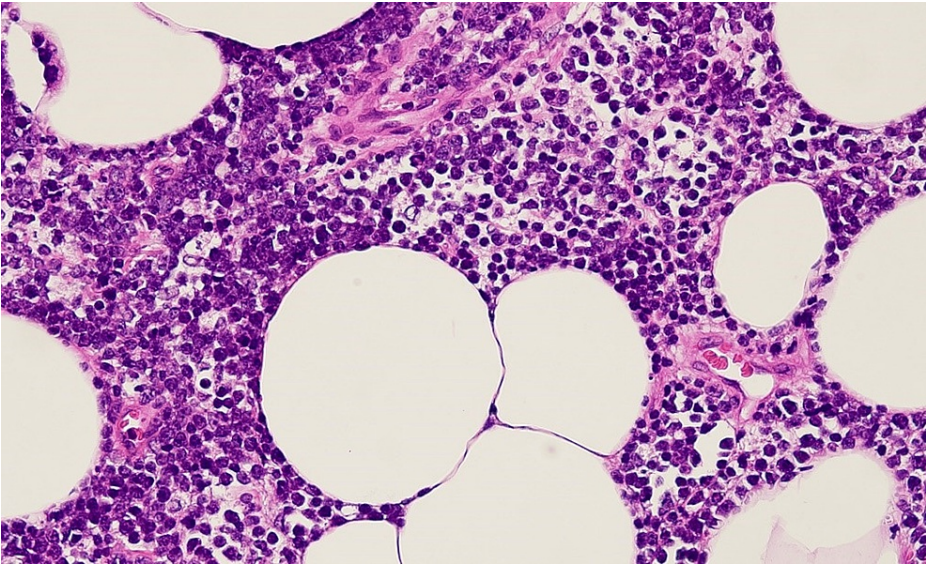
A few days later, the surgical team was able to obtain an omentum biopsy sample which showed infiltration by diffuse sheets of monomorphic appearing intermediate-sized abnormal cells with the following immunophenotype CD20+/PAX5+ and CD10+; and are negative for CD3, CD5, BCL2, MUM1, CD30, CD34, and Cyclin D1 (Figures 3-5). The abnormal lymphoid cells are negative for TdT (Terminal deoxynucleotidyl transferase) immunostain. EBER ISH stain was negative for EBV (Epstein-Barr virus). C-MYC showed equivocal staining in the lesional cells. CD21 and CD23 immunostains do not show any discreet FDC meshwork. The Ki-67 proliferation fraction is very high, approximately >95% in the lesional cells.



**FIGURE 3: Omental biopsy with infiltration by lymphoma**



**FIGURE 4: CD20 positive neoplastic cells**



**FIGURE 5: Lymphoma cells with admixed tangible body macrophages**

FISH (fluorescence in situ hybridization) study showed t(8;14) MYC/IGH fusion in approximately 84% of nuclei. No rearrangement of BCL2 or BCL6 was observed (Table 1).

Abnormality Name	Result	Abn %	Cutoff %
8q24.1 (MYC sep)	Abnormal	91	<7.0
t(8;14) MYC/IGH fusion	Abnormal	84	<5.0
18q21 (BCL2 sep)	Normal		<9.0
3q27 (BCL6 sep)	Normal		<6.0

**TABLE 1: FISH study showing t(8;14) MYC/IGH translocation**

FISH: fluorescence in situ hybridization

The findings were consistent with Burkitt lymphoma. The patient was then transferred to the hospital with oncology service and he passed away one day later as he had another cardiac arrest secondary to another hyperkalemic episode.

Discussion

Lactic acidosis is divided into two subtypes according to pathophysiology type A which is more common and results from tissue hypoxia and low perfusion [5], and type B which happens in conditions with normal perfusion and is usually a result of toxins or drugs that alert cellular metabolism or due to nutritional deficiency that leads to mitochondrial dysfunction [6].

Malignancy although rare but considered to be a life-threatening cause of type B lactic acidosis [2,5]. Hematological malignancies account for the majority compared to solid organ malignancies [7]. The exact underlying mechanism is not well understood and is likely to be multifactorial [2]. Warburg effect also termed aerobic glycolysis was first described by the German physician Otto Warburg in 1923 [8].

Because of their higher proliferative rate compared to normal cells, tumor cells tend to increase their metabolism of glucose to lactate despite the presence of adequate oxygen. Under this condition, the conversion rate of glucose to lactate is around 100 times faster than through the citric acid cycle resulting in similar ATP (adenosine triphosphate) production over a similar period [9,10]. The association between lactic acidosis and hypoglycemia is uncommon but well-documented in some malignant causes, especially in lymphoproliferative tumors such as lymphomas [11].



In this case, the history of night sweats, weight loss, and generalized fatigue can be explained by B symptoms. The patient had refractory lactic acidosis that was not explained by hypoperfusion, toxins, or drugs. Omental biopsy and FISH study confirmed the diagnosis of Burkitt lymphoma. The rare combination of type B lactic acidosis, refractory hypoglycemia, ketoacidosis, and Burkitt lymphoma that presented as isolated peritoneal involvement was not reported in the literature previously.

The treatment approach for type B lactic acidosis should concentrate on treating the underlying cause, and the effect of acid correction and intravenous fluid rehydration treatment is not optimal [12].

The mortality rate from lactic acidosis secondary to malignancy is very high. Previously reported data showed that >70% of cases with lymphoma-associated Warburg effect died within 30 days [4,13,14].

## Conclusions

Warburg effect is a rare but very serious complication of hematological malignancies. Workup for lactic acidosis should rule out common etiologies and at the same time consider critical ones, especially in refractory cases. In any patient who presents with lactic acidosis and hypoglycemia with possible or confirmed lymphoma, the Warburg effect should be in the differential diagnosis. As in many other medical emergencies, time to treatment initiation is considered a significant factor in determining prognosis.

## Additional Information

### Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## References

1. Pattharanitima P, Thongprayoon C, Petnak T, et al.: Machine learning consensus clustering approach for patients with lactic acidosis in intensive care units. *J Pers Med*. 2021, 11:1132. [10.3390/jpm11111132](https://doi.org/10.3390/jpm11111132)
2. Sillos EM, Shenep JL, Burghen GA, Pui CH, Behm FG, Sandlund JT: Lactic acidosis: a metabolic complication of hematologic malignancies: case report and review of the literature. *Cancer*. 2001, 92:2237-46. [10.1002/1097-0142\(20011101\)92:9%3C2237::AID-CNCR1569%3E3.0.CO;2-9](https://doi.org/10.1002/1097-0142(20011101)92:9%3C2237::AID-CNCR1569%3E3.0.CO;2-9)
3. Dhup S, Dadhich RK, Porporato PE, Sonveaux P: Multiple biological activities of lactic acid in cancer: influences on tumor growth, angiogenesis and metastasis. *Curr Pharm Des*. 2012, 18:1319-30. [10.2174/138161212799504902](https://doi.org/10.2174/138161212799504902)
4. Wang C, Lv Z, Zhang Y: Type B lactic acidosis associated with diffuse large B-cell lymphoma and the Warburg effect. *J Int Med Res*. 2022, 50:3000605211067749. [10.1177/03000605211067749](https://doi.org/10.1177/03000605211067749)
5. Kreisberg RA: Lactate homeostasis and lactic acidosis. *Ann Intern Med*. 1980, 92:227-37. [10.7326/0003-4819-92-2-227](https://doi.org/10.7326/0003-4819-92-2-227)
6. Stacpoole PW: Lactic acidosis and other mitochondrial disorders. *Metab Clin Exp*. 1997, 46:306-21. [10.1016/S0026-0495\(97\)90259-6](https://doi.org/10.1016/S0026-0495(97)90259-6)
7. 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. *ScientificWorldJournal*. 2011, 11:1316-24. [10.1100/tsw.2011.125](https://doi.org/10.1100/tsw.2011.125)
8. Warburg O: The metabolism of carcinoma cells. *Cancer Res*. 1925, 9:148-63. [10.1158/jcr.1925.148](https://doi.org/10.1158/jcr.1925.148)
9. Warburg O, Wind F, Negelein E: The metabolism of tumors in the body. *J Gen Physiol*. 1927, 8:519-30. [10.1085/jgp.8.6.519](https://doi.org/10.1085/jgp.8.6.519)
10. Demetrius L, Tuszynski JA: Quantum metabolism explains the allometric scaling of metabolic rates. *J R Soc Interface*. 2010, 7:507-14. [10.1098/rsif.2009.0310](https://doi.org/10.1098/rsif.2009.0310)
11. Friedenber 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, 86:225-32. [10.1097/MD.0b013e318125759a](https://doi.org/10.1097/MD.0b013e318125759a)
12. Duriseti P, Moreno Vanegas Y, Jaber BL, Balakrishnan VS, Madias NE: Malignancy-induced lactic acidosis in adult lymphoma. *Clin Nephrol*. 2021, 95:1-21. [10.5414/CN110116](https://doi.org/10.5414/CN110116)
13. Martinez-Outschoorn UE, Whitaker-Menezes D, Valsecchi M, et al.: Reverse Warburg effect in a patient with aggressive B-cell lymphoma: is lactic acidosis a paraneoplastic syndrome?. *Semin Oncol*. 2013, 40:403-18. [10.1053/j.seminoncol.2013.04.016](https://doi.org/10.1053/j.seminoncol.2013.04.016)
14. He YF, Wei W, Sun ZM, et al.: Fatal lactic acidosis and hypoglycemia in a patient with relapsed natural killer/T-cell lymphoma. *Adv Ther*. 2007, 24:505-9. [10.1007/BF02848772](https://doi.org/10.1007/BF02848772)