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CASE REPORT

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# Relapsed mantle cell lymphoma presenting with lactic acidosis and hypoglycemia: A case report

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**Abstract**

Lactic acidosis and hypoglycemia are rare presentations of malignancy with a poor prognosis. We present the case of a mantle cell lymphoma patient who relapsed with lactic acidosis and hypoglycemia. Although blood glucose, pH, and lactate normalized following chemotherapy and intensive care support, the patient died from ventilator-associated pneumonia.

**KEYWORDS**

hypoglycemia, lactic acidosis, mantle cell lymphoma

## 1 | BACKGROUND

Mantle cell lymphoma is a rare, aggressive B-cell non-Hodgkin's lymphoma, accounting for 6% of lymphoma diagnoses.[1] Typical presentation includes extensive painless lymphadenopathy, splenomegaly-related discomfort, B symptoms including night sweats, weight loss and fever, as well as symptomatic cytopenias due to bone marrow replacement by disease.[2] Concurrent lactic acidosis and hypoglycemia is a rare presentation of lymphoma and is considered an oncological emergency due to its high mortality and the necessity for rapid cancer-directed treatment.[3] We present the case of a mantle cell lymphoma patient who developed severe lactic acidosis and hypoglycemia in the context of new-onset pancytopenia 7 months after starting ibrutinib therapy, despite marked improvement in lymphadenopathy on radiological imaging. Bone marrow biopsy-confirmed relapsed disease. Although blood glucose, pH, and lactate normalized following second-line chemotherapy and intensive care support, the patient died from ventilator-associated pneumonia.

## 2 | CASE PRESENTATION

A 67-year-old man, with no significant past medical or drug history, initially presented with widespread lymphadenopathy and massive splenomegaly. Computed tomography (CT) revealed a large retroperitoneal mass which extended into a further mesenteric mass (Figure 1). His blood results showed pancytopenia (white blood cell count 2.4 $\times 10^9$/L, hemoglobin 97 g/L, platelets 90 $\times 10^9$/L), acute kidney injury (urea 22.7 mmol/L, creatinine 175 μmol/L), hypoalbuminemia (29 g/L) and a raised LDH (332 U/L), and uric acid (813 μmol/L). A diagnosis of mantle cell lymphoma was made based on bone marrow morphology, flow cytometry, and fluorescence in situ hybridization demonstrating the IGH-CCND1 t(11; 14) rearrangement. He was treated with ibrutinib monotherapy and aside from initial mild tumor lysis syndrome, the patient tolerated the drug well and had a good clinical response with normalization of his peripheral blood values. Ibrutinib was chosen in this case as it was approved for first-line treatment in mantle cell lymphoma under NHS England interim COVID-19 agreements.

In the seventh month, he presented clearly unwell with fatigue and a fever of 38°C. Blood pressure was 137/73, heart rate 106 bpm, respiratory rate 24/min, and oxygen saturations 98% on air. He had a palpable liver edge and splenomegaly as well as a petechial rash on his legs and mild edema. Blood test results showed pancytopenia (hemoglobin 67 g/L, platelets 67 $\times 10^9$/L, neutrophils 0.72 $\times 10^9$/L), raised serum urea (14.6 mmol/L), low albumin (25 g/L), and raised CRP (176 mg/L). Venous blood gas showed raised lactate (12.65 mmol/L), mild acidosis (pH 7.33), blood glucose of 3 mmol/L, and a base excess of −12.6 mmol/L. All other results were unremarkable. The patient was resuscitated with 2 L of saline and 2 units of packed red cells, potential B vitamin deficiency was corrected with Pabrinex, and broad-spectrum IV antibiotics were commenced.

The patient was admitted to the intensive care unit 1 day later with worsening hyperlactatemia and poor urinary output and was started on rasburicase, prednisolone, and continuous veno-venous hemofiltration. CT showed complete regression of the lymphomatous masses, no evidence of lymphadenopathy, but massive splenomegaly (Figure 1). At Day 4, it was concluded that there was no evidence of Type A lactic acidosis: The patient had normal kidney and liver function, was taking no causative drugs, and had no evidence of tissue ischemia or sepsis. Bone marrow biopsy showed almost complete replacement of marrow with the known mantle cell lymphoma, with no evidence of hemophagocytic lymphohistiocytosis (Figure 2). The patient was given more fluids with the aim of reducing lactate, and G-CSF to reverse neutropenia, but by Day 7 of admission, lactate remained high (peaking at 19.5 mmol/L), so the decision was made to start rituximab and bendamustine chemotherapy despite his poor performance status. The hypoglycemia worsened, and the patient became severely pancytopenic (platelets 2 $\times 10^9$/L), and further glucagon, glucose and blood products were required. On Day 10 of admission, the patient required increasing cardiovascular and blood glucose support and was intubated. Although the patient was no longer acidotic, intravenous bicarbonate was started on Day 12, as lactate remained elevated at 7.6 mmol/L. Unfortunately, despite the best efforts of the intensive care team, and an eventual normalization of blood glucose control, pH, and lactate following the initiation of chemotherapy, the patient developed ventilator-associated pneumonia and

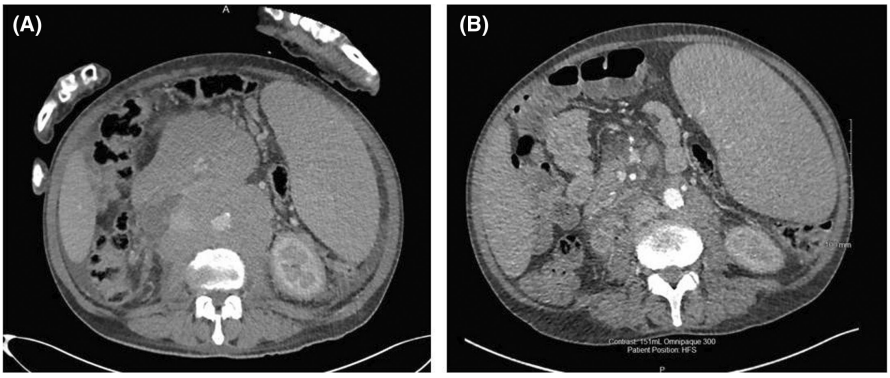


**FIGURE 1** Axial IV contrast-enhanced CT image through the abdomen (A) retroperitoneal mass, mesenteric mass, and splenomegaly, prior to commencing ibrutinib therapy (B) regression of lymphomatous masses but massive splenomegaly, after 7 months of ibrutinib therapy when presenting with lactic acidosis

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| **Morphology** | Hypercellular particulate bone marrow aspirate in which normal haemopoiesis has been largely replaced by lymphoid cells. This is most suggestive of heavy bone marrow infiltration with the known mantle cell lymphoma. |
| **Flow cytometry** | Flow cytometry of bone marrow aspirate identifies 68% lymphocytes (gated by strong CD45/low SSc). Of these 77% are B cells (CD19+) which express CD5, CD20, CD22, C43, CD79b, CD81 and lambda light chains. There is no expression of CD10, CD23, CD38 or CD200. Conclusion: 52% of nucleated cells in this bone marrow aspirate are monoclonal B cells with the phenotype of the known mantle cell lymphoma. |
| **Trephine biopsy** | This trephine biopsy samples a good length of hypercellular (80-90%) bone marrow. PAX5/CD20 highlight a diffuse infiltrate of >90% pleomorphic B cells which as Cyclin D1+. Erythropoiesis and granulopoiesis are markedly reduced. Megakaryocyte frequency is slightly reduced and forms do not show significant atypia. Clustering and micromegakaryocytes are not a feature. There is no excess of CD34+/CD117+ cells, these account for <5% of all nucleated cells. Macrophages (CD68P+) are slightly increased in number. There are occasional examples of haemophagocytic activity. Bony trabeculae are unremarkable. Conclusion: Hypercellular sample with >90% Cyclin D1+ B cells, in conjunction with flow cytometry of the aspirate sample the findings are in keeping with heavy infiltration by the known mantle cell lymphoma. |

**FIGURE 2** Bone marrow findings at relapse, including morphology and flow cytometry of bone marrow aspirate and histopathological features of bone marrow trephine.

required increasing cardiovascular, renal, and blood product support. After consulting with the family, supportive measures were withdrawn on Day 23 of admission, and the patient died from multi-organ failure shortly after.

## 3 | DISCUSSION

Lactic acidosis has been defined as pH ≤7.35 in association with hyperlactatemia (typically ≥5 mmol/L).[4] Lactic acidosis may also be diagnosed in patients with normal pH, for example, in the context of co-existing respiratory or metabolic alkalosis.[5] Therefore, the values of $PaCO_2$ or base excess can be included when defining the condition. Typically, lactic acidosis is categorized as either Type A or B.[6] Type A lactic acidosis occurs as the result of a mismatch between oxygen delivery and demand, whereas Type B occurs as a result of impaired oxidative phosphorylation, in conditions such as sepsis, congenital defects in metabolism, in response to toxins, and in malignancy. In some conditions, such as sepsis, there may be overlap between Type A and Type B lactic acidosis.[5] The pathophysiology and clinical consequences of hyperlactatemia are still poorly understood and fundamental questions, such as the importance of hyperlactatemia without acidosis, remain unclear.

The exact pathogenesis of lactic acidosis in malignancy is debated, with proposed mechanisms including reduced lactate clearance as a result of liver dysfunction, thiamine deficiency shunting glucose down anaerobic pathways,[7] and the metabolic switch commonly seen in cancer cells, known as the Warburg Effect. In our patient, liver dysfunction, tissue ischemia, sepsis, and thiamine deficiency were all ruled out as causes of lactic acidosis, and it was concluded that the Warburg Effect was the most reasonable explanation. The preferential production of lactate from glucose in the presence of oxygen was first observed by Otto Warburg in 1927,[8] yet the benefit to cancerous cells is still debated. Evidence suggests that rapid ATP production allows fine tuning of production to demand and that lactate production supports anabolic processes required for rapid proliferation. In solid tumors, acidification of the tumor micro-environment may provide a selective advantage and aid invasion. Glycolysis may also confer advantage by altering cell signaling via modification of histone acetylation and reactive oxygen species in cancer cells.[9] The proposed mechanism of glycolysis upregulation involves increased HIF-1α expression,[10] as well as IGF signaling via the MAPK and PI3K pathways,[11] both of which upregulate expression of important enzymes in the glycolytic pathway, such as hexokinase II. An alternative model, the "reverse Warburg Effect" has also been proposed more recently, in which increased glycolytic activity takes place in the surrounding stroma, providing by-products for cancer cell metabolism.[12] Regardless of mechanism, the Warburg Effect is the fundamental principle underlying fluorodeoxyglucose (FDG)-positron emission tomography (PET), which allows us to identify abnormal areas of high metabolic rate in malignancy.

Lactic acidosis is an under-recognized presentation of lymphoma; however, it is well recognized that lactic acidosis is a very poor prognostic marker in cancer patients, with a reported mortality of 80%.[12] Mantle cell lymphoma presenting with concurrent lactic acidosis is only described four times in the literature.[13-16] A 2009 review of lactic acidosis in lymphoma patients detailed 29 cases, of which only 7 patients went into partial or full remission.[3] It is important to note, however, that of these 29 patients, most had features of systemic inflammatory response, and it is therefore difficult to define the exact etiology of the lactic acidosis.[3] Nevertheless, of those patients that did survive, all received chemotherapy, and evidence from case reports would indicate that prompt chemotherapy should be considered in all oncology patients presenting with lactic acidosis, regardless of performance status.[14,17] These findings have been reflected in our patient, who saw improvements in serum lactate, LDH, base excess, and glucose after the initiation of chemotherapy (Figure 3), despite deterioration in clinical status.

Renal replacement therapy and intravenous sodium bicarbonate are other approaches taken to reduce lactate and improve acidosis, and indeed treatment of lactic acidosis by these means was attempted in 21 of the 29 reported patients, including 6 of the 7 that achieved remission.[3] However, evidence is lacking for these methods. Renal replacement therapy is only able to achieve a small additional lactate clearance compared with endogenous mechanisms. Sodium bicarbonate therapy remains controversial in the treatment of acidosis, as increases in $CO_2$ production and reversal of acidemia may shift the oxygen-hemoglobin dissociation curve to the left, reducing oxygen release. Other adverse effects of sodium bicarbonate therapy may include hypernatremia, hyperosmolality, and extravasation injuries.[18] Nonetheless, anecdotal evidence from the 6 cases mentioned previously would suggest that in these cases at least, sodium bicarbonate had no adverse effect on whether the patient went into remission.

Lactic acidosis in lymphoma has also been reported to occur in conjunction with hypoglycemia, as was seen in our patient. This feature can again be explained by the Warburg Effect, as glucose is rapidly utilized in glycolytic pathways. This combination of lactic acidosis and hypoglycemia is rare as a presenting feature of lymphoma, with a 2013 review finding only 14 cases, of

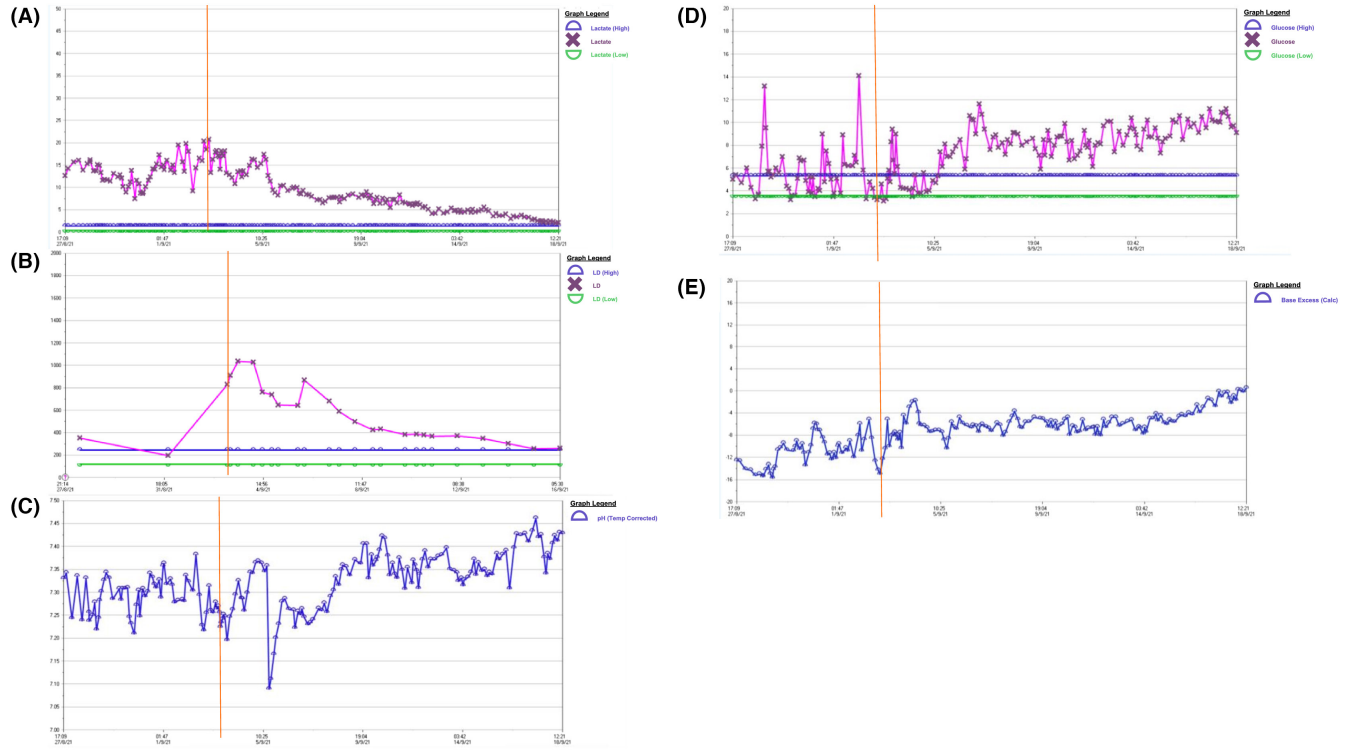


**FIGURE 3** Serum (A) lactate, (B) lactate dehydrogenase, (C) pH, (D) glucose, (E) base excess, plotted over time. Orange line indicates time of commencement of rituximab and bendamustine chemotherapy.

which one was mantle cell.[19] Other lymphomas reported in this review included 6 cases of large B-cell lymphoma, and others ranging from Burkitt's lymphoma to immature B cell and polymorphous T-cell lymphomas. Again, mortality was high in these patients, with positive outcomes for these patients dependent on prompt initiation of chemotherapy. Of the 12 reported long-term outcomes, only 3 patients in this review achieved remission. Notably, lactic acidosis and hypoglycemia resolved 2 days after initiation of chemotherapy in the mantle cell lymphoma patient reported by Diab et al.[16] A key complication in this subset of patients in the management of blood glucose: Careful management is required, as corrective high concentration glucose infusion has been reported to worsen lactic acidosis by providing a substrate pool for further lactate production, and thereby malignant cell anabolic processes, while making minimal impact on blood glucose levels.[20,21] These findings were seen in our patient, as glycemic control was only achieved after the initiation of chemotherapy, and correlated with improvement in serum lactate, LDH, and pH (Figure 3).

## 4 | CONCLUSION

This case demonstrates the need for prompt recognition and careful management of lymphoma patients with unusual presentations of disease relapse. Hyperlactatemia in these patients requires a multi-disciplinary approach to assess the relevant contributing factors and formulate an appropriate and timely management plan. In cases of Type B lactic acidosis, prompt chemotherapy should be considered. Further work is required to explore risk stratification of patients with hyperlactatemia using biochemical, clinical, and radiological markers.

## AUTHOR CONTRIBUTIONS

**Lucy Carson:** Writing – original draft; writing – review and editing. **Andrew Johnston:** Writing – review and editing. **George Follows:** Supervision; writing – review and editing. **Anna Santarsieri:** Supervision; writing – review and editing.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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