

## CASE REPORT

# Fatal cardiac arrhythmia caused by tumor lysis in a patient with diffuse large B-cell lymphoma upon start of R-CHOP

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### Key Clinical Message

Tumor lysis syndrome is rare in diffuse large cell lymphoma, but it is important to recognize the risk in patients with massive tumor burden and reduced kidney function. Very intense vigilance can be necessary despite adequate prophylactic measures and certain drugs may exacerbate electrolyte derangements.

### Keywords

Diffuse large B-cell Lymphoma, emergency medicine, hematology, hyperkalemia, tumor lysis syndrome.

## Introduction

Tumor lysis syndrome (TLS) is rare in diffuse large cell lymphoma (DLBCL). We present a DLBCL case with TLS developing upon first treatment with R-CHOP despite prophylactic measures. Overnight, the patient developed severe hyperkalemia, which resulted in a fatal arrhythmia.

Tumor lysis syndrome (TLS) is an oncologic emergency resulting from massive cancer cell lysis that occurs spontaneously or upon the start of chemotherapy. The release of intracellular tumor cell content (potassium, phosphorus, and uric acid) into the bloodstream leads to critical hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia [1]. TLS ranges from mild and transient asymptomatic electrolyte derangement to severe cases of renal failure, cardiac arrhythmias, and death, but fulminant TLS is a rare event in diffuse large cell lymphoma (DLBCL). We report a case of fatal TLS in a patient with DLBCL upon the start of R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

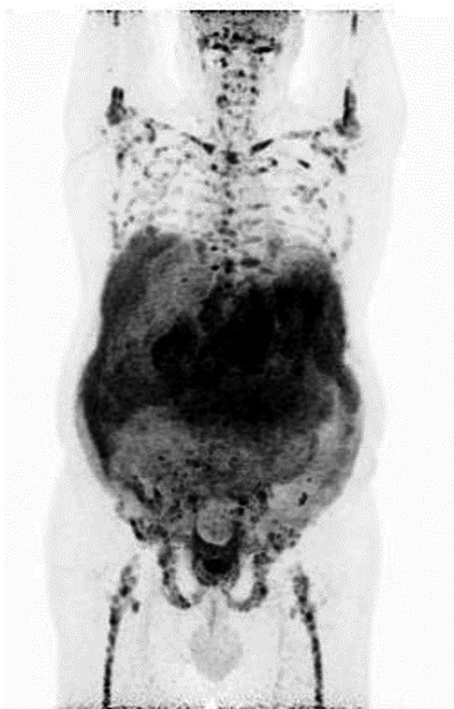
## Case History

A 62-year-old man with a medical history of diabetes and ischemic heart disease with preserved ejection fraction was admitted to hospital with a 2 months history of upper dyspepsia, increasing abdominal circumference, dark urine, night sweats, and fatigue. The patient was on treatment with spironolactone, metformin, allopurinol, and clopidogrel.

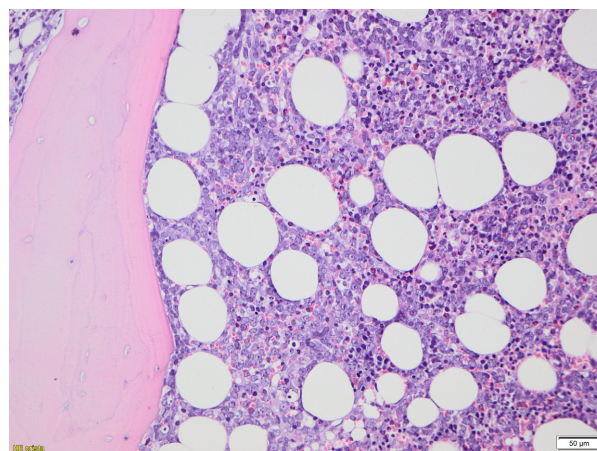
On admission, blood tests revealed renal impairment with creatinine of 430  $\mu\text{mol/L}$  (normal range 60–105  $\mu\text{mol/L}$ ), elevated lactate dehydrogenase of 800 U/L (normal range 105–205 U/L), alkaline phosphatase of 1270 U/L (normal range 35–105 U/L), alanine transaminase 560 U/L (normal range 10–50 U/L), and bilirubin of 101  $\mu\text{mol/L}$  (normal range 5–25  $\mu\text{mol/L}$ ). Magnetic resonance imaging (MRI) of the abdomen to evaluate malignancy in the pancreas or liver revealed no signs of such, but signs consistent with peritoneal carcinomatosis and a thickened gallbladder. A subsequent 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/

CT) showed enlarged and FDG-avid lymph nodes in several regions as well as pathological high FDG-uptake in the peritoneum and omentum, gallbladder, stomach, pancreas, and bone marrow (Fig. 1). An iliac crest biopsy revealed massive bone marrow infiltration (>50%) by large lymphoid cells with irregular nuclei (Fig. 2) and positive for CD20, CD79a, and CD10 on immunohistochemical evaluation. Additional fluorescence in situ hybridization (FISH) was positive for MYC translocation, but not for BCL 2 or BCL 6 translocation. Immunohistochemical stainings for BCL2 and BCL6 over expression were also negative. Peripheral blood smear showed circulating lymphoma cells (Fig. 3). Cells identical to those found in the bone marrow were also present in the peritoneal fluid and germinal center B-cell (GCB) DLBCL was finally diagnosed.

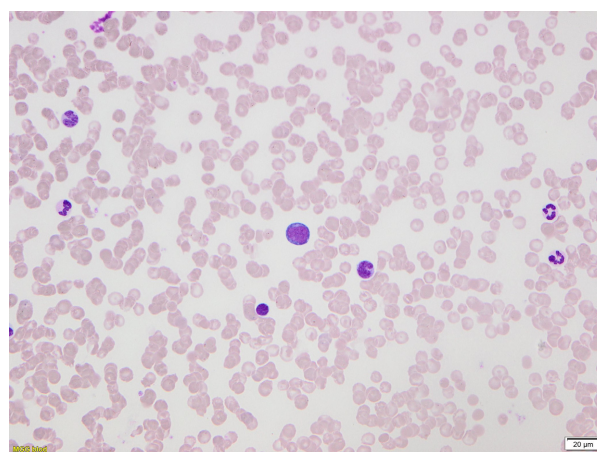
The patient was transferred to a hematology department for further treatment 16 days after hospital admission. At that time, rehydration had lowered creatinine level to 170  $\mu\text{mol/L}$  and pre-phase treatment with 100 mg prednisolone daily was initiated. Rehydration and allopurinol treatment was given continuously during this phase of treatment. R-CHOP was commenced on day 21 together with rasburicase. On that day, potassium was 3.6 mmol/L (normal range 3.5–4.6 mmol/L), uric acid 1.0 mmol/L (normal range 0.23–0.48 mmol/L), calcium



**Figure 1.** PET maximum intensity projection showing multiple FDG-avid lesions. Note the extensive pathological FDG-uptake corresponding to peritoneal involvement.



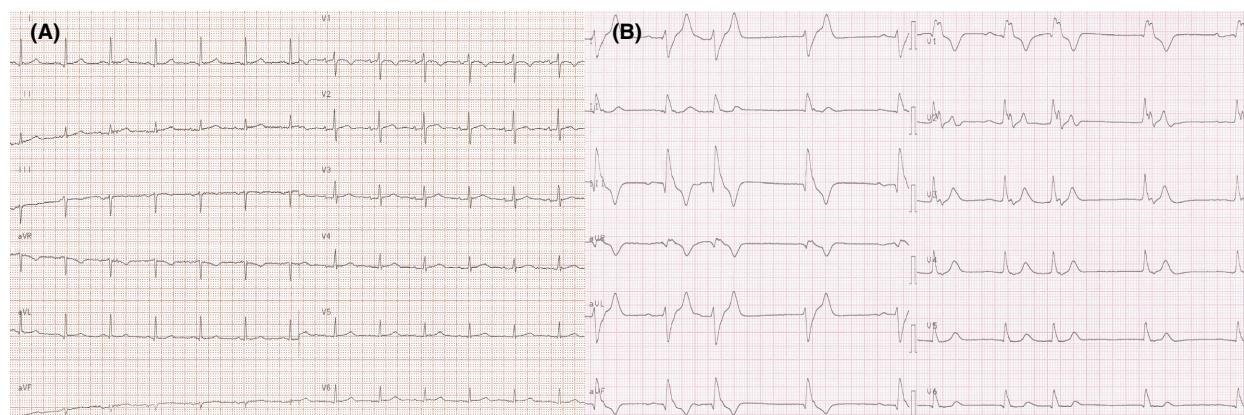
**Figure 2.** Hematoxylin and eosin stained bone marrow biopsy showing massive bone marrow infiltration (>50%) by large lymphoid cells with irregular nuclei.



**Figure 3.** Peripheral blood smear showing circulating lymphoma cells.

2.21 mmol/L (normal range 2.20–2.55 mmol/L), creatinine 171  $\mu\text{mol/L}$ , and LDH 1960 U/L.

The day after receiving first R-CHOP treatment, the patient complained of respiratory difficulties. Vital measures were unremarkable (blood pressure 117/81, pulse 69, saturation 95%), but an arterial puncture revealed severe hyperkalemia of 7.8 mmol/L, pH 7.37 and elevated lactate of 4.5 mmol/L (normal range 0.2–2.5 mmol/L), while creatinine had increased to 227 mmol/L. The electrocardiogram showed an irregular broad complex rhythm with frequency 51 with changing atrial foci with variable 1st degree AV-blockage and nodal beats with similar QRS-configuration. The QRS width was 200 msec with right bundle branch block and left posterior fascicular block and the QT interval was prolonged 520 msec (Bazett's correction 479 msec). There were no signs of ischemia (Fig. 4).



**Figure 4.** ECG before (A) and after (B) tumor lysis.

Treatment with ipratropium and salbutamol inhalation, intravenous calcium chloride, bicarbonate, and glucose-insulin infusion was started promptly, but the patient developed cardiac arrest shortly after. Spontaneous circulation was re-established after 10 min of resuscitation, but asystole developed again after few minutes and after 20 min of intensive resuscitation, death was declared.

An echocardiography performed during resuscitation was without signs of pulmonary embolism (right ventricular dilatation) or myocardial infarction (regional hypokinesia). A post-mortem examination did not identify any other obvious causes for the cardiac arrest than hyperkalemia.

## Discussion

According to the Cairo–Bishop definition, laboratory-defined TLS is characterized by presence of two or more of the following criteria presenting within 3 days before or 7 days after commencement of chemotherapy: uric acid  $\geq 0.47$  mmol/L (8 mg/dL) or  $\geq 25\%$  increase, potassium  $\geq 6$  mmol/L (6 mEq/L) or  $\geq 25\%$  increase, phosphorus  $\geq 1.45$  mmol/L (4.5 mEq/L) or  $\geq 25\%$  increase, and calcium  $\leq 1.75$  mmol/L (7 mg/dL) or  $\geq 25\%$  decrease. Clinical TLS is defined by those laboratory abnormalities accompanied by a rise in creatinine, cardiac arrhythmias, and/or seizures [2].

Our patient had more than twofold increase in potassium after R-CHOP from 3.6 to 7.8 mmol/L and uric acid was 1.1 mmol/L prior to R-CHOP. Calcium showed a 15% decrease from 2.21 to 1.88 mmol/L. Clinically, creatinine levels increased from 171 to 227 mmol/L after R-CHOP and a fatal arrhythmia occurred. Thus, we conclude that our patient met the relevant criteria for clinical TLS.

The incidence of TLS varies according to the type of malignancy, but fatal tumor lysis in DLBCL is a rare

event. To the best of our knowledge, cases of fatal tumor lysis were not reported in the three pivotal trials of R-CHOP encompassing 2445 patients of whom 1225 received R-CHOP [3–5]. In a literature review, we retrieved nine cases of clinical TLS in patients with DLBCL planned for treatment with immunochemotherapy or single-agent rituximab; five patients developed spontaneous TLS before the commencement of therapy and four patients developed TLS after rituximab infusion [6–8]. Of the latter four cases, single-agent rituximab was planned in two patients and two patients were scheduled for R-CHOP but developed TLS during their rituximab infusion. Thus, the immediate cellular effects of rituximab seem to induce TLS in rare cases. Of the four reported cases, three died from multi-organ failure within one month of beginning their treatment despite appropriate TLS prophylaxis with allopurinol or rasburicase and subsequent aggressive treatment of TLS. The single contribution of rituximab to the development of TLS in our patient is difficult to assess as the patient received a full course of R-CHOP before clinical TLS was diagnosed. However, given the aggressiveness of the disease with widespread extranodal involvement, including peritoneal involvement, rituximab may have induced significant cell lysis.

Tumor lysis syndrome is more likely to occur in patients with chemo-sensitive disease and massive tumor load (manifested by bulky disease of  $>10$  cm in diameter, white blood cell count more than  $50 \times 10^9$  per L, organ involvement, bone marrow infiltration or LDH  $>2$  times upper normal limit. Pre-existing renal impairment also increases the risk of TLS [1].

Based on massive tumor load including bone marrow infiltration, markedly elevated LDH and impaired renal function already before R-CHOP, the patient presented in our case was at substantial risk of TLS. We conclude that electrolyte derangements leading to fatal arrhythmia was

the most likely cause of death given the absence of significant autopsy findings. Theoretically, the abrupt increase in potassium levels could have been exacerbated by the concomitant use of spironolactone, a potassium-sparing diuretic drug that antagonizes the effect of aldosterone and thereby impairs normal sodium-potassium exchange in the renal tubules. In the fatal TLS case reported by Mourad *et al.* [8], hyperkalemia  $>7$  mmol/L was also present, but information on concomitant use of potassium-sparing medications was not reported.

## Conclusion

Clinical TLS is a potentially fatal complication of immunochemotherapy in DLBCL. We suggest intensified focus on preventive measures in high-risk patients, ensuring proper hydration, use of uric lowering drug, and avoidance of potassium-sparing drugs.

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## Authorship

NS, PJ, and TE-G: contributed to the main article, analysis of patient progress, critical revising, and final approval. EC-L: contributed with histological descriptions, acquisition of histological material, critical revising, and final approval. JML: contributed with analysis of ECGs, and the cardiac status of the patient as well as critical revising, and final approval.

## Conflict of Interest

None declared.

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