A Clinical Triad with Fatal Implications in Recrudescent Diffuse Large B-cell Lymphoma

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Background

- Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for up to 40% of all NHL cases worldwide.
- Despite this, DLBCL rarely presents (1) in the leukemic phase (2) with dysregulation of the TP53 tumor suppressor gene and (3) an elevated serum lactic acid level.

Objectives

- We describe the clinical course of a patient with recrudescent DLBCL, who presented with this unfortunate triad of poor prognostic features associated with an aggressive and ultimately fatal clinical course.
- We review the literature on leukemic presentations of DLBCL, discuss the significance of TP53 tumor suppressor gene mutations, and describe the pathogenesis of an elevated serum lactic acid level.

Case Report

- A 53-year-old Caucasian man with moderate obesity, hyperlipidemia, and hepatic steatosis was diagnosed with stage IIIA DLBCL in October 2015 after initially presenting with cervical and axillary lymphadenopathy.
- He demonstrated a partial response to induction chemotherapy with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). He then underwent salvage chemotherapy with three cycles of R-ifosfamide, carboplatin, and etoposide (ICE). In the context of a complete response, he received consolidation chemotherapy consisting of R-carmustine, etoposide, cytosine arabinoside, and melphalan (BEAM), followed by an autologous stem cell transplant in October 2016.
- He maintained in remission for nearly three years until he presented to medical attention with a prodrome of fevers, night sweats, and severe pancytopenia. His bone marrow aspirate showed a clonal population of small lymphocytes with plasmacytoid features, indicative of a low-grade lymphoma.
- He experienced a spontaneous clinical remission of three months duration until he developed recrudescent fevers, night sweats, upper respiratory symptoms, widespread lymphadenopathy, and an elevated serum lactic acid level of 3.24 mmol/L. Peripheral blood smear showed 47% large atypical lymphocytes, and flow cytometry showed an abnormal B-cell population. Fluorescence in situ hybridization (FISH) studies were notable for dysregulation of the TP53 tumor suppressor gene. The overall findings were most consistent with DLBCL, not otherwise specified, of non-germinal center phenotype.
- The patient's initial blood and sputum cultures were unremarkable. Furthermore, bronchoalveolar lavage, extensive serologic and molecular tests, and additional blood and sputum cultures did not point to an infectious source.
- In the backdrop of increasing oxygen needs and worsening pulmonary infiltrates, he received corticosteroids and broad spectrum antibiotic and antifungal therapy. For his cytopenias, he received multiple red blood cell and platelet transfusions.
- Despite best supportive care, his condition worsened, and he died on day 15 of his hospitalization.

Conclusions

- A leukemic presentation of de novo or relapsed DLBCL is rare and may be related to differential expressions of adhesion molecules on cell surfaces.
- TP53 gene mutations are present in approximately 20-25% of DLBCL cases and foreshadow worse clinical outcomes.
- An elevated serum lactic acid level in DLBCL that is not clearly associated with sepsis syndrome is a negative prognostic factor for survival and manifests as a type B lactic acidosis through a phenomenon known as the Warburg effect.

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Figures and Tables

Figure 1. **(A)** Peripheral blood smear from July 2019 showing scattered atypical large lymphocytes with irregular nuclei. **(B)** Bone marrow aspirate from July 2019 showing increased numbers of small lymphocytes with round nuclei and variable plasmacytoid morphology, suggestive of a low-grade lymphoma. The large lymphocytes with irregular nuclei present on peripheral blood were not seen in the bone marrow aspirate. Flow cytometry of the bone marrow aspirate showed 10% monoclonal B-cells with negative to dim CD19, bright CD20, dim CD5 on a subset, negative CD10, moderate FMC7, and negative CD200. **(C)** Peripheral blood smear from December 2019, again showing atypical large lymphocytes with irregular nuclei, similar to that seen on peripheral blood from July 2019. **(D)** Left axillary lymph node biopsy from December 2019 showing large atypical B-cells, consistent with involvement by diffuse large B-cell lymphoma.

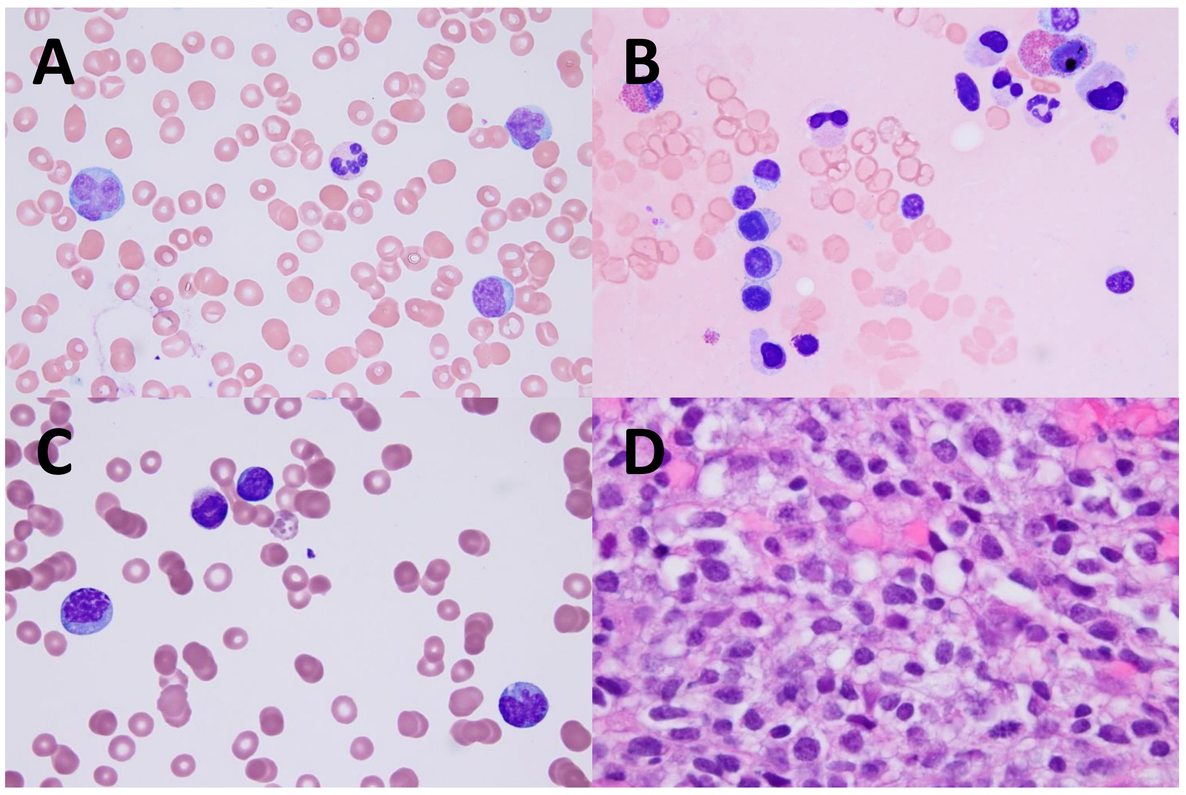

Table 1. Laboratory data when the patient established care at our clinic in September 2019 were largely normal. At time of hospital admission in December 2019, he developed a leukocytosis with a lymphocytic predominance, anemia with a blunted reticulocyte count, as well as elevated serum ferritin, lactate dehydrogenase, and lactic acid levels.

	September 2019	December 2019
WBC	5.9 x 10^9 cells/L with 21% lymphocytes	17.8 x 10^9 cells/L with 47% lymphocytes
Hemoglobin	13.4 g/dL	8.1 g/dL with 3.3% reticulocytes
Platelet	250 x 10^9 cells/L	28 x 10^9 cells/L
Serum iron TIBC Iron saturation Ferritin	88 mcg/dL 293 mcg/dL 30% 1136 mg/dL	76 mcg/dL 220 mcg/dL 35% 3012 mg/dL
LDH	177 U/L	1047 U/L
SPEP	No monoclonal bands	
FACS	Unremarkable	
Lactic acid		3.24 mmol/L

Figure 2. **(A)** Whole-body CT imaging at time of admission in December 2019 showed numerous enlarged lymph nodes (circles) and at least one necrotic lymph node (arrow). **(B)** CT chest one week after admission demonstrated worsening of multifocal alveolar filling process, concerning for diffuse alveolar hemorrhage and/or lymphocytic infiltrate of lymphoma.