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Case Report

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Treating Acquired Factor VIII Inhibitor and Tumor-Induced Hypoglycemia in a Case of Relapsed Diffuse Large B-Cell Lymphoma

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Abstract

Diffuse large B-cell lymphoma (DLCBL) is a heterogenous disease, with many phenotypic subtypes and occasional paraneoplastic syndromes being present. Herein, we describe a case of a 63-year-old woman, with relapsed/refractory DLBCL (RR-DLBCL) with artifactual hypoglycemia on laboratory testing, likely related to the mechanical effects of a new factor VIII inhibitor. We demonstrate our workup, consideration, treatment, and her clinical course. This patient did not present with a bleeding phenotype despite her aberrant laboratory results, and therefore determining her risk of bleeding to weigh against further diagnostic procedures presented a difficult decision. We utilized rotational thromboelastometry (ROTEM) to assist with clinical decision making regarding her paraneoplastic factor VIII inhibitor and the patient's bleeding risk. This led to a short course of dexamethasone. Her ROTEM improved, and an excisional biopsy was performed without any bleeding. To our knowledge, this is the only reported instance where this technology was utilized in this setting. We believe utilizing ROTEM to determine bleeding risk may be a beneficial tool for clinical practice in such additional rare cases.

Keywords: Thromboelastogram; ROTEM; DLBCL; Factor VIII; Inhibitor; TIH

Introduction

Non-Hodgkin lymphoma (NHL) characterizes a heterogenous group of lymphoid malignancies with varied etiologies, presentations, and natural histories. Diffuse large B-cell lymphoma (DLBCL) makes up the most common subtype of NHL and has long been one of the most aggressive malignancies with high rates of mortality [1, 2]. This high mortality is primarily driven by cases that are not responsive to first-line therapy, known as either primary refractory if complete remission (CR) is not achieved with induction chemotherapy, or relapsed remitting DLBCL if relapse occurs within 6 months of achieving CR [2-5]. Therefore, adequate differentiation between the NHLs and staging are paramount to provide the most appropriate trade-off between treatment toxicity and benefit [6]. Complicating this, NHLs are well known to cause various paraneoplastic syndromes, ranging from neurologic to rheumatologic, and these may delay appropriate care [7, 8]. Herein we will discuss an unusual case of relapsed/refractory DLBCL (RR-DLBCL) with a rare presentation of a rare paraneoplastic syndrome at the time of admission for induction chemotherapy, detailing the workup, treatment, and outcomes.

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Case Report

Investigations

Patient history and initial presentation

A 63-year-old woman with a history of stage IV marginal-zone lymphoma with large cell transformation with CR following one cycle of rituximab, cyclophosphamide, vincristine sulfate, and prednisone, and six cycles of cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine, was admitted to the hospital for workup of a painful abdominal mass identified on surveillance computed tomography. At the time of presentation, the patient had constitutional B-symptoms including unintentional weight loss, lightheadedness, and severe fatigue concerning disease relapse. Computed tomography scan showed diffuse lymphadenopathy present throughout the neck, chest, abdomen, and pelvis, and hepatosplenomegaly. Plan was made for exploratory laparotomy to obtain an excisional biopsy to confirm the diagnosis of RR-DLBCL. Routine preoperative studies were significant for severe hypoglycemia, normal anion gap metabolic acidosis, and a significantly elevated activated partial thromboplastin time (aPTT) (Table 1). Other than a lacy, reticular rash that was first noticed by the patient a few days before admission, there were no physical exam findings present to endorse the presence of a coagulopathic phenotype. The patient denied any history of clinically significant bleeding episodes, but did

Table 1. Preoperative Labs Ordered for Inpatient Workup of Relapsed Lymphoma

Na^+	129 mmol/L
K^+	4.2 mmol/L
Cl^-	100 mmol/L
CO_2	18 mmol/L
Blood urea nitrogen (BUN)	17 mmol/L
Serum creatine (Cr)	1.03 mg/dL
Serum glucose	< 20 mg/dL
POC glucose	98 mg/dL
Hemoglobin (Hb)	12.3 g/dL
White blood cell (WBC)	$3.92 \times 10^3/\mu L$
Platelets (Plt)	$137 \times 10^3/\mu L$
Prothrombin time (PT)	13.6 s
Internal normalized ratio (INR)	1.2
Activated partial thromboplastin time (aPTT)	93.3 s

POC: point-of-care.

have a history of a provoked, superficial lower extremity deep vein thrombus over 20 years prior. The patient also denied any symptoms of hypoglycemia including new onset fatigue, lightheadedness, confusion, palpitations, or tremor. She was started on an intravenous (IV) dextrose drip with improvement of her serum glucose to the 80 - 100 s (Table 1).

Workup of coagulopathy

Factor levels and mixing studies as well as lupus anticoagulant studies were obtained to work up for any acquired deficiency or antibody explaining the elevated aPTT (Table 2). The rotational thromboelastometry (ROTEM) was performed to confirm the presence of coagulopathy. Rationale for utilization of ROTEM was based on the institution's availability, the rapidity of results of testing, and its known utility in the perioperative setting. Results of ROTEM were consistent with the serologic studies that had been performed prior that confirmed the patient's high risk of bleeding, with a severely prolonged clotting time and weak clot strength (Fig. 1a).

Workup of hypoglycemia

Endogenous causes of hypoglycemia were ruled out including insulinoma, adrenal insufficiency, and tumor-induced hypoglycemia (TIH) (Table 2). Workup for an insulinoma, pituitary insufficiency, and iatrogenic hypoglycemia was negative, increasing concern for TIH secondary to refractory DLBCL. The decision was also made to simultaneously draw capillary glucose readings with each basic metabolic panel (BMP), which showed discordance between the two values. This was interpreted as confirmation that the falsely decreased serum glucose levels on BMP's, was at least partially a laboratory

Table 2. Further Workup of Coagulopathy and Hyperglycemia Identified at Admit

Mixing study	71.7 s
Factor VIII	≥ 76%
Factor IX	235%
Factor XI	223%
Factor XII	80%
Factor VIII inhibitor	+ 3.8 Bethesda U
Cardiolipin IgG	9.0 GPL U/mL
Cardiolipin IgM	> 150.0 MPL U/mL
B2 glycoprotein IgG	< 9 SGU U/mL
B2 glycoprotein IgM	101 SMU U/mL
Fibrinogen	149 mg/dL
Fibrin split products	10,240 mg/L
Insulin	7 MU/L
C-peptide	3.4 ng/mL
Pro-insulin	17.3 pmol/L
ACTH	38 pg/mL
Cortisol	16 µg/dL
IGF-1	40 ng/mL
Lactate	1.8 mmol/L

Ig: immunoglobulin; ACTH: adrenocorticotrophic hormone; IGF-1: insulin-like growth factor-1.

artifact likely derived from the mechanical effects of her newly acquired monoclonal paraprotein, which is a known entity in other diseases such as Waldenstrom's macroglobulinemia.

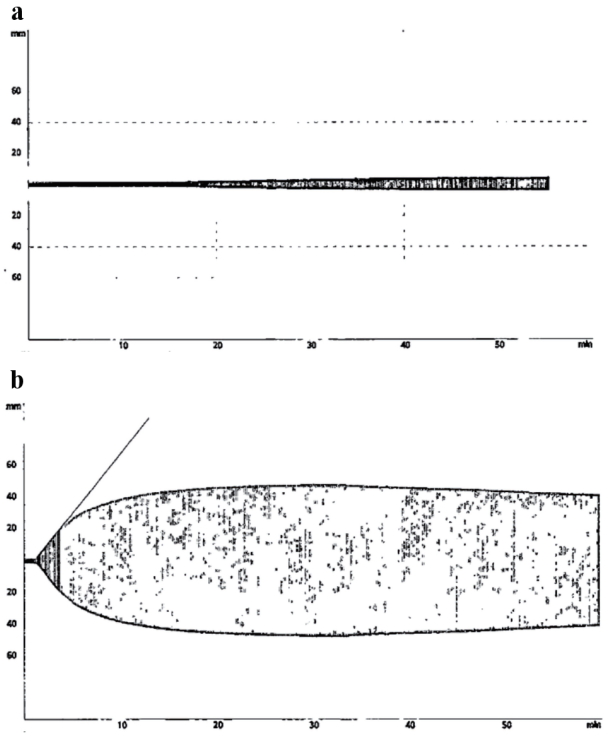
Treatment and outcomes

Treatment of coagulopathy

On hospital day 10, the presence of an inhibitor to factor VIII was confirmed on repeat testing. The decision was made to treat the patient with a 4-day high-dose dexamethasone pulse to rapidly reduce the B-cell clone producing the factor VIII inhibitor and decrease factor VIII clearance. Follow-up factor inhibitor levels showed a small change in the concentration of the inhibitor (Table 3), but repeat ROTEM testing on hospital day 14 showed only mild delayed clotting time as well as mild clot fibrinolysis, a significant improvement from prior (Fig. 1b).

Workup and treatment of relapsed DLBCL

Initially, the decision was made to defer exploratory laparotomy for diagnosis due to persistent hypoglycemia and concern for a possible acquired coagulopathy. Anticoagulation was held, and a bone marrow biopsy was obtained showing lymphoplasmacytic lymphoma. No signs or symptoms of bleeding occurred follow-



Parameter	Result	Normal Limit
Clotting Time (CT)	**1043 sec**	43 – 82 sec
Clot Formation Time (CFT)	**n/a**	48 – 127 sec
α°	**0°**	50 – 70 °
Amplitude 10 minutes after CT	**4 mm**	46 – 67 mm
Maximum Clot Firmness	**4 mm**	50 – 70 mm

Parameter	Result
CT	76 sec
CFT	147 sec
α °	63 °
A10	41 mm
MCF	48 mm

Figure 1. Rotational thromboelastometry (ROTEM) profile of the patient before and after treatment with pulse dose steroids. (a) The ROTEM results at the time of admission. Patient had a severely prolonged clotting time (CT) at 1,043 s, an immeasurably long clot formation time (CFT), consistent with severe coagulopathy. Due to the patient's immeasurable CFT, the alpha angle (α) could not be measured. (b) The ROTEM results following a 4-day course of high-dose dexamethasone with normalization of CT and the CFT, and α angle normalized as well, consistent with a strong clot strength. Of note, the patient's maximum lysis time was significantly reduced indicating defective fibrinolysis even after the course of dexamethasone.

ing the procedure. After the dexamethasone course, the patient's ROTEM improved, showing only an insignificant coagulopathy. Combined with the patient's consistent lack of bleeding, the benefits of lymph node biopsy in guiding disease management were deemed to outweigh the risks. A cervical deep lymph node biopsy was performed without complications, and the diagnosis of DLBCL was confirmed. The patient was treated with a salvage chemotherapy regimen of rituximab, ifosfamide, carboplatin, and etoposide. Following treatment labs demonstrated resolution of the patient's acquired hemophilia (Table 3), although ROTEM was not performed again.

Discussion

Herein, we described a case of RR-DLBCL, presenting with artifactual hypoglycemia, and paraneoplastic acquired hemophilia, representing the disseminated and aggressive nature of NHL. To the best of our knowledge, this is the first reported case of DLBCL in which the patient had lab evidence of hypoglycemia and an acquired coagulopathy.

Acquired factor inhibitors and the development of new lupus anticoagulant antibodies are rare but known phenomena in lymphoproliferative disorders [9-14]. This paraneoplastic syndrome is frequently reported as a presenting symptom in recurrent or rare lymphomas that are frequently aggressive in nature. It is presumed that the acquired coagulopathy resolves with treatment of the underlying malignancy [10]. As seen in this case, tumors can produce a heterogenous profile of antibodies towards the coagulation cascade, varying in both serum concentration and binding profile. This leads to substantial variability in the observed bleeding risk from patient to patient. Lab abnormalities can even be false positives, with one case report confirming the values erroneous with further testing [15]. Although further

Table 3. Coagulation Studies and Factor VIII Levels Over Time

Study	At admit	Post-IV steroids	Post-induction chemotherapy
aPTT	93.3 s	56.8 s	32 s
Factor VIII	≥ 76%	≥ 88%	≥ 200%
Factor VIII inhibitor	3.8 Bethesda U	3.4 Bethesda U	Untraceable

IV: intravenous.

research is needed to validate ROTEM as an optimal tool in assessing an individual's coagulopathic phenotype, its application could be of significant use to clinicians in assessing bleeding and clotting risk in patients with factor inhibitors.

TIH is a life-threatening complication of many non-islet cell malignancies, including lymphomas [16-22]. It is likely that the presence of hypoglycemia typically represents advanced disease, and urgent treatment is necessary; however, our case represents an alternate presentation where the abnormality was likely artifactual due to laboratory processing. This is a rare but reported finding typically associated with elevated M protein in multiple myeloma or lymphoplasmacytic lymphoma [23]. In these cases, point-of-care glucose monitoring also demonstrated the discordant results and presented a simple solution for the clinician to determine an accurate glucose [23].

Excisional lymph node biopsy is a critical component of management of lymphoma, which is highlighted in this case where the bone marrow had discordant pathology from the lymph node [3, 24]. The patient's complications described above represent barriers that could have prolonged the initiation of optimal therapy and exposed the patient to unnecessary therapies such as hypotonic fluids to correct hypoglycemia, and blood products to correct coagulopathy. Triaging abnormalities such as factor VIII inhibitors may interrupt adequate workup, and ROTEM may be an invaluable tool going forward.

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We received no funding and have no financial conflict to disclose.

Conflict of Interest

We have no conflict of interest to disclose.

Informed Consent

Patient consented to the publishment of this case.

Author Contributions

PB: writing and literature search. JN: writing, literature search, and editing. NH: concept and editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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