Case Reports

Rare Case of Refractory Shock Secondary to Large B Cell Lymphoma

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Abstract

A previously healthy 69-year-old female admitted to the hospital with refractory hypotension fevers and diarrhea. She had two prior hospitalizations with similar presentations and no clear etiology could be identified. During her current hospitalization, she was admitted to the intensive care unit (ICU) due to refractory shock. Despite an extensive work up with multiple subspecialty consultation, the patient ultimately transitioned to comfort care. Autopsy report revealed extensive large b-cell lymphocyte involvement within the vasculature of the majority of her organs. This case of intravascular large B-cell lymphoma (ILBCL) exemplifies the necessity to include it on a broadened differential when shock becomes refractory.

BACKGROUND

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of large-cell lymphoma. It is defined by the propagation of lymphoma cells within the lumen of small or medium blood vessels, primarily capillaries and postcapillary venules. Its onset is insidious because it does not typically cause extravascular masses or observable lymphoma cells in the bloodstream. Clinical presentation includes constitutional B symptoms with varied and sporadic symptoms of organ dysfunction caused by occlusion of blood vessels. B symptoms are present in 76% of patients.[1] Other more common organ system involvement is seen with the skin, CNS, bone marrow, and spleen.[2,3] The true incidence is unknown.

CASE PRESENTATION

A previously healthy 69 -year-old female presented to the emergency department (ED) with a generalized weakness, fatigue, and drenching night sweats. Two months prior to her current hospitalization, she was admitted for similar symptoms. Initial workup at the last hospitalization was notable for hyponatremia 125mmol/L (reference 135-145mmol/L), TSH 0.120 uIU/mL (reference 0.3 – 4.0 uIU/mL), free T30.8pg/mL (reference: 2.0-4.4 pg/mL), total T42.1ug/dL (reference: 4.5 – 12.0ug/dL), prolactin 47.1ng/mL (reference :1.4 – 24.2ng/mL) and AM cortisol 22.5 ug/dL (reference 5.3-22.5ug/dL). MRI pituitary showed a 6 mm area of hypo-enhancement that may be consistent with a pituitary microadenoma. The etiology of the patient's weakness and fatigue was thought to be a pituitary adenoma causing central hypothyroidism. The etiology of the patient's hyponatremia was likely hypotonic hypovolemic in nature. The patient was volume resuscitated with improvement of her symptoms and discharged home with endocrinology follow up. One month prior to her current hospitalization, the patient had two more visits to the emergency department where she was noted to be hypotensive and tachycardic. She was fluid responsive and was sent home with levothyroxine and stress dose steroids for the presumptive treatment of adrenal insufficiency and central hypothyroidism.

During the current hospitalization, the patient initially presented to the emergency room with worsening symptoms of fatigue, weakness and drenching night sweats. Upon arrival, her blood pressure was 68/41mmHg, pulse 116 beats per minute, temperature 101.0 F, respiration 22/minute and SpO2 96% on room air. On physical exam, she was non-toxic appearing. Her cardiopulmonary exam was normal. The abdomen was soft but exhibited mild tenderness to deep palpation in the mid-epigastric region. Initial labs are shown (**Table 1**). CT abdomen showed small volume ascites and inflammatory stranding at the gastric fundus related to gastritis. nondistended and nontender. Blood cultures were drawn and broad-spectrum antibiotics were initiated due to sepsis concerns. The patient was again given stress dose steroids. The patient's clinical condition continued to deteriorate as she continued to experience fever, hypotension and weakness. Infectious disease consultation was obtained, and extensive evaluation for infectious cause of fever was negative (**Table 2**). Additionally, an extensive workup by rheumatology and neurology for the evaluation of fever and weakness were normal (**Table 2**). A peripheral blood smear was non-specific and showed leuko-

Table 1. Laboratory values on presentation.

Parameter	Results	Normal Values
WBC	12.44 K/uL	3.80-11.00 K/uL
RBC	4.39 M/uL	3.70- 5.10 M/ uL
Hemoglobin	13.1 g/dl	11.3-15.5 g/dL
Hematocrit	40.3%	34.0-46.0%
Platelets	197 K/ul	150-400 K/uL
Sodium	131 mmol/L	135-145 mmol/L
Potassium	3.5 mmol/L	3.5-5.0 mmol/L
Chloride	98 mmol/L	99-109 mmol/L
Bicarbonate	25 mmol/L	21-28 mmol/L
BUN	12 mg/dl	8-25 mg/dL
Creatinine	0.64 mg/dl	0.50-1.00 mg/dL
Calcium	8.5 mg/dl	8.5-10.2 mg/dL
Phosphorus	2.5 mg/dl	2.6-4.4 mg/dL
ALK Phosphatase	258 U/L	35-115 U/L
ALT	72 U/L	10-65 U/L
AST	54 U/L	10-45 U/L
CRP	21 mg/dl	0-1.5 mg/dL
FT4	1.72 ng/dl	0.60-1.30 ng/dL
TSH	0.008 mlU/L	0.300-4.000 uIU/mL
Lactate	2.5 mmol/L	0.5-2.0 mmol/L

cytosis, normochromic anemia and thrombocytopenia. Peripheral blood flow cytometry revealed possible B-cell lymphoma with monoclonal gammopathy. Subsequent bone marrow biopsy showed hypercellular bone marrow multiple benign lymphoid aggregates without morphologic or immunophenotypic evidence of lymphoma. Unfortunately, the patient was transferred to the intensive care unit for refractory hypotension, lactic acidosis, and respiratory distress. Given the critical nature of her condition, the patient was transitioned to comfort measures only to honor her wishes. An autopsy was performed to help investigate a clearer cause of death. A microscopic evaluation revealed a large B-cell neoplasm permeating throughout the intravascular vessels of the majority of organ systems - a posthumous diagnosis of IVLBCL.

DISCUSSION

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive subtype of non-Hodgkin lymphoma characterized by the proliferation of lymphoma cells within small blood vessels. The estimated annual incidence is 0.5 cases per million. The prognosis is poor, with survival rates at 1 and 3 years 42.3% and 11.5%, respectively, in a review of 182 pathologically confirmed cases of IVLBCL.[4]

The presentation of IVLBCL can be highly variable and unpredictable, as it can spread rapidly to affect multiple organs. The three variants described are the classic, cutaneous, and hemophagocytic syndrome associated variant. The classic and cutaneous variants are mostly seen in Western counties and are characterized by symptoms related to the organs involved, high frequency of CNS and skin involvement.[3] The cutaneous variant is 25% of total IVLCBCL presentations, with signal or multiple skin lesions with negative evidence of systemic staging.[3,5] The hemophagocytic syndrome variant is seen almost exclusively in Asia, showing hepatomegaly, bone marrow involvement, and fever.[6]This is the most aggressive variant, with a median survival time of two to eight months.

A meta-analysis of 654 cases of intravascular lymphoma published between 1957 and 2012 revealed that CNS symptoms were seen in 42% of all cases, with the most common complications being cognitive impairment/dementia (60.0%), paralysis (22.2%), and seizures (13.4%).[7] The most common serologic findings are anemia (63%), high lactate dehydrogenase (82%), and beta 2-microglobulin levels (86%)[8]

Neuroimaging findings are often nonspecific, and findings on imaging are detected in only half of patients. Lumbar punctures rarely establish the diagnosis. There is no standard procedure for organ biopsy to diagnose IVLBCL, as it typically presents as a disseminated disease. Unfortunately, many cases of IVLBCL are confirmed via autopsy post-mortem. Immunohistochemical staining should target CD20, CD24, and PD-L1 markers.[3]

Rituximab-containing chemotherapy regimens can improve outcomes of patients with IVLBCL, but the prognosis remains poor. One review of retrospective studies of IVLBCL from 2008 to 2018 notes overall survival (450 days vs. 180s days) and progression-free survival (420 days vs. 150 days) were longer in patients who

Table 2. Comprehensive Workup.

Parameter	Results	Normal Values
SARS-COV2 NAAT	Negative	Negative
Influenza A/B NAAT	Negative	Negative
Blood Cultures	No growth to date	Negative
Chest X-ray	No acute cardiopulmonary abnormality	No acute findings
CT Chest, Abdomen, Pelvis	No acute pathology. Unchanged 5 mm RML pulmonary nodule.	No acute findings
Meningitis Encephalitis Panel	Negative	Negative
Fungus Culture	Negative	Negative
Indium labeled white blood cell scan	Increased radiotracer in areas of compressive atelectasis.	No areas of radiotracer activity
Lumbar Puncture	Clear and colorless fluid with opening pressure of 22 cm H_2O. 6 nucleated cells/mm^3 , 3/mm^3 RBC, 75 mg/dL protein, 55 mg/dL glucose	Normal opening pressure: 10-25 cm H_2O Nucleated cells: 0-5/mm^3 RBC: 0-1/mm^3 Protein: 15-45 mg/dL Glucose: 60-80 mg/dL
Lyme IgG/IgM	<0.91 ISR Negative	<0.91 ISR
Treponema Pallidum Antibodies	Non-Reactive	Non-Reactive:<1:1
Hepatitis A,B,C Panel	Negative	Negative
HIV 1 and 2 antibodies	Non-Reactive	Non-Reactive
Myeloperoxidase antibody	<9.0 U/mL	0.0- 9.0 U/mL
Proteinase 3 antibody	<3.5 U/mL	0.0-3.5 U/mL
C-ANCA	<1:20	Neg:<1:20 Titer
P-ANCA	<1:20	Neg:<1:20 Titer
Atypical ANCA	<1:20	Neg:<1:20 Titer
Anticardiolipin IgM	10 GPL U/mL	0-14 GPL U/mL
Anticardiolipin IgG	<9 U/mL	0-12 MPL U/mL
Beta 2 glycoprotein IgM	14 units	0-32 GPI IgM units
Beta 2 Glycoprotein IgG	<9 units	0-20 GPI IgG units
Cyclic Citrulline Peptide Antibodies	4 units	0-19 units
Cryoglobulin 24H	Negative	Negative
Cryoglobulin 48H	Negative	Negative
Cryoglobulin 72H	Negative	Negative
Cryoglobulin 7 days	Positive	Negative
C4 Complement	6 mg/dL	12-38 mg/dL
C3 Complement	67 mg/dL	82-167 mg/dL
Lambda quant free light chain	17.1 mg/L	5.7-26.3 mg/L
Kappa/Lambda free light chain ratio	1.27 mg/L	0.26-1.65 mg/L
Aldolase	10.2 U/L	3.3- 10.3 U/L
Arsenic, urine	<10 ug/L	0-9 ug/L
Lead, urine	None detected	0-49 ug/L
Mercury, urine	None detected	0-19 ug/L
Anti MAG	Negative	Negative

received rituximab-containing regimens than those treated in other regimens.[4] R-CHOP has allowed to prolong life in these individuals, but there have been cases of pulmonary failure from rituximab resulting in treatment interruptions.[9] While there is no real standardization of chemotherapy regiments given the rarity and aggressive-

ness of this disease, common regimens include rituximab-based regimens (i.e., R-CHOP versus R-DA-EPOCH) because of the expression of CD20 by lymphoma cells[10] Patients with CNS involvement, LDH greater than 700 U/L, and hemophagocytic syndrome had poorer prognosis. Unfortunately, blood-brain-barrier penetrating drugs, such as methotrexate, which have essential components for treating CNS lymphomas, fail to provide additional survival benefit.[4,11]

In this patient, the autopsy microscopic evaluation of every organ system, except the hematopoietic system and lymph nodes, revealed intravascular infiltration by atypical leukocytes. IVLBCL is an octopus with many faces, making the diagnosis of IVLBCL exceptionally difficult as the disease is not only rare but insidious in its course. In this case, the patient's persistent shock was attributed to a multitude of causes and was refractory to antibiotics, vasopressors, and fluids. With this case, we propose that when a patient is in shock and refractory to a myriad of treatments, the differential must be broadened to include intravascular large cell lymphoma.

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures/Conflicts of Interest

The authors declare they have no conflicts of interest

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