CLINICAL VIGNETTE

An Unusual Case of Fever and Hypotension: Intravascular Large B-cell Lymphoma

Mark W. Dodson, MD and Magdalena E. Ptaszny, MD

Presentation

Fever of unknown origin led to a prolonged hospital course and unusual diagnosis in a 63-year-old Caucasian male. The patient presented to the hospital with two weeks of daily fevers to 102° F, night sweats, and fatigue. He also noted some mild postural lightheadedness, but no syncope, and denied any other localizing symptoms.

The patient was not aware of any sick contacts and had recently moved to California from Connecticut to be closer to his first grandchild, who had been born a few weeks earlier. He had minimal outdoor exposure and had not noted recent insect bites. He denied any significant animal exposures and did not have risk factors for tuberculosis. He had a history of hypertension and hyperlipidemia, for which he was taking atorvastatin and bisoprolol/hydrochlorothiazide. He had a 20 pack-year smoking history, but quit over 20 years ago.

Assessment

On initial presentation, the patient was well-appearing, with a temperature of 99.2° F (37.4° C), heart rate of 110 beats per minute, blood pressure of 84/54, respiratory rate of 18 breaths per minute, and oxygen saturation of 96% on room air. Aside from the tachycardia, his physical exam was unremarkable.

Initial laboratory studies are shown in Table 1. Notable findings were a normal WBC, mild normochromic anemia, thrombocytopenia, hyponatremia, hypoalbuminemia, elevated C-reactive protein, D-dimer, lactate dehydrogenase, and ferritin. Extensive laboratory evaluation for infectious and rheumatologic causes of fever of unknown origin was negative.

Chest radiography was negative. Computed tomography (CT) of the chest, abdomen, and pelvis was remarkable for two enlarged mesenteric lymph nodes, the largest measuring 19 x 22 mm, neither of which was amenable to percutaneous biopsy (Figure 1).

Peripheral blood smear showed normocytic anemia and thrombocytopenia, and flow cytometry of peripheral blood showed no monotypic or aberrant B- or T-cell populations. Serum protein electrophoresis showed decreased total protein with no monoclonal bands. Due to ongoing pancytopenia, a bone marrow biopsy showed hypercellular marrow with normal trilineage maturation. However, small clusters of large highly atypical B-cells were seen within vascular structures, raising the possibility of an intravascular large B-cell lymphoma. A positron emission tomography (PET/CT) scan showed avid uptake of F^{18}-flurodeoxyglucose (FDG) in the spleen, multiple foci in the liver and lung, and in the enlarged mesenteric lymph nodes (Figure 2). Aside from these mesenteric lymph nodes, there was no clear CT correlate for the other lesions, and the spleen size was within normal limits.

Diagnosis

The bone marrow biopsy and PET scan findings were suspicious for intravascular large B-cell lymphoma (IVLBCL). IVLBCL is a rare form of extranodal non-Hodgkin's lymphoma characterized by the growth of lymphoma cells within the lumina of blood vessels, typically capillaries.[1] It is more common in elderly patients, with a median age at diagnosis of 67 in the largest case series.[2] Anemia and thrombocytopenia are common, and an elevated lactate dehydrogenase is almost universal.[2] In a large Asian cohort, hemophagocytic syndrome was seen in 59% of patients with IVLBCL,[2] whereas in the largest European cohort, hemophagocytic syndrome was absent but skin and CNS involvement were more common[3]. Because nearly any organ can be involved, symptoms are quite heterogeneous, but fever is common.[2,3]

The diagnosis of IVLBCL is often difficult given the nonspecific symptoms and the absence of significant lymphadenopathy.[4] Tissue diagnosis can potentially be achieved by biopsy of any affected organ, including the bone marrow.[4] Interestingly, several case reports and small case series suggest that random skin biopsies, even in the absence of noticeable skin lesions, can be diagnostic.[5-7] In our patient, the only enlarged lymph nodes were buried deep in the mesentery and were not amenable to percutaneous biopsy. Surgical biopsy was considered, however, the patient was considered too unstable. While PET scans can be useful when the diagnosis is unclear, PET has a low sensitivity for detecting pathologically proven IVLBCL lesions,[8] presumably because the density of tumor cells is lower in intravascular versus nodal lymphomas.

Management

The patient continued to have daily fevers as high as 104° F (40.0° C) associated with hypotension and sinus tachycardia.

His blood pressure responded to small boluses of normal saline and albumin, however, he developed worsening anasarca. On hospital day three, he developed a non-ST segment myocardial infarction which was thought to be due to myocardial supply/demand mismatch in the setting of tachycardia and hypotension. He was initially not started on empiric antibiotics given the duration of the fevers and lack of a clear infectious source. However, on hospital day five, he had worsening hypotension, and transferred to the intensive care unit, and started on broad spectrum empiric antibiotics with vancomycin and pipercillin/tazobactam. Antibiotics were discontinued when repeat sets of cultures were again negative. He completed an empiric treatment course for babesiosis with azithromycin and atovaquone given his epidemiologic risk factors.

Given the pathologic findings, the patient was started on chemotherapy despite ongoing hypotension. There are no randomized trials to guide treatment decisions for IVLBCL. Expert consensus guidelines based on observational studies support the use of rituximab plus anthracycline-based chemotherapy.[9] In the retrospective study of 106 Asian patients with IVLBCL, addition of rituximab to standard chemotherapy increased the complete response rate from 51% to 82%, and two year progression-free survival increased from 27% to 56%.[2] Our patient was treated with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (R-EPOCH). His first round of chemotherapy was complicated by tumor lysis syndrome and acute kidney injury which improved with aggressive hydration and a single dose of rasburicase.

Interestingly, the patient's hypotension completely resolved during his first cycle of chemotherapy, and his anasarca began to improve. For several days, he diuresed more than 5 L of fluid per day without diuretic treatment. By hospital discharge, his blood pressure had recovered to his baseline hypertension with systolics in the 150s and diastolics in the 90s, and his peripheral edema had completely resolved. A few cases of hypotension and anasarca due to IVLBCL have been reported.[10-12] In one case, the diagnosis was made post-mortem.[11] In the other two, chemotherapy was not given due to hemodynamic instability, and the patients died shortly after diagnosis.[10,12] Presumably the anasarca and hypotension are related to vascular leak, which may be due to the inflammatory response to the lymphoma, or possibly more directly related to intravascular infiltration of lymphoma cells. Our experience suggests that chemotherapy should be considered for patients with IVLBCL and hypotension if there is no documented source of infection.

Our patient received six rounds of R-EPOCH chemotherapy, as well as intrathecal chemotherapy, as he had evidence of rhomboencephalitis on magnetic resonance imaging. Repeat bone marrow biopsy and PET scan after treatment showed complete remission. The patient is doing well clinically and is back to his previous functional status.

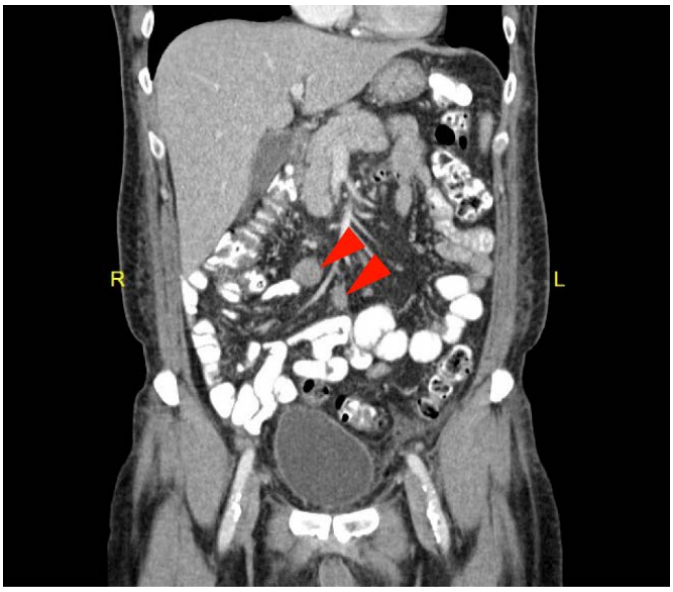

Figure 1. Coronal section from CT scan of the abdomen and pelvis with oral and intravenous contrast, showing two enlarged mesenteric lymph nodes (marked with red arrowheads), the largest measuring 1.9x 2.2 cm. No other lymphadenopathy was noted on CT of the chest, abdomen, or pelvis.

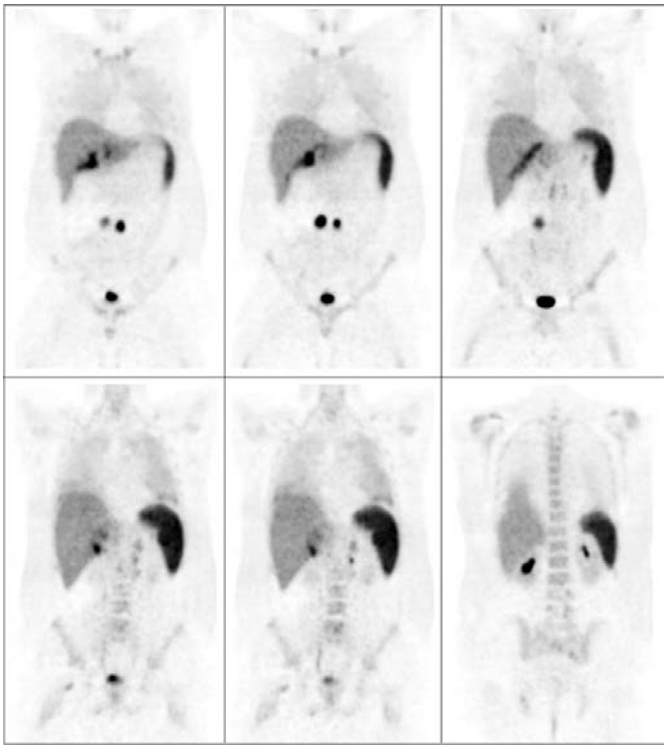

Figure 2. Coronal PET scan images demonstrating marked FDG uptake in the spleen, the two enlarged mesenteric lymph (seen on images 1-3), multifocal uptake in the liver and the region of the porta hepatis, and a focus in the left adrenal gland. There is also diffusely increased FDG avidity throughout both lungs. Only the two enlarged mesenteric lymph nodes had a CT correlate, as shown in figure 1. Note that there is physiologic FDG uptake in both kidneys, ureters, and the bladder. Images go from anterior to posterior as moving from left to right and top to bottom.

Initial admission laboratory values	
White blood cell count	4.69 x 10^3 cells/μL
Hemoglobin	9.8 g/dL
Mean corpuscular volume	88.5 fL
Platelet count	63 x 10^3 cell/μL
Sodium	131 mmol/L
Potassium	4.3 mmol/L
Chloride	96 mmol/L
Bicarbonate	29 mmol/L
Blood urea nitrogen	22 mg/dL
Creatinine	1.2 mg/dL
AST	22 U/L
ALT	8 U/L
Alkaline phosphatase	45 U/L
Total bilirubin	0.6 mg/dL
Total protein	4.5 g/dL
Albumin	2.8 g/dL
INR	1.3
Fibrinogen	296 mg/dL
Erythrocyte sedimentation rate	29 mm/hr
C-reactive protein	4.3 mg/dL
D-dimer	2707 ng/mL
Lactate dehydrogenase	834 U/L
Ferritin	1956 ng/mL
Beta-2-microglobulin	2.4 mg/L
Infectious studies	
Blood cultures	Negative
Urine cultures	Negative
Malaria and babesia smears	Negative
Quantiferon-Gold ELISA	Negative
RPR	Negative
PCR studies:	
Cytomegalovirus	Negative
Epstein-Barr virus	Negative
Parvovirus B19	Negative
Adenovirus	Negative
Human immunodeficiency virus	Negative
Ehrlichia/Anaplasma	Negative
Serologies:	
Mycoplasma	Negative
Borellia burgdorferi	Negative
Coxiella burnetti	Negative
Bartonella henselae	Negative
Brucella	Negative
Rickettsia	Negative
Toxoplasma	Negative
Coccidioides immitis	Negative

Rheumatologic studies	
Anti-nuclear antibody	Negative
Double stranded DNA	<200 IU/mL
Anti-SSA and SSB antibodies	Negative
Rheumatoid factor	Negative
Anti-neutrophil cytoplasmic antibody	Negative
Cryocrit	Negative
C3	93 mg/dL
C4	30 mg/dL
Cerebrospinal fluid studies	
White blood cells	2 cells/cmm
Red blood cells	25 cells/cmm
Protein	49 mg/dL
Glucose	61 mg/dL
Bacterial and fungal cultures	Negative
Cytology	Negative

REFERENCES

1. **Nakamura S, Ponzoni M, Campo E**. Intravascular large B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO classification of tumurs of hematopoietic and lymphoid tissues*. Lyon, France: IARC Press, 2008: 252–53.
2. **Shimada K, Matsue K, Yamamoto K, Murase T, Ichikawa N, Okamoto M, Niitsu N, Kosugi H, Tsukamoto N, Miwa H, Asaoku H, Kikuchi A, Matsumoto M, Saburi Y, Masaki Y, Yamaguchi M, Nakamura S, Naoe T, Kinoshita T**. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. *J Clin Oncol*. 2008 Jul 1;26(19):3189-95. doi: 10.1200/JCO.2007.15.4278. Epub 2008 May 27. PubMed PMID:18506023.
3. **Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, Zucca E, Rossi G, López-Guillermo A, Pavlovsky MA, Geerts ML, Candoni A, Lestani M, Asioli S, Milani M, Piris MA, Pileri S, Facchetti F, Cavalli F, Ponzoni M; International Extranodal Lymphoma Study Group (IELSG)**. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. *Br J Haematol*. 2004 Oct;127(2):173-83. Review. PubMed PMID: 15461623.
4. **Shimada K, Kinoshita T, Naoe T, Nakamura S**. Presentation and management of intravascular large B-cell lymphoma. *Lancet Oncol*. 2009 Sep;10(9):895-902. doi: 10.1016/S1470-2045(09)70140-8. Review. PubMed PMID: 19717091.
5. **Gill S, Melosky B, Haley L, ChanYan C**. Use of random skin biopsy to diagnose intravascular lymphoma presenting as fever of unknown origin. *Am J Med*. 2003 Jan;114(1): 56-8. PubMed PMID: 12543290.
6. **Asada N, Odawara J, Kimura S, Aoki T, Yamakura M, Takeuchi M, Seki R, Tanaka A, Matsue K**. Use of random skin biopsy for diagnosis of intravascular large B-

cell lymphoma. *Mayo Clin Proc*. 2007 Dec;82(12):1525-7. PubMed PMID: 18053461.

7. **Le EN, Gerstenblith MR, Gelber AC, Manno RL, Ranasinghe PD, Sweren RJ, McGirt LY**. The use of blind skin biopsy in the diagnosis of intravascular B-cell lymphoma. *J Am Acad Dermatol*. 2008 Jul;59(1):148-51. doi: 10.1016/j.jaad.2008.03.010. Epub 2008 Apr 11. PubMed PMID: 18406005.
8. **Shimada K, Kosugi H, Shimada S, Narimatsu H, Koyama Y, Suzuki N, Yuge M, Nishibori H, Iwata Y, Nakamura S, Naoe T, Kinoshita T**. Evaluation of organ involvement in intravascular large B-cell lymphoma by 18F-fluorodeoxyglucose positron emission tomography. *Int J Hematol*. 2008 Sep;88(2):149-153. doi: 10.1007/s12185-008-0102-7. Epub 2008 May 22. PubMed PMID: 18496649.
9. **Ponzoni M, Ferreri AJ, Campo E, Facchetti F, Mazzucchelli L, Yoshino T, Murase T, Pileri SA, Doglioni C, Zucca E, Cavalli F, Nakamura S**. Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. *J Clin Oncol*. 2007 Jul 20;25(21):3168-73. Epub 2007 Jun 18. PubMed PMID: 17577023.
10. **Yagita M, Tabata R, Konaka Y, Ohno T, Takatsuki K**. [Intravascular large B-cell lymphoma associated with hypoalbuminemia and hypoxemia]. *Rinsho Ketsueki*. 2000 Nov;41(11):1189-94. Japanese. PubMed PMID: 11193438.
11. **Zlotnick DM, Merrens EJ, Fingar EL, Levy NB**. A 69-year-old male presenting with hypotension and anasarca. *Am J Hematol*. 2008 Apr;83(4):311-4. PubMed PMID: 18095301.
12. **Srivali N, Prasidthratsint K, Ammannagari N, Cheungpasitporn W, Ungprasert P**. Intravascular large B cell lymphoma presenting as anasarca: an unusual presentation of a rare lymphoma. *Ann Hematol*. 2013 Jan;92(2):275-6. doi: 10.1007/s00277-012-1548-5. Epub 2012 Aug 25. PubMed PMID: 22926495.

Submitted September 23, 2018