

The Diagnostic Dilemma of Intravascular Lymphoma

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Abstract

Introduction

Intravascular large B-cell lymphoma is a rare subtype of diffuse large B-cell lymphoma with an estimated frequency of less than one percent of all lymphomas. It has a variety of presentations and is known as “the great imitator” as it may mimic other conditions. It has a fulminant course with high mortality if left untreated.

Case Presentation

We report a 65-year old male who presented with exertional dyspnea, dry cough, and hoarseness of a few days. Work-up did not reveal any specific condition or lesion in the cardiopulmonary systems. He developed worsening pancytopenia within one week, underwent a bone marrow biopsy, and was found to have intravascular diffuse large B cell lymphoma with hypertetraploidy (karyotype XYYY). His symptoms improved after one cycle of chemotherapy. Bone marrow biopsy after six cycles of chemotherapy showed no evidence of lymphoma and a normal karyotype.

Discussion

Intravascular large B-cell lymphoma is a type of extranodal large B-cell lymphoma where growth is restricted to the lumina of vessels. It is a rapidly fatal malignancy when diagnosis and treatment is delayed. There are two forms: the Western form presents with skin, neurologic findings and lymphadenopathy, and the Asian form presents with

fever, anemia, thrombocytopenia, hepatosplenomegaly, bone marrow invasion, respiratory disturbance and disseminated intravascular coagulopathy. Our patient presents as a hybrid of both variants despite being of Western origin.

Conclusion

Even mild cases of cytopenia in a patient with dyspnea and hoarseness may be worth further investigation for the diagnosis of intravascular lymphoma

Abbreviations: ABG: Arterial blood gas; CD: Cluster of differentiation; CT: Computerized tomography; H&E: Hematoxylin and eosin (stain)

Keywords: Hypertetraploidy; Intravascular; Lymphoma

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Introduction

Intravascular large B-cell lymphoma is a rare subtype of diffuse large B-cell lymphoma with an estimated frequency of less than one percent of all the lymphomas. Zuckerman et al [2] called it “the great imitator”, as the disease has variable presentations which may mimic other conditions. We report a 65-year old male who presented with exertional dyspnea and

hoarseness for a few days. He developed worsening pancytopenia within one week of the hospital stay, underwent a bone marrow biopsy, and was found to have intravascular diffuse large B cell lymphoma. This case report highlights the atypical presentation of this disease entity, and the need to have a high clinical suspicion in a patient presenting with cytopenia and local organ symptoms without any local organ system pathology during initial investigation.

Case Presentation

A 65-year old African American man presented with exertional dyspnea, dry cough, fatigue, and new-onset hoarseness of two days' duration. He had a history of hypertension, sleep apnea, and gout, had never smoked, and had never been diagnosed with chronic obstructive pulmonary disease. He claimed to be well prior to developing the symptoms two days before admission, and denied chest pain, weight changes, sweating, or weakness. On admission, he was afebrile, with vital signs within the normal limits. A complete physical examination was significant for coarse crackles over the right lower lung field and examination of the skin revealed non-pruritic hyper pigmented macules over the upper and middle back. Other organ systems were unremarkable. A complete blood count showed mild pancytopenia (Table 1), specifically mild neutropenia, mild normocytic normochromic anemia, and mild thrombocytopenia. An ABG showed mild respiratory alkalosis. A chest radiograph was unremarkable. The electrocardiogram was unremarkable. Chest computerized Tomography (CT) scan with IV contrast was unremarkable. He was then given intravenous steroids, nebulization with albuterol and ipratropium bromide, and started on moxifloxacin for a possible atypical pneumonia. Echocardiography and cardiac catheterization were unremarkable; pulmonary function tests revealed only a mild restrictive disease.

Over the first few days of hospital admission, the patient developed worsening pancytopenia (Table 1), with severe thrombocytopenia and leukopenia, as well as moderate anemia. Coagulation studies were slightly prolonged (Table 2), while fibrinogen was normal. He also had worsening renal and liver

function tests (Table 2), showing pre-renal and intrahepatic involvement. He continued to have hoarseness and some dyspnea without any notable improvement, and developed intermittent low-grade fever. A peripheral smear was then done, revealing helmet cells and evidence of microangiopathic hemolytic anemia. Lactate dehydrogenase was also found to be elevated to 8726 IU/L, with a slightly elevated beta-microglobulin level of 3.81 mg/L (normally less than 2.51). A bone marrow biopsy was then performed, as well as a CT scan of the neck, which did not reveal any lymphadenopathy or masses. A CT scan of the abdomen and pelvis with IV contrast also did not reveal any masses or lymphadenopathy. The bone marrow biopsy with flow cytometry later revealed intravascular large B cell lymphoma, with immunophenotype of slambda bright positive, CD 19+, CD20 bright, CD 10+, CD 5+, CD 23-, CD 11c-, CD 38+, comprising 20% of all cells in the bone marrow (Figure 1). Karyotyping and cytogenetic analysis of the bone marrow cells (Figure 2) also revealed hypertetraploidy (93-103 chromosomes), deletion of 1p, 6p, and 17p, and a rearranged 13q. In addition, Fluorescence In-Situ Hybridization (FISH) analysis also showed tetraploidy of the 8q24 (MYC)/CEP 8/14q32 genes. He was then started on R-CHOP chemotherapy (comprising of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The intermittent episodes of fever resolved, and the liver and renal function tests improved to normal or near-normal levels. His hoarseness and dyspnea improved after the first cycle of chemotherapy. The patient was eventually discharged with recovery of the leukocyte and platelet fractions, as well as improvement of anemia (Table 1).

Table 1: Complete Blood Count during Hospital Stay

Parameters	Admission	Lowest Level	Discharge
Leukocyte count (x 10 ⁹ /L)	4.2	0.1	8.5
Hemoglobin (g/dl)	12.5	7.4	9.3
Hematocrit (%)	38.1	23.6	28.5
Platelet count (x 10 ⁹ /L)	135	9	51

Abbreviations:

g/dl: grams per deciliter

L: Liters

Figure: 1

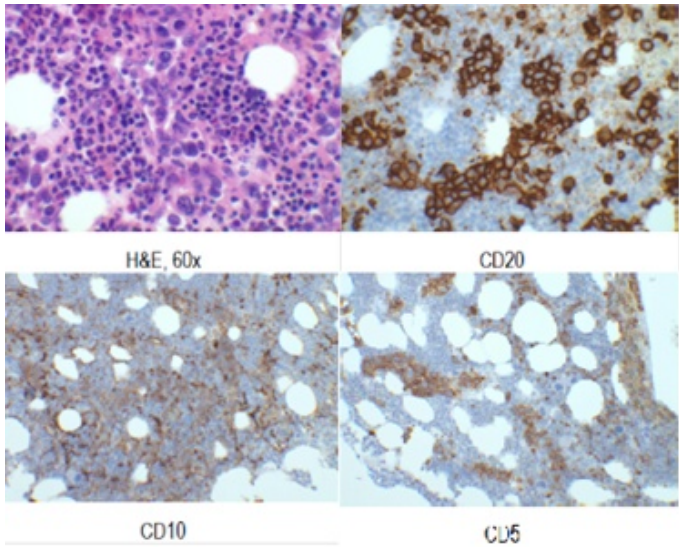


Figure 1: Bone Marrow Biopsy Stains. The H&E stain (top left) shows neoplastic B-cells which are predominantly intravascular. The cells occupied approximately 10%-20% of the bone marrows space. They were strongly positive for CD 20 (top right), indicating B=cell lineage, and dimly positive for CD 10 and CD 5 (bottom left and right).

Figure: 2



Figure 2: Karyotype from bone marrow cells. The karyotype obtained was 101,XXYY, +Y, idic (1)(p13), +3, del(6)(q13)x2, +9, +12, add(13)(q34)x2, +16, +16, add(17)(p11)x2, +18, +18, +19

He subsequently completed five more cycles of chemotherapy in the out-patient setting within the next six months. A repeat bone marrow aspiration done thereafter revealed no evidence of acute leukemia or a T-cell or B-cell neoplasm, with karyotype being the normal 46XY. He continues to follow-up with his hematologist/oncologist and is doing well at the time of writing of this report.

Table 2: Other Significant Laboratory Results

Coagulation Studies		Liver Function Tests	Admission	Highest Level	Discharge
Prothrombin time (sec)	14.4	Total bilirubin (mg/dl)	1.4	2.7	1.5
Partial thromboplastin time (sec)	52.1	Direct bilirubin (mg/dl)		1.23	0.8
International Normalized Ratio	1.54	Aspartate transaminase (IU/L)	296	670	15
Fibrinogen (mg/dl) (180-500)	422	Alanine transaminase (IU/L)	52	66	43
		Alkaline phosphatase (IU/L)	132	244	66
Renal Function Tests	Admission	Highest Level	Discharge		
Blood urea nitrogen (mg/dl)	22.3	89.1	17.2		
Serum creatinine (mg/dl)	1.4	1.7	0.7		

Abbreviations:

Sec: seconds

Mg/dl: milligrams per deciliter

IU/L: International units per liter

Discussion

A highly interesting and challenging aspect of this case is the fact that the patient presented acutely with local symptoms of dyspnea, dry cough, and hoarseness, but could not be found to have any local pulmonary disease. He neither initially present with any B symptoms suggesting the diagnosis of a diffuse large B-cell lymphoma nor did he have detectable lymph node disease or splenomegaly either clinically or by imaging. Pancytopenia, which is an important symptom of bone marrow lymphoma, was mild at the initial presentation. Only after he developed worsening pancytopenia, acute kidney and liver injury, with elevated lactate dehydrogenase and beta-microglobulin levels, that a bone marrow biopsy was performed which revealed of an intravascular diffuse large B-cell lymphoma.

Intravascular large B-cell lymphoma is rare, occurring at an estimated frequency of less than 1 person per million [1, 2] equivalent to less than 1% of all lymphomas [3]. In 2008, the World Health Organization defined intravascular large B-cell lymphoma as a type of extranodal large B-cell lymphoma where growth is restricted to the Lumina of vessels, particularly capillaries [4]. It is most frequently a disease of B-lymphocytes, although rare cases of lymphoma of T-cell or histiocytic origin with an angiotropic growth pattern have also been reported [3, 5, 6].

Intravascular large B-cell lymphoma is aggressive, and is a rapidly fatal malignancy when diagnosis and treatment is delayed [1]. It occurs slightly more frequently in men (male to female ratio of 1.1:1) and most often in the setting of advanced age (median age 67 years; range, 41–85 years) [7]. The disease is often discovered during an autopsy, as it affects any organ, thus presenting with a myriad of nonspecific symptoms. There

is significant variation in presentation and prognosis among the forms of intravascular large B-cell lymphoma [1]. In one of the larger case series in 2004, the most common presenting symptoms included the following: fever (45%), cutaneous symptoms (39%), Central Nervous System (CNS) presentations (34%), pain secondary to cutaneous or abdominal involvement (21%), fatigue (16%), weight loss without fever (11%), gastrointestinal symptoms (5%), urinary symptoms (5%), cardiac dysfunction (5%), edema (5%), and dyspnea (3%) [8].

Despite its recognition as a distinct entity, no large studies of intravascular lymphoma have been reported [8]. Two forms have been described: classical, also known as the Western form, and an Asian form occurring more frequently in the East, with most reports coming from Japan [1, 9]. The Western form presented with predominantly skin and neurologic findings, lymph node disease, and rarely had bone marrow invasion. The Asian form (also known as hemophagocytosis-positive intravascular lymphoma), on the other hand, presented with fever, anemia, thrombocytopenia, hepatosplenomegaly, hemophagocytosis, bone marrow invasion, respiratory disturbance and disseminated intravascular coagulopathy, but usually lacked lymphadenopathy, mass formation, neurological abnormalities, and skin lesions [9]. In 2007, Ferrari et al [10], on studying 50 patients from the Western Hemisphere and 123 patients from the Eastern Hemisphere as previously reported in various papers, confirmed that Western patients were not reported to have hemophagocytosis syndrome. However, as there were patients from the East who also presented with hemophagocytosis-negative intravascular lymphoma (or the classic/Western form), it was proposed that the subcategories be known instead as the classic intravascular lymphoma and the hemophagocytosis-positive intravascular lymphoma, the latter having a more fulminant course and poorer prognosis.

It is interesting to note that in our patient who is from the Western hemisphere developed neither neurologic nor skin findings. He did have some macules on his back, but he did not have neurologic deficits nor alteration in his mental status. He

also did not have lymphadenopathy but had bone marrow involvement when diagnosed. His presentation was more closely related to what is known for some as the Asian variant or diffuse large B-cell lymphoma with hemophagocytic syndrome. Murase et al in 2000 [9] proposed the following criteria to diagnose this entity, namely fulfilling at least three of the following four conditions: (1) hemophagocytosis in the hemopoietic system, (2) hepatomegaly and/or splenomegaly, (3) bone marrow invasion of the lymphoma cells, and (4) a lack of overt lymphadenopathy and tumor formation. Our patient satisfies the last two criteria only, and therefore seems to present as a hybrid of both variants.

There have been multiple reports of dyspnea caused by intravascular lymphoma, with many reported in the Japanese literature [11-13]. In many of these cases, there is no definite pathology seen in the lungs by physical examination or imaging, although CT scan sometimes reveals ground-glass opacities in the lungs. There have been several studies in Japan of patients presenting with hypoxia and dyspnea who subsequently had a transbronchial lung biopsy and were found to have intravascular lymphoma by cytology. Unfortunately, this is a difficult procedure to perform in patients with hypoxia and thrombocytopenia, and is therefore likely not a favorable option among health-care practitioners in the Western world. Nevertheless, it may be worth doing in those patients with unexplained dyspnea, as the chance of survival might be improved should the diagnosis be made earlier and treatment initiated thereafter. The diagnosis may be made with a bone marrow biopsy should there be bone marrow involvement, which was the case in our patient; unfortunately, this procedure may not be helpful in antemortem diagnosis in some cases without such involvement [3].

Whereas dyspnea is not an uncommon finding in intravascular lymphoma [11], hoarseness is not commonly reported in the literature. Hadjileontis et al in 2003 [14] reported a case of a patient presenting with hoarseness who was found to have laryngeal squamous cell carcinoma coexisting with an

intravascular lymphoma. To our knowledge, there are no other cases reported. Laryngeal involvement of a diffuse large B-cell lymphoma, but not an intravascular lymphoma, has been presented in some case reports, but is also a rare entity. In our patient, the reason for his hoarseness was not fully elucidated. There was no etiology seen by imaging; nonetheless, we believe that the symptom was still caused by intravascular lymphoma, as the hoarseness improved after only the first cycle of chemotherapy. There may have been microvascular involvement and infiltration of the vocal cords or the surrounding tissue by the lymphoma.

To our knowledge, there have not been any reports of hypertetraploidy in patients with intravascular lymphoma, as was found in our patient. Lackowska et al in 1999 [19] claimed that hypertetraploidy in non-Hodgkin's lymphoma in general was a favorable prognostic indicator, while near-tetraploid lymphomas had unfavorable outcome. We have not yet encountered a more recent study addressing this issue.

The treatment for all patients with diffuse large B-cell lymphoma in general, including intravascular lymphoma, is combination chemotherapy. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP-like chemotherapy have achieved positive objective responses [1]. On the other hand, there are reports of anthracycline-based chemotherapy having superior remission and overall survival rates [7, 10, 17]. Despite treatment, the prognosis of patients treated with any chemotherapy regimen alone remains disappointing, with one large series of 62 patients receiving anthracycline-based chemotherapy reporting a mean survival of only 13 months [7]. Recently, the inclusion of rituximab to combination chemotherapy has produced a profound positive response in cases of intravascular lymphoma as both initial and salvage therapy. One analysis found complete remission to have occurred in 11 of 12 patients with no relapses at a median follow-up of 15 months [10].

Regarding this patient's prognosis, in the Revised International

Prognostic Index (R-IPI) developed for diffuse large B-cell lymphoma, the prognosis is poor, with a predicted 4-year progression-free survival of 53% and overall survival of 55% [18]. The patient has the negative prognostic factors of extranodal disease (bone marrow and intravascular), with stage IV disease due to the same involvement. As the Ann Arbor staging for lymphoma is primarily based on the areas of lymph node involvement, it may be difficult to apply this staging system to our patient who did not have any lymphadenopathy. No staging system is currently specified for intravascular lymphoma. At this point, however, it appears that the patient is doing relatively well after 31 months of the initial presentation.

Conclusion

Intravascular lymphoma is a rapidly fatal disease without treatment, often difficult to diagnose due to its imitation of other diseases. This condition should be considered in patients with symptoms of unknown etiology (like hoarseness and dyspnea) despite investigation, and appropriate work-up.

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