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CASE REPORT

Intravascular Large B Cell Lymphoma – Still a Diagnostic Dilemma

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Abstract

Intravascular large B cell lymphoma (IVLBCL), a rare subtype of diffuse large B cell lymphoma (DLBCL), presents with non- specific symptoms and is an extremely difficult diagnosis to make despite extensive workup. It very rarely presents with endocrinologic abnormalities. We present a case of an 81-year-old woman whose predominant presenting manifestation was endocrinopathy, who passed away from multiorgan failure, and was diagnosed to have IVLBCL on post mortem autopsy.

Keywords: Intravascular large B cell lymphoma, Endocrine, Post mortem, Autopsy, Histopathology, Skin biopsy

1. Introduction

Intravascular large B- cell lymphoma (IVLBCL), defined by a growth of large B cells primarily within the lumen of various sized blood vessels, was described over 30 years ago but still remains a mystery. Posing as an imitator due to vague presentations, it provides an additional layer of complexity for diagnosticians.[1] In its rarity, it presents as two variants, a classic form (Western type) and a hemophagocytic syndrome form (Eastern/Asian variant).[2]

Endocrine abnormalities are among the rarest presenting manifestations of IVLBCL.[3] Over the years, the incidence of IVLBCL has slowly been increasing, with a current age adjusted incidence rate of 0.095 (case/1,000,000). Unfortunately, prognosis still remains poor with limited treatment options.[4]

Here we present the case of an elderly Caucasian woman whose predominant presenting manifestation of Eastern/Asian variant IVLBCL was endocrinopathy.

2. Case report

An 81-year-old female presented to an outlying hospital with complaints of generalized weakness, fatigue and loss of consciousness leading to a ground level fall and a small occipital laceration. Four days prior to her presentation, she was diagnosed with cystitis at a prompt care facility and prescribed nitrofurantoin. Past medical history was pertinent for osteoporosis treated with denosumab, asthma, hyperlipidemia, anxiety, recurring urinary tract infections and multiple cystoscopies with ureteral stent exchanges. Family history was remarkable for leukemia in her brother and ischemic heart disease in her mother. The patient reported drinking a glass of wine daily and had quit smoking 22 years prior.

Examination was noteworthy for hypotension and initial laboratory analysis showed hyponatremia. She was stabilized with intravenous fluid resuscitation and broad-spectrum antibiotic coverage was initiated for suspected sepsis syndrome. Further laboratory studies (Table 1) were remarkable for central hypothyroidism (TSH 0.087 mIU/L, fT4 0.6 ng/dL and fT3 1.1 pg/mL) with borderline low cortisol level and a probable diagnosis of hypothalamic pituitary dysfunction was made. However, imaging of the brain including CT scan and MRI were unremarkable.

Other tests including an electrocardiogram, transthoracic echocardiogram, CT angiography chest and duplex of carotids were all unremarkable. The patient was treated with stress dose steroids, levothyroxine and midodrine and ultimately

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Table 1. Pertinent laboratory findings hospitalization #1.

Thyroid function tests	Value	Reference range	Unit
fT4	0.6	0.7−1.9	ng/dL
fT3	1.1	1.7−3.7	pg/mL
TSH	0.087	0.30−5.00	mIU/L

discharged to a skilled nursing facility with endocrinology and cardiology follow up.

Two days post hospital discharge, the patient was rehospitalized for persistent generalized weakness, low grade fever, hypotension and bipedal edema. Repeat metabolic profile (Table 2) showed mild hyponatremia, elevated creatinine, anemia, thrombocytopenia, elevated ferritin and elevated lactate dehydrogenase. Repeat hormonal workup revealed low TSH (0.011 mIU/L), normal fT4, high reverse T3 (36 ng/dL), normal LH, FSH, IGF, prolactin, and negative anti-TPO and anti 21 hydroxylase antibodies.

Due to persistent hypotension and third spacing, the patient was treated with albumin, intravenous hydrocortisone and fludrocortisone. The patient's hospital course was later complicated by a left peroneal deep venous thrombosis, triggering a CT angiography chest/abdomen/pelvis which, although negative for pulmonary embolism, revealed bibasilar pleural effusions.

Endocrinology consultation was obtained and her thyroid function tests were interpreted as euthyroid sick syndrome rather than central hypothyroidism or hypopituitarism. Additionally, the patient's hyponatremia and hypotension were felt to be unlikely due to hypopituitarism or adrenal insufficiency since high dose intravenous steroids had had minimal impact on either. It was concluded that her endocrine abnormalities from her second hospitalization, including low fT4, suppressed ACTH and LH were likely secondary to high dose steroids she received during her initial admission and critical illness rather than hypopituitarism or other underlying endocrine etiologies.

Autoimmune studies including PF4 Ab, ANCA, anti- MPO Abs, anti-proteinase 3 Abs, and SPEP were unremarkable as were findings on both bone marrow biopsy and flow cytometry of peripheral blood. A PET-CT reported diffusely abnormal bone marrow activity, increased throughout the axial skeleton and long bones, suggesting both a

Table 2. Pertinent laboratory findings hospitalization #2.

Component	Value	Reference range	Unit
Sodium	132	136−145	mmol/L
Bun	22	10−20	mg/dL
Blood creatinine	1.04	0.60−1.00	mg/dL
Albumin	2.7	3.5−5.0	g/dL
Hemoglobin (HGB)	11.0	12.0−15.8	g/dL
Platelet count	130	140−440	10 (3)/mcL
Ferritin	697	5−204	ng/mL
LDH	573	125−220	U/L

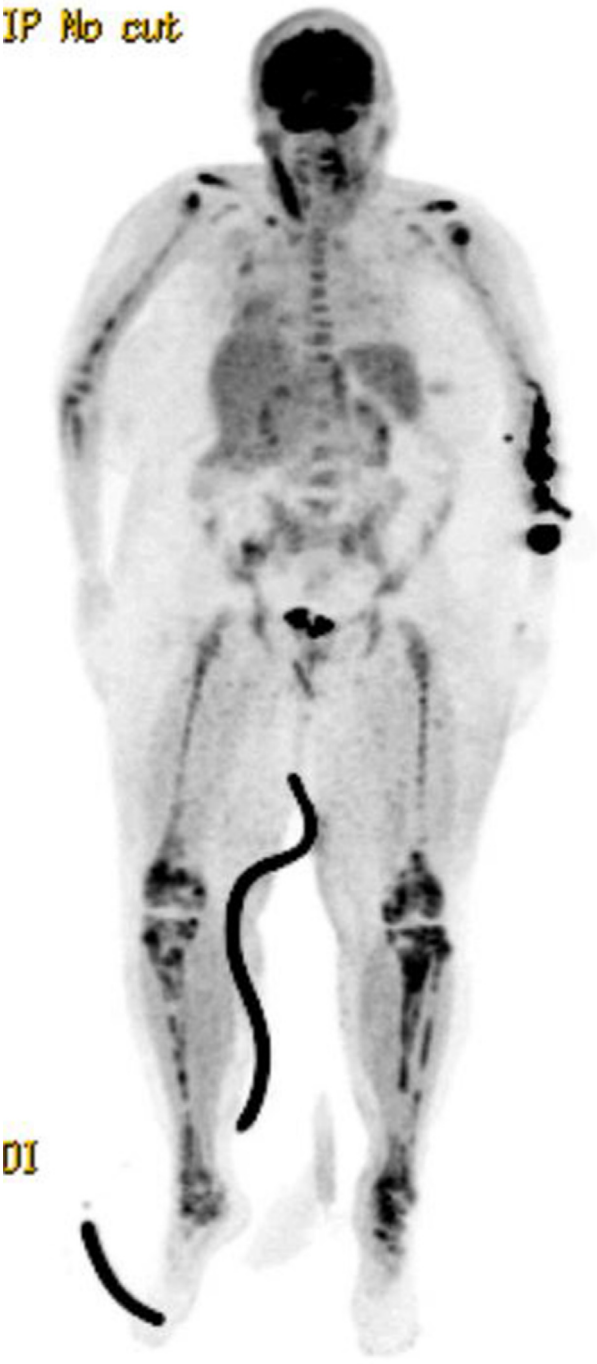

Fig. 1. PET- CT showing faintly FDG avid peribronchial ground glass opacities, right upper and lower lobe consolidation and diffusely abnormal bone marrow activity throughout the skeleton including multifocal uptake at the long bones of the lower extremities.

markedly stimulated bone marrow pattern and a diffuse marrow replacement disorder (Fig. 1). In addition the bilateral lung bases were also positive for increased uptake.

During this second hospitalization, the patient developed acute respiratory failure with repeat CT angiography of the chest revealing bilateral patchy ground glass opacities and small bilateral pleural effusions. She was restarted on empiric antibiotic coverage due to concerns for pneumonia. She was additionally tested for SARS-COv-2 which was negative. Next generation sequencing of cell free DNA (Karius) testing revealed HSV-1 and she was started on acyclovir. Micafungin was added to cover for possible underlying fungal infection in the setting of steroid use.

Despite aggressive measures, the patient's clinical status continued to deteriorate with worsening encephalopathy, respiratory failure and hemodynamic collapse. She eventually passed away after being transitioned to comfort care. A post-mortem autopsy, conducted at the request of the patient's family, revealed intravascular large B cell lymphoma involving the heart, lungs, kidneys, pancreas and thyroid. Immunohistochemistry on the lung (Figs. 2 and 3) demonstrated positive results for CD20, CD5, BCL-2 as well as BCL-6; negative for CD3, CD10, CD30, CD34, BCL-1, Mum-1 and Alk-1.

3. Discussion

Intravascular large B cell lymphoma, a very rare form of diffuse large B cell lymphoma, is characterized by growth and spread of neoplastic lymphocytes within blood vessels. It usually affects individuals of both genders equally, in their 6th or 7th decade of life. Diagnosis is immensely challenging as the disease may present with a wide spectrum of signs and symptoms ranging from fever of unknown origin (most common) to multiorgan failure.[5,6] These vague signs and symptoms likely arise as a result of diffuse involvement of the vasculature in multiple organs affecting their function.[3]

Historically, the disease was divided into two types according to the clinical features and geographic predominance. 'Western variant' presents with neurological symptoms (e.g., cognitive impairment, seizures, neuropathy, paresis) and skin involvement (e.g., cellulitis, plaques, erythematous eruption, ulcerated nodules, telangiectasia). The other type, 'Eastern or Asian variant', is characterized by hemophagocytic syndrome clinically

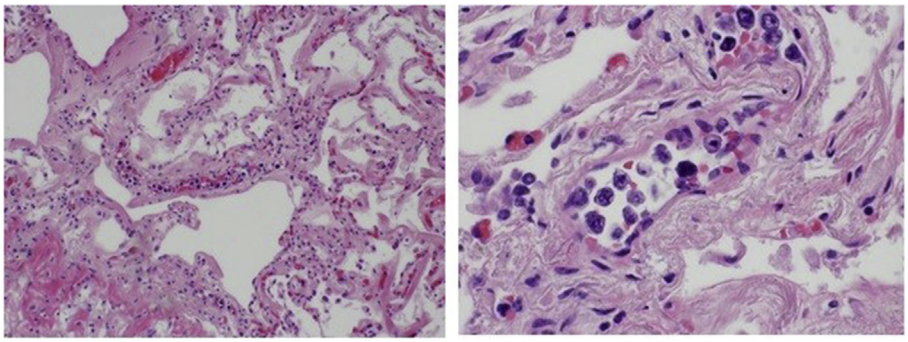

Fig. 2. Hematoxylin and eosin (H/E) staining highlighting pulmonary blood vessels distended by intravascular collection of malignant lymphocytes.

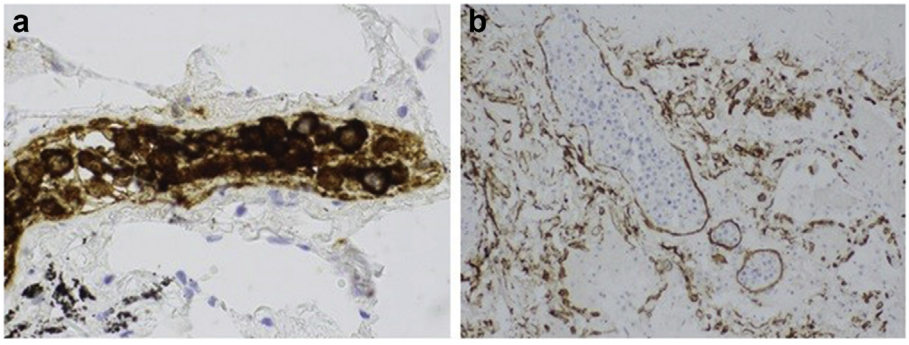

Fig. 3. Immunohistochemistry staining demonstrating (a) tumor cells and (b) vessel walls.

manifesting as fever, hepatomegaly, splenomegaly, anemia, thrombocytopenia and bone marrow involvement.[7] The most common laboratory findings include anemia, thrombocytopenia, elevated ESR, hypoalbuminemia, elevated LDH and elevated beta-2 microglobulin.[5]

Our patient's presentation cannot be neatly categorized under any of the above variants. Although she was Caucasian residing in the Western Hemisphere, her manifestations more so resembled the Eastern variant of IVLBCL in terms of anemia, thrombocytopenia, elevated LDH, hypoalbuminemia and low-grade fever. Our patient manifested no neurologic symptoms or signs and post-mortem exam revealed no evidence of CNS involvement.

Our patient's commonplace symptoms of generalized fatigue, hypotension and hyponatremia lead to an extensive workup. The abnormal thyroid function tests were later interpreted as euthyroid sick syndrome. Although there are many cases of IVLBCL reported in the literature, cases confounded by endocrinopathies are rarely reported. In our patient's case, the endocrinopathies were felt to be a direct sequelae of disseminated intravascular lymphoma. It is likely that these endocrine abnormalities were secondary to end-organ atrophy resulting from chronic organ ischemia, hemorrhage or infarction due to lymphocyte involvement of the vasculature supplying these organs.[3] This was seen with the involvement of our patient's thyroid gland on autopsy. Involvement of her lungs may have eventually led to her death from respiratory failure.

The role of imaging is limited in coming to a diagnostic conclusion in patients with IVLBCL. Due to nonspecific symptoms and the typical absence of lymphadenopathy in this type of lymphoma, imaging findings on CT can remain vague, such as splenomegaly and hepatomegaly. Furthermore, whole body PET-CT can reveal hypermetabolic uptake in the vertebral bodies and lungs bilaterally, if involved.[2] However, a PET scan alone cannot confirm the diagnosis but can play a role in identifying an appropriate site for skin or organ biopsy.[8]

Uptake in our patient's lungs was non-specific and possibly attributable to infection (our patient did test positive for HSV) or inflammation. PET scan in our patient did reveal increased uptake in the axial skeleton, long bones and bilateral lung bases. However, bone marrow biopsy and flow cytometry in our case was inconclusive and argued against the diagnosis.

Fever of unknown origin and elevated LDH prompts a bone marrow biopsy in many cases which can aid in diagnosis. In order to make a diagnosis, localization of lymphoma cells in bone marrow vessels or sinuses is required. Studies on bone marrow biopsy diagnostic yield have shown a low sensitivity of 60% in detecting lymphoma and a specificity of 16.7% in identifying IVLBCL involvement. The low sensitivity is likely related to a scarce reserve of lymphoma cells in the biopsy specimens.[9,10]

Skin manifestations can trigger random skin biopsies (RSB), which now have become one of the common methods of diagnosing IVLBCL. RSB of healthy skin, in highly suspicious cases, has also proven to be highly sensitive and has increased diagnostic yield.[11,12] In our case, our patient did not have any evidence of skin involvement however it may be plausible to obtain a biopsy of normal skin tissue when faced with such diagnostic uncertainty.[3,9] Our patient, unfortunately, did not have a skin biopsy done.

On retrospective review, some clues that had pointed to a possibility of lymphoma in our patient were low grade fever and elevated LDH. However, these are common and very nonspecific findings, and it was difficult to explain the disturbances of multiple organ systems with one unified diagnosis.

It would be worth mentioning that even if diagnosed antemortem, IVLBCL holds a poor prognosis. Treatment with anthracycline based chemotherapy with the addition of rituximab has shown to improve clinical outcomes.[13] However, chemotherapy alone has not shown any effect on survival. Autologous hematopoietic stem cell transplantation, when pursued, has been shown to improve long term survival in some studies and remains an option in eligible candidates.[14,15]

As is evident from this case discussion, despite an extensive workup, the diagnosis of IVLBCL remained undetermined until the autopsy results. The purpose of reporting this case is to make readers aware of the dilemma physicians face when challenged by such vague and nonspecific signs and symptoms. IVLBCL is a rare entity and physicians across the world need to be cognizant of the fact that it could present as endocrinopathies. A random skin biopsy regardless of skin manifestations may aid in making an early diagnosis.

Informed consent

Written informed consent for publication of their details was obtained from the next of kin.

Conflict of interest

The authors have no conflicts of interest to disclose.

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