

Intravascular large B-cell lymphoma: The Great Imitator

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ABSTRACT

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of diffuse large B-cell lymphoma with an estimated incidence of less than one per million. Unlike other hematopoietic malignancies, lymphadenopathy and hepatosplenomegaly are uncommon, and patients typically present with nonspecific symptoms. IVLBCL presents a diagnostic challenge and patients are usually diagnosed late in the disease course, if at all, and the prognosis is poor. The differential diagnosis is broad, and physicians often pursue multiple diagnostic possibilities during patient workup. We present a case of IVLBCL discovered at autopsy in an 80-year-old male who presented with history and symptoms pointing to the tick-borne illness ehrlichiosis.

Keywords

Lymphoma, non-Hodgkin; Lymphoma, B-cell; Ehrlichiosis; Blood Vessels; Autopsy

CASE REPORT

An 80-year-old Caucasian man presented to an outside hospital with one month of non-productive cough, fatigue, low-grade fever, 2.5 kg weight loss, and a syncopal episode. His past medical history was significant for hypertension, hyperlipidemia, nephrolithiasis, benign prostatic hyperplasia, and Lyme disease. He had a 22 pack-year smoking history, quitting 45 years before the admission. He was diagnosed with Lyme disease one year prior and was treated successfully. Of note, he had a tick bite three months before the current admission for which he was prescribed amoxicillin. His symptoms improved slightly but recurred, and he was started on doxycycline. The patient reportedly did not finish the course of antibiotics.

On admission, the patient had a low-grade fever of 38.2°C and a platelet count of 66,000/mm³ (reference range [RR]; 141-320 × 10³/mm³). His hospital course was complicated by progressive anemia and thrombocytopenia. Computed tomography (CT) scans of the head, chest, abdomen, and pelvis showed no

evidence of central nervous system (CNS) lesions, lymphadenopathy, hepatosplenomegaly, or other altered finding. Small bilateral pleural effusions were noted. Bone marrow biopsy was unrevealing, and flow cytometry showed no immunophenotypic evidence of a clonal cell population.

The patient developed hypotension and tachycardia and was transferred to the medical intensive care unit at our institution after 16 days at the outside hospital. A panel of labs was performed on admission, revealing elevated glucose, lactic acid, D-dimer, BUN, AST, and unconjugated bilirubin; low sodium, CO₂, ionized calcium, albumin, prealbumin, total protein, total T₃, free T₄, and amylase. He was mildly anemic with hemoglobin of 12.2g/dl (RR; 13.8 – 17.3g/dL). White blood cell count was 6,870/mm³ (RR; 4.0-10.4 × 10³/mm³), with 76% neutrophils, 16% lymphocytes, 8% monocytes, and 1% nucleated red blood cells. Peripheral smear showed mild anisocytosis, ovalocytosis, and macrocytosis.

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Platelet count was 13,000/mm³. The physical exam revealed the patient had a blanching, tan-pink maculopapular rash on the right lower extremity.

He was transfused with two units of platelets, which temporarily elevated his count to 39,000/mm³; however, he required platelet transfusions throughout his stay. Multiple services were consulted for expertise in this difficult case. Lyme titers were negative, as were HAV, HBV, HIV, syphilis, and rheumatologic serologies. Cardiac function was normal for age. Central hypothyroidism was considered due to low TSH and free T4; however, imaging showed a normal pituitary and no evidence of hemorrhage.

With multiple specialties involved in the patient's care, the differential diagnosis was still broad, and an infectious process such as ehrlichiosis was thought to be most likely. Serologies for ehrlichia were sent, as well as CSF studies for HSV, Cryptococcus, and Lyme titers. The patient was placed on a regimen of antibiotics (vancomycin, doxycycline, piperacillin-tazobactam) to cover ehrlichiosis or other tick-borne illness, pneumonia, and abdominal processes.

On hospital day 3, the patient required 14 liters of fluid over 18 hours due to worsening lactic acidosis and hypotension. CT scan of the abdomen revealed anasarca and possible peritonitis. Due to the patient's condition and poor prognosis, care was withdrawn, and the patient passed away on the morning of hospital day 4.

AUTOPSY FINDINGS

The gross findings at autopsy did not point to a clear cause of death with only signs of long-standing hypertensive and atherosclerotic cardiovascular disease in addition to generalized edema. Because of the clinical suspicion of ehrlichiosis, blood was collected and sent for special studies; however, Ehrlichia antibody panel and polymerase chain reaction (PCR) both returned negative.

The cause of death was discovered on microscopy. Tissue sections from multiple organs, including the brain (Figures 1 and 2), heart (Figures 3A and 3B), adrenal, kidney, prostate, thyroid (Figures 3C and 3D), lung,

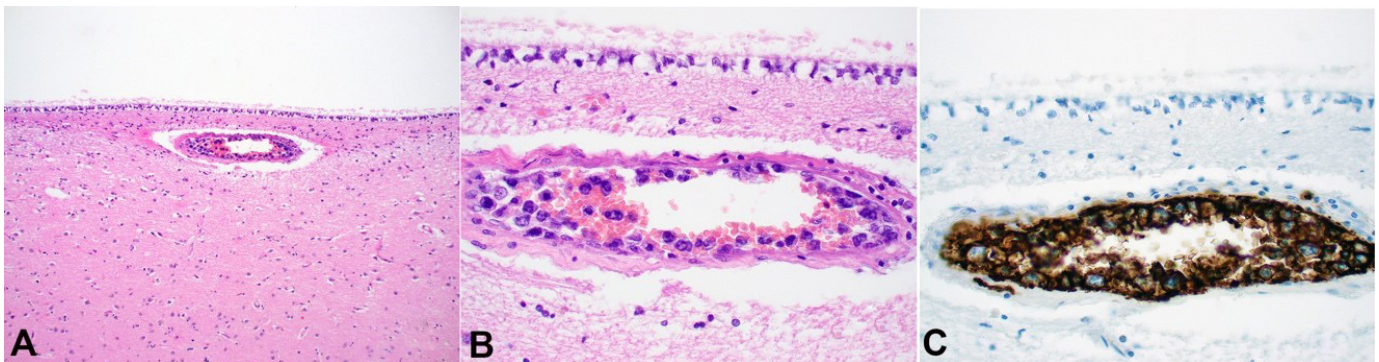


Figure 1. Photomicrographs of the brain. **A-** (H&E, 10X), **B-** (H&E, 40X) show pleomorphic, highly atypical cells within blood vessels of the brain. **C-** (CD20, 40X) shows strong positivity for CD20.

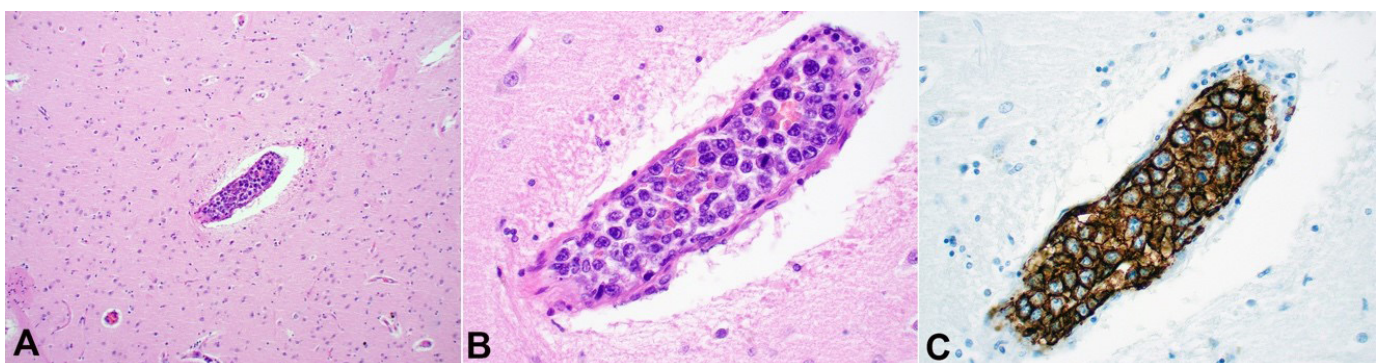


Figure 2. Photomicrographs of the brain. **A-** (H&E, 10X), **B-** (H&E, 40X) show pleomorphic, highly atypical cells within blood vessels of the brain. **C-** (CD20, 40X) shows strong positivity for CD20.

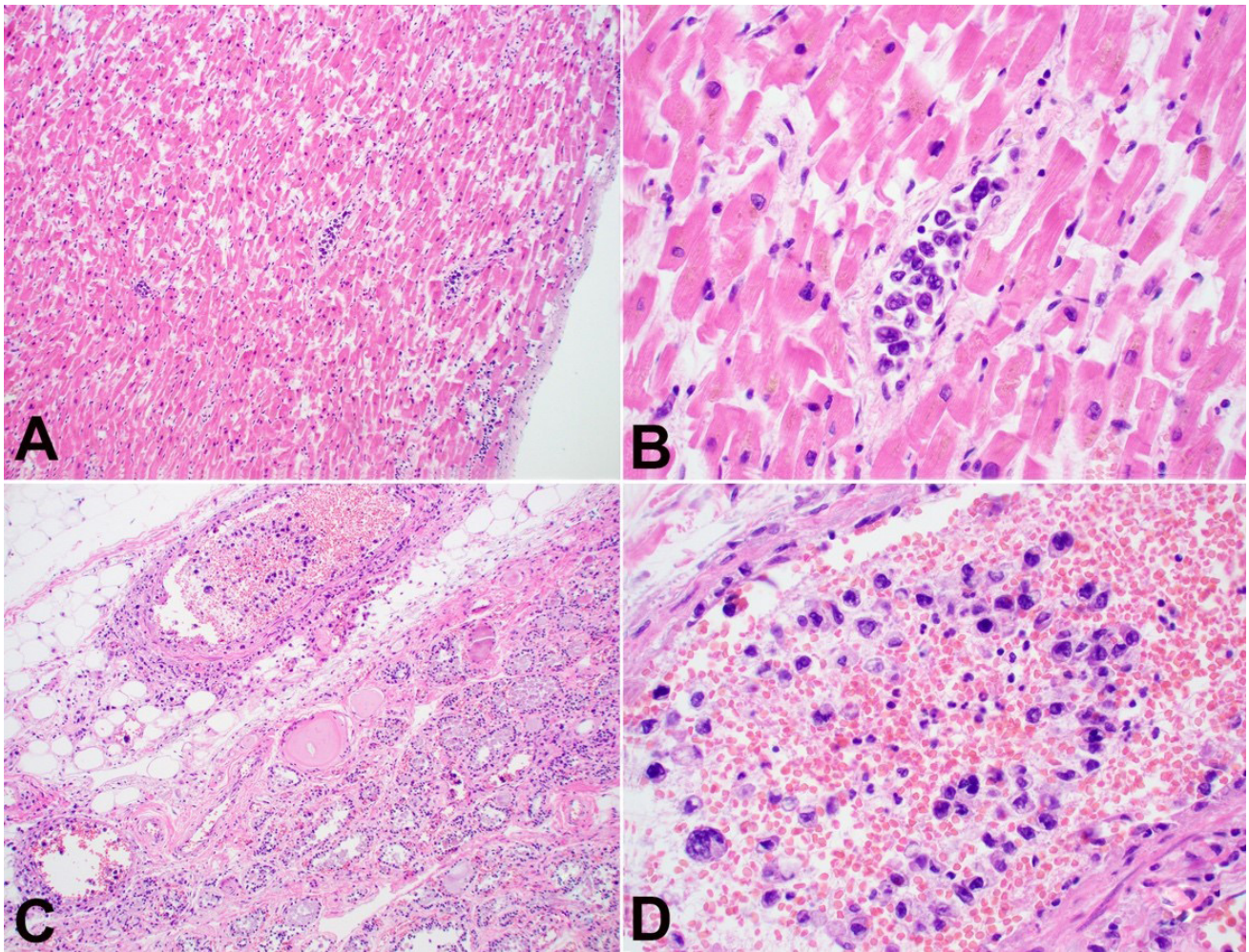


Figure 3. Photomicrographs of the heart and thyroid at autopsy. **A-** (H&E, 10X) and **B-** (H&E, 40X) shows cardiac muscle containing atypical cells within blood vessels. **C-** (H&E, 10X) and **D-** (H&E, 40X) highlight similar atypical cells within blood vessels of the thyroid.

and liver, showed collections of highly atypical cells with enlarged, pleomorphic, hyperchromatic nuclei. These cells were predominantly found within blood vessels but were also noted focally in the interstitium. A panel of immunohistochemical stains including cytokeratin, CD3, CD20 and Pax5 revealed that the cells were of B-cell origin, and a postmortem diagnosis of intravascular large B-cell lymphoma was made (Figures 1C and 2C). The final cause of death was listed as: Malignant non-Hodgkin lymphoma, intravascular large B-cell type, involving: Brain, thyroid, liver, lungs, prostate, kidneys, pancreas, heart, adrenals.

DISCUSSION

This patient's symptoms of fatigue, cough, fever and weight loss are non-specific and thus did not point to a clear etiology. The clinical history of a

recent tick bite led the team to be concerned for the tick-borne illness ehrlichiosis. Ehrlichiosis is caused by *Ehrlichia chaffeensis*, a rickettsial tick-borne illness. The white-tailed deer is the only known vertebrate reservoir for the bacterium, and it is transmitted via the tick species *Amblyomma americanum*.¹ Once transmitted to humans, *E. chaffeensis* primarily infects lymphocytes and monocytes. Infected patients develop a prodrome within 1-2 weeks of infection, characterized by fatigue, malaise, fever, low back pain, and gastrointestinal symptoms. Up to 40% of patients develop a multisystem disease, including cough, lymphadenopathy, vomiting, diarrhea, abdominal pain, and mental status changes.² Rash is reported in 30%.³ Diagnosis is made by serology, indirect immunofluorescence, Western Blot, and PCR. *E. chaffeensis* is susceptible to tetracycline. The death rate in untreated patients is 3% and results from multiorgan failure, hemorrhage, or secondary infection.³

The patient's true diagnosis was made postmortem, which is not uncommon in IVBCL. IVLBCL is a rare subtype of diffuse large B-cell lymphoma, with an estimated incidence of less than one per million. It is characterized by clonal populations of lymphocytes in small blood vessels, with relative sparing of the peripheral blood and lymphoid tissues. It widely disseminates and can involve any organ.

Patients usually present in their 7th and 8th decades of life with fever, CNS involvement, and skin lesions. Common laboratory findings include anemia, elevated lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR), with thrombocytopenia and leukopenia being more infrequent.⁴ Clinical diagnosis is extremely difficult as the presentation is non-specific. Its varied clinical presentations have earned it the title "The oncologist's 'Great Imitator.'"⁴ Numerous case reports have described its mimicking a variety of illnesses, including Guillain-Barre,⁵ nodular goiter,⁶ dementia,⁷ asthma exacerbation,⁸ and CNS vasculitis,⁹ among others.

According to the 2017 revised WHO classification, two variants of IVLBCL are now recognized; a classic form characterized by symptoms relating to the main organ involved, and a hemophagocytic variant heralded by multiorgan failure, hepatosplenomegaly, and pancytopenia.¹⁰ Unlike other hematopoietic malignancies, adenopathy and hepatosplenomegaly are uncommon. Premortem diagnosis is most commonly made on skin biopsy, as approximately 40% of patients will have cutaneous lesions in the form of subcutaneous nodules and/or indurated plaques.¹¹ Bone marrow biopsy is only helpful in one-third of cases. Multiorgan failure can develop rapidly, and the prognosis is poor unless an early diagnosis is made. Even with treatment, the disease can recur in the CNS in up to 25% of patients within 3 years.¹²

The underlying mechanism of IVLBCL remains an enigma. Neoplastic cells proliferate within the lumina of small- and medium-sized blood vessels, yet the peripheral blood and cerebrospinal fluid remain uninvolved. We present this interesting case to highlight the importance of considering IVBCL in enigmatic patients with non-specific symptoms as timely diagnosis can have significant implications for prognosis and therapy.

Informed consent was obtained to perform an autopsy in accordance with the University of Vermont Medical Center policy.

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