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Case Report

Diagnosing Intravascular Large B-Cell Lymphoma: A Tale of Hide and Seek

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Intravascular large B-cell lymphoma · Diffuse large B-cell lymphoma · Muscle biopsy

Abstract
We are reporting the first documented case of intravascular large B-cell lymphoma (IVLBCL) manifesting in the endomysial and perimysial capillaries with its associated diagnostic dilemma. Our patient presented with progressive paraplegia. Initial laboratories were remarkable for hyponatremia, hypochloremia, lactic acidosis, elevated C-reactive protein, and lactate dehydrogenase. The bone marrow biopsy was unrevealing. However, a subsequent muscle biopsy confirmed the diagnosis of IVLBCL. As hyponatremia, endocrinopathies, connective tissue disease, rheumatological disorders, and occult cancer could all present similarly, our patient is a unique diagnostic dilemma. Randomized skin biopsy remains the best way to diagnose this disease, and rituximab-based chemotherapy with high-dose intrathecal methotrexate has proven to be a safe and effective regimen. With this initial evidence of IVLBCL involving the endomysial and perimysial capillary, we believe that muscle biopsy could be of value in diagnosing IVLBCL patients with neuromuscular symptoms.

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive subtype of diffuse large B-cell lymphoma (DLBCL). It predominantly grows intravascularly in the small to medium blood vessels of the central nervous system, bone marrow, and skin. Sporadic case reports also illustrated IVLBCL with primary thyroid and adrenal involvements. We report

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the first documented case of IVLBCL manifesting as acute onset bilateral paraplegia and the involvement of endomysial and perimysial capillaries.

Case Report/Case Presentation

Our patient is a 77-year-old female with a history of type II diabetes mellitus, sick sinus syndrome, diastolic heart failure, and dementia who presented with 4 weeks of progressively worsening bilateral lower extremity weakness. She concurrently experienced orthostatic hypotension, rigors, and night sweats.

She was hemodynamically stable, afebrile, alert, and oriented on admission. The physical exam on admission was pertinent for anasarca up to the umbilicus and weakness in multiple limb movements. She was unable to flex her hip against gravity (2/5), abduction or adduct her legs against examiner's full strength (4/5). Her cranial nerve functions II through XII were intact.

Her medications were metformin, midodrine, ropinirole, and trazodone, which do not seem to have contributed to her presentation. Her social and family history was noncontributory as well.

The initial laboratory showed mild leukocytosis (11.6 K/MM3) with a neutrophilic predominance, new-onset anemia (hemoglobin decreased from 12 g/dL to 10.4 g/dL), normal platelet count, hyponatremia (125 mmol/L), hypochloremia (85 mmol/L), and lactic acidosis (3.8 mmol/L). Thyroid-stimulating hormone level was normal, but T3 and T4 levels were low (41 ng/dL and 3.4 μg/dL, respectively). Random cortisol was elevated at 31.5 μg/dL. The iron study was consistent with anemia of chronic disease, with ferritin being elevated to 619 ng/mL. Lipid study shows mild hyperlipidemia with triglyceride being 204 mg/dL. Inflammatory markers such as C-reactive protein (CRP) and lactate dehydrogenase (LDH) were elevated (CRP 226 mg/L, LDH 1,016 U/L, respectively). Initial CT scans of the head, chest, abdomen, and pelvis showed anasarca in the lower abdomen and upper thighs, consistent with clinical exam. No new mass or lymphadenopathy was seen. An MRI scan of her thoracic and lumbar spine with gadolinium contrast was obtained to rule out spinal cord compression as well as potential neurolymphomatosis. The scan showed no canal stenosis, cord compression, or abnormal enhancement except for a small bony hemangioma within the L4 vertebral body (Fig. 1).

After the initial studies, we treated the hyponatremia with fluid restriction, diuretics, and oral salt tablets. The hyponatremia resolved soon after; however, the patient's paraplegia and functional status continued to worsen. We considered potential endocrine etiologies such as hypothyroidism, but our patient's T3/T4 level does not correlate to the degree of severity for her weakness.

Our next suspicion was inflammatory muscle disease as our patient's weakness was mainly located in her proximal muscles and was not accompanied by pain. Her very elevated CRP and LDH also supported this. We subsequently started our patient on empiric corticosteroid and checked her creatine phosphokinase level. Her symptom continued to worsen, and her creatine phosphokinase returned normal.

At this time, the patient's presentation was deemed highly consistent with a hidden, nonsolid tumor with paraneoplastic and infiltrative property. A bone marrow biopsy was performed, which did not show any granuloma, atypia, or malignancy. Due to the relatively unrevealing studies and lack of clinical improvement, a muscle biopsy was performed.

The biopsy report showed atrophic muscle fibers but no myonecrosis, myophagocytosis, inclusion bodies, or amyloidosis. However, scattered large atypical lymphoid cells were seen in the endomysial and perimysial arteriole and capillary lumina (Fig. 2), consistent with IVLBCL. The tumor cells stained positive for CD20, CD5, BCL-6, MUM-1, and BCL-2. We

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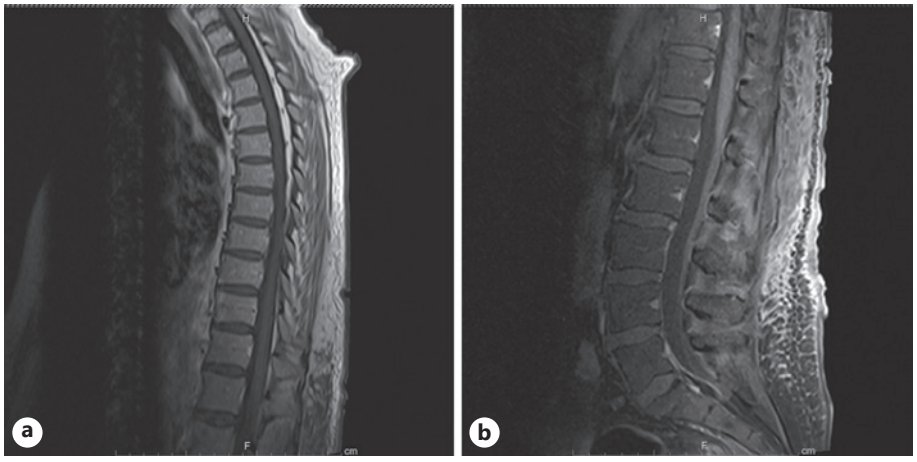

Fig. 1. a Sagittal view of the thoracic spine on MRI showing no abnormal enhancements or cord canal compression. **b** Sagittal view of the lumbar spine on MRI showing the same findings.

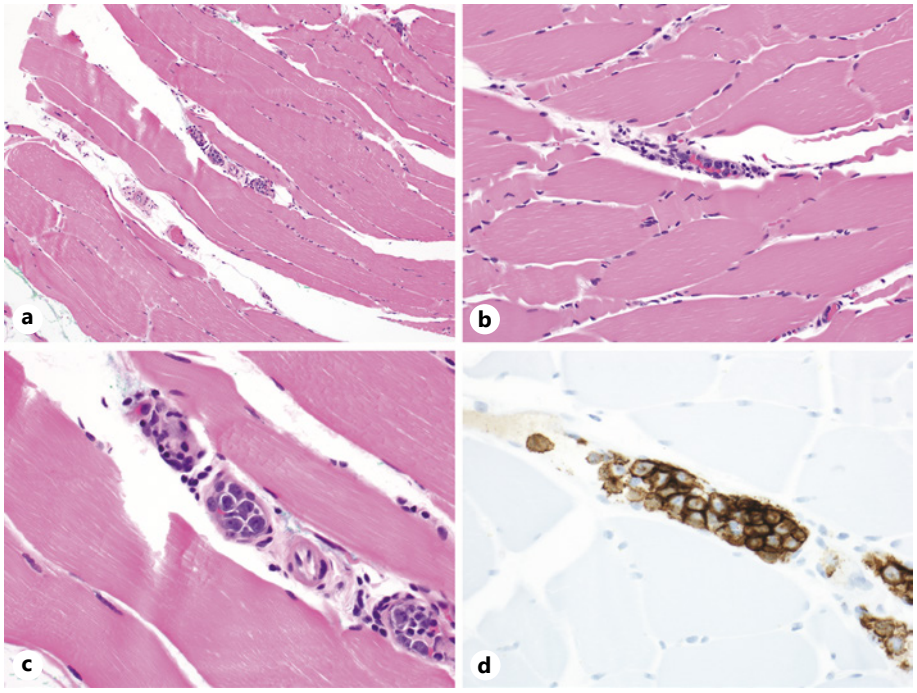

Fig. 2. a–c H&E images showing atypical lymphocytes confined to intravascular spaces (×10, ×20, and ×40, respectively). **d** Immunohistochemical stain for CD20 demonstrating that atypical lymphocytes are diffusely and strongly positive (×40).

have verified this finding with our colleague from the University of Michigan, Department of pathology and confirmed the diagnosis.

The oncology team planned chemotherapy; she was premedicated with allopurinol, rasburicase, and IV hydration given the propensity of nonsolid tumors being complicated by tumor lysis syndrome upon the initiation of treatment, as well as her poor functional status. Unfortunately, the patient developed flash pulmonary edema and was transferred to the ICU. She was intubated and maintained on ventilator support as she continued to clinically deteriorate. Given

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her advanced age, poor functional status, and low likelihood for meaningful recovery, the patient's family decided to halt all therapies and pursue comfort measures. The patient passed later that day.

Discussion

IVLBCL is a subtype of DLBCL that is most prevalent in the elderly, with a median age of diagnosis at around 70 years. It is a rare and aggressive disorder with an incidence of one per 10 million and a 5-year survival rate of 45–55%, depending on the subtype of IVLBCL [1, 2]. Given its rarity, most literature on the disease is in case reports and case series. Due to its pleomorphic and variable presentation, there are no established diagnostic criteria. Treatment guidelines were challenging to develop due to a lack of sufficient cases for randomized controlled trials. This effectively makes IVLBCL a complicated disease to diagnose and treat, turning the process into a game of hide and seek.

IVLBCL has been divided into the cutaneous, hemophagocytic syndromes, and classical variants. The cutaneous subtype is more prevalent in Asia and carries a more favorable prognosis, while the hemophagocytic syndrome variant usually displays a rapid and aggressive disease course [3]. The classical variant is the most represented subtype in the USA, characterized by a mix of heterogenous symptoms including fever, chills, weight loss, night sweat, rapid deterioration of performance status, neuropathies, hemiparesis, paresthesia, seizures, and altered consciousness. This is partly due to the frequent involvement of the central nervous system [3]. Our patient's presentation is highly consistent with the classical variant of IVLBCL due to her progressive neurological symptoms such as dementia, confusion, and paraplegia. Had an MRI of the brain been completed, it could show ischemic foci and vasculitis, which is considered extremely helpful in establishing the diagnosis [3]. IVLBCL is also known to cause pituitary, thyroid, and adrenal endocrinopathies, which could explain our patient's hyponatremia.

DLBCL in general has also been shown to cause hemophagocytic lymphohistiocytosis (HLH), where about one-third of patients develop neurological manifestations including seizure, mental status change, PRES syndrome, and ataxia [4]. We have considered the possibility of HLH in our patient. While this differential diagnosis fits the picture of our case, our patient lacks the other associated findings including fever, peripheral blood cytopenia, abd hemophagocytosis seen in the bone marrow. H-score was calculated to be 63 points, showing a <1% probability of HLH.

Given its vague symptomatology, IVLBCL often elicits a wide array of differential diagnoses, including hyponatremia, stroke, adrenal insufficiency, thyroid disease, polymyositis, vasculitis, and other connective tissue diseases. Other malignancies may also present similarly to our patient's presentation, as demonstrated by a case of Guillain-Barre Syndrome caused by angioimmunoblastic T-cell lymphoma shown in a recent report [5]. As such, the diagnosis of this disease is a lengthy and arduous process. Despite being an intravascular disease, IVLBCL patients often exhibit normal leukocyte count without lymphocytosis. Only 5–10% of IVLBCL would exhibit atypical cells on peripheral blood smear [6]. The exact mechanism for this anomaly is still unclear, but many hypothesized that the tumor cells may lack the expression of required extravasation proteins, namely CD29, CD54, MMP-2, and MMP-9 [7]. Other common but nonspecific laboratory abnormalities may include cytopenia, elevated LDH, CRP, and ferritin. For a complete workup of the disease, whole-body CT, MRI, PET should be considered [7].

As some patients present with overt B symptoms, many astute clinicians order a bone marrow biopsy. Unfortunately, a bone marrow biopsy is only diagnostic in about 20–30% of the cases [2, 8]. The current recommendation for the diagnosis of suspected IVLBCL involves randomized skin biopsy (RSB), which reports a sensitivity of 65.2% [9, 10]. Surgical excision

is preferred over punch biopsy as the latter often does not incorporate enough hypodermis tissue to reveal the intravascular tumor cells. Classical pathological findings of IVLBCL involve clumps of large abnormal lymphocytes coalescing in the lumen of small to medium-sized vessels [5]. Immunohistochemical staining shows strong pan-B-cell markers including CD5 (20–50%), BCL-2 (>90%), c-MYC (~70%), MUM-1/IRF-4 (~75%), BCL-6 (25–60%), and CD10 (~10%) [1]. The muscle biopsy served a similar purpose as the RSB in identifying the intraluminal tumor cells in our patient. Further studies would be needed to examine if this is an acceptable method of diagnosis in IVLBCL patients with neuromuscular symptoms. To our knowledge, this is the first demonstration of IVLBCL in endomysial and perimysial capillaries. It is difficult to determine whether this presence is a primary phenomenon due to a lack of biopsies from other sites and our patient's precipitous decline. However, should this be due to distant metastases, one would presume to find positive findings on bone marrow biopsy and MRI scans.

Being a rare disease with insufficient data on clinical trials, there is no standardized treatment for IVLBCL. Historically, the anthracycline-based CHOP therapy was utilized, yielding a nearly 60% response rate and 3-year overall survival of around 30% [10]. Rituximab was added to form R-CHOP to intensify the regimen, and intrathecal methotrexate was introduced for CNS involvement. Recently, a multicenter, phase 2 trial from Japan demonstrated a 2-year progression-free survival of 76%, with a tolerable side effect profile [11]. Therefore, rituximab monotherapy can be considered for the elderly and frail patients who cannot tolerate the R-CHOP therapy. In addition, an autopsy report has recently demonstrated strong PD-L1 expression in an IVLBCL patient, which may provide further insight into the patients who experienced severe adverse reactions to rituximab [12].

Conclusion

In conclusion, we report for the first time a unique case of IVLBCL manifesting as progressive bilateral paraplegia without the sign of spinal involvement and with the presence of tumor cells in the endomysial and perimysial capillaries. This particular presentation and localization of tumor cells have not been described before. IVLBCL is an elusive disease that requires prolonged workup that often delays the diagnosis. While it is unfortunate that our patient passed before completing a full workup, we believe that muscle biopsy could benefit future patients with similar symptoms and should be performed in conjunction with the recommended RSB.

Acknowledgments

We would like to acknowledge Dr. Pinarbasi and Dr. Pratt from the Department of Pathology, University of Michigan for their assistance in obtaining and identifying the pathology slides for this case.

Statement of Ethics

This case report is in compliance with the ethical guidelines of COPE. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. The consent form is available for review if requested. This retrospective review of patient data did not require ethical approval in accordance with local guidelines.

Conflict of Interest Statement

We have no conflict of interest to disclose. There was no financial involvement in the development of this manuscript.

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Author Contributions

Dr. Nathanael Adjei-Kyeremeh and Dr. Heather Bartz were involved in the care of this patient. Dr. JiaXi Dong and Dr. Daniel Barnett drafted the case report. All the authors were involved in literature review and editing of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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