Neurologic manifestations of intravascular large B-cell lymphoma

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Abstract

Purpose of review: Intravascular large B-cell lymphoma is a rare subtype of large B-cell lymphoma that affects various organs including the nervous system. The diagnosis is challenging and frequently made at autopsy. **Recent findings:** We report 5 cases with an array of neurologic manifestations. All patients were initially evaluated for alternative diagnoses. Three patients were diagnosed at autopsy, one with brain biopsy, and another with muscle biopsy. Muscle was involved in all 3 patients who had muscle tissue available for analysis. **Summary:** Our observations suggest that random open muscle biopsy may present a high-yield, less invasive option for the diagnosis of this disorder.

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Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of lymphoma characterized by occlusion of small vessels by malignant cells within affected organs, including the nervous system.¹ The heterogeneity of clinical presentation and lack of specific laboratory and imaging findings make diagnosing IVLBCL challenging. We present 5 patients with IVLBCL with early neurologic manifestations who were diagnosed and followed at our institution over a 5-year period.

Patient 1

A 66-year-old man presented with a 5-month history of paraparesis and urinary retention followed by progressive encephalopathy (tables 1 and 2). An extensive workup was nondiagnostic. Spinal MRI demonstrated a cord lesion that extended more than 3 vertebrae (longitudinally extensive transverse myelopathy [LETM]), a finding present in a variety of autoimmune/inflammatory, infectious, metabolic, and neoplastic conditions. Electrodiagnostic testing showed a sensorimotor axonal polyneuropathy. See the tables for additional diagnostics. Empiric high-dose IV methylprednisolone ([IVMP], 1 g IV $\times$ 5 days) and IV immunoglobulin (2 g/kg IV over 4 days) had no benefit. Sural nerve and gastrocnemius

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Intravascular large B-cell lymphoma represents a diagnostic challenge because of its protean clinical manifestations and lack of specific laboratory and imaging findings.

biopsies, evaluating for evidence of an immune-mediated polyneuropathy, showed IVLBCL (figure, A–C). The patient received 2 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) but died soon thereafter. No autopsy was performed.

Patient 2

A 78-year-old man presented with a 7-month history of fevers, night sweats, fatigue, vertigo, gait instability, and cognitive decline. An extensive infectious workup was negative and empiric antibiotics were of no benefit. Bone marrow examination showed chronic lymphocytic leukemia with no abnormalities on whole-body PET. Symptoms resolved spontaneously but returned 6 months later. Empiric steroids led to resolution of symptoms that again returned as steroids were tapered. A repeat bone marrow biopsy was unchanged. He deteriorated rapidly and died of cardiac arrest. An autopsy showed IVLBCL (figure, D–F).

Patient 3

A 77-year-old woman presented with a 5-month history of progressive paraparesis and urinary retention. MRI of the spine showed LETM. Infectious causes were excluded and empiric IVMP, 5 g over 5 days, resulted in resolution of deficits. However, symptoms recurred weeks later, and the patient received another course of IVMP with a similar response. After a third relapse, azathioprine was added without benefit and a repeat MRI showed subacute brain infarcts. Cerebral angiography was nondiagnostic. A brain biopsy was not performed due to the patient's declining clinical status. Empiric plasmapheresis, initiated for a presumed immune disorder, was never completed as the patient died of multiorgan failure and an autopsy showed IVLBCL (figure, G–I).

Patient 4

A 78-year-old man presented with a 3-month history of unintentional weight loss, fevers, and fatigue, followed by rapid cognitive decline, visual hallucinations, tremor, and gait instability. Brain MRI showed bilateral subacute infarcts. Echocardiography showed mitral valve vegetations, supporting a diagnosis of culture-negative endocarditis. Symptoms initially improved with antibiotics, but returned 1 month later, with multiple new infarcts on MRI. Repeat echocardiography did not show vegetations, and an extensive infectious, paraneoplastic, and inflammatory workup was nondiagnostic. The patient eventually died of respiratory failure and a brain-only autopsy showed IVLBCL (figure, J–L).

Patient 5

A 77-year-old woman presented with an expressive aphasia secondary to a stroke. Workup for additional stroke risk factors was unremarkable. Her cognitive function declined over the next 10 months and a repeat brain MRI showed multiple infarcts. Paroxysmal atrial fibrillation was identified and oral anticoagulation initiated. A cerebral angiogram performed after the patient developed additional strokes (figure, M–O) showed diffuse arterial narrowing without significant atherosclerosis. A cerebellar biopsy showed IVLBCL. Treatment with IVMP led to rapid improvement of her encephalopathy. Given her age and poor performance status, R-CEOP (etoposide substituted for doxorubicin in R-CHOP) was started. She received 6 cycles of treatment with significant cognitive improvement and remains in remission currently.

Table 1 Demographics and clinical characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	66	78	77	78	78
Sex	Male	Male	Female	Male	Female
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Presentation	B-symptoms, myelopathy, encephalopathy	B-symptoms, vertigo, gait instability, RPD	Myelopathy	B-symptoms, abnormal movements, RPD	Strokes, dementia
Major working diagnoses	NMO, PNS	CJD, PACNS	NMO, PNS, DAVF	PACNS	PACNS
Treatments	IVIg, R-CHOP (2 cycles), steroids	IVIg, steroids	Azathioprine, steroids, pheresis	Steroids	R-CEOP (6 cycles), steroids
Response to therapy	No response	Initial response	Initial response	No response	In remission
Survival	Dead	Dead	Dead	Dead	Alive
Symptom onset to diagnosis, mo	5.5	14.9 ^a	6.0 ^a	5.7 ^a	11.1
Survival from symptom onset, mo	7.5	14.9	6.0	5.7	>24.8
Survival from diagnosis, mo	2.0	0 ^a	0 ^a	0 ^a	>13.7

Abbreviations: B symptoms = fever, night sweats, and weight loss; DAVF = dural arteriovenous fistula; IVIg = IV immunoglobulins; NMO = neuromyelitis optica; PACNS = primary angiitis of CNS; PNS = paraneoplastic syndrome; CJD = Creutzfeldt-Jakob disease; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RPD = rapidly progressive dementia.

^aPostmortem diagnosis.

DISCUSSION

IVLBCL is a rare subtype of extranodal large B-cell lymphoma characterized by uncontrolled proliferation of lymphoma cells confined to the lumen of small- and medium-sized vessels.² Tumor cells express B-cell antigens (CD20, CD79a), with variable expression of CD5 and CD10³ (table 2). Lack of homing receptors (e.g., β 1 integrin and ICAM-1) on the neoplastic cells may explain the predilection for these cells to remain in the intravascular space,⁴ distinguishing IVLBCL from more common forms of lymphoma. IVLBCL primarily afflicts the elderly, with no race or sex predilection. In our series, all 5 patients were white (60% male), with an age range of 68–78 years (table 1). B-symptoms (fever, night sweats, and weight loss) are common. Although any organ may be involved, the skin and CNS are the most frequently affected sites.⁵ In our series, 3 patients had B-symptoms but no dermatologic manifestations. Over 60% of patients develop neurologic manifestations at some point in their disease course, including encephalopathy, seizure, myelopathy, radiculopathy, or neuropathy.^{5,6} An Asian variant is associated with the hemophagocytic lymphohistiocytosis syndrome in >44% of cases, characterized by fever, organomegaly, coagulopathy, and bone marrow involvement.⁷

IVLBCL represents a diagnostic challenge because of its protean clinical manifestations and lack of specific laboratory and imaging findings. Inflammatory markers and lactate dehydrogenase may be elevated (table e-1 at Neurology.org/cp) but are nonspecific in isolation. Almost any pattern of CNS involvement may be seen on imaging, including nonspecific white matter changes, scattered microinfarcts, and widespread enhancement.⁸ Given the tendency of B-cells in IVLBCL to remain intravascular, PET is usually negative. Differential diagnoses include primary angiitis of the CNS, paraneoplastic syndromes, and neuromyelitis optica.

Table 2 Radiologic and pathologic characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Location of lesions on imaging	Spine, LM	Normal HCT and MRI	Spine and brain	Brain	Brain
Pathologic examinations					
Diagnostic method	Gastrocnemius biopsy	Autopsy	Autopsy	Brain only autopsy	Cerebellum biopsy
Involved structures	M	C, BS, AP	C, BG, Ce, BS, SC, LM, AP, PN, M, L, K, B, HB, P	C, LM, CP	C, LM
Muscle involvement	Skeletal	Cardiac (no skeletal muscle available)	Skeletal	NA	NA
Bone marrow involvement	NA	Yes	No	NA	NA
Immunostaining					
Positive	CD20	CD5, CD20, MUM1	CD20	CD20	CD20
Negative		BCL6, CD138	BCL6		EBER
Proliferative index (Ki-67)	NA	High	High	High	High

Abbreviations: AP = anterior pituitary; B = bladder; BG = basal ganglia; BS = brainstem; C = cortex; Ce = cerebellum; CP = choroid plexus; HB = hepatobiliary; HCT = head computerized tomography scan; K = kidney; L = liver; LM = leptomeninges; M = muscle; NA = not available; P = pancreas; PN = peripheral nerve; SC = spinal cord.

Supplemental Data

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Adding to the challenges associated with the clinical management of IVLBCL is the requirement of a tissue-based diagnosis to justify and guide treatment, particularly in cases presenting with neurologic signs/symptoms. Anthracycline-based multiagent chemotherapy along with rituximab (e.g., R-CHOP) is the most commonly used regimen,⁹ with reported complete response rates and 2-year overall survival rates of 80% and 60%, respectively.^{9,10} Nevertheless, IVLBCL is an aggressive lymphoma with a dismal prognosis and CNS involvement portends a poor prognosis. Reasons for poor prognosis include late diagnosis, widespread disease, organ dysfunction at the time of diagnosis, and in rare cases, extravascular extension of lymphoma cells or neoplastic perivascular infiltrates,¹¹ which make common chemotherapy combinations with limited CNS bioavailability inadequate.

As evidenced in this series, empiric treatments in the absence of definite diagnosis and the risks associated with brain and spine biopsy contributed to delays in treatment and 3 tissue-based diagnoses were established after death. These findings exemplify the need for less-invasive diagnostic methods. To this end, random skin biopsy has been proposed as a potential means of establishing a tissue diagnosis in patients with the Asian variant of IVLBCL.¹² However, when systematically evaluated in a subsequent study, the diagnostic yield of skin biopsy was low, even in cases with skin involvement.¹³ Of the patients with full postmortem examination in our series, multiple organ systems were involved (figure and table 1). Of particular interest is the observation that disease was detectable in muscle specimens available from all 3 patients who underwent sampling of this tissue (table 2). The rate of skeletal muscle involvement has not been explicitly reported in most of the published larger series,^{7,14–16} although involvement of cardiac muscle is illustrated in one of them.¹⁶ In a large study¹⁷ reporting a series of 96 patients with IVLBCL, psoas muscle was the diagnostic site in only 1/81 cases with an antemortem diagnosis. On the other hand, muscle involvement by IVLBCL and antemortem diagnosis of the disease by (nerve and) muscle biopsy has been reported in a few case reports.^{18,19} Our findings suggest that early, random, open muscle biopsy (sample size comparable to a standard open muscle biopsy) may be considered in patients with suspected

Figure Intravascular large B-cell lymphoma (IVLBCL) as a multisystem disease

Multiple brain regions were involved by IVLBCL in the patients examined. Patient 1 (A–C), patient 2 (D–F), patient 3 (G–I), patient 4 (J–L), patient 5 (M–O). (A) Hematoxylin & eosin (H&E)-stained section of skeletal muscle from patient 1 shows atrophic fibers along with IVLBCL, which is CD20-positive (B). (C) The endothelial marker CD34 highlights that the tumor cells are contained within the vessel lumen. (D) Pituitary examination shows extensive involvement of IVLBCL in patient 2, involving the rich vascular network of the adenohypophysis, which again demonstrates CD20 positivity (E) with a high Ki67 proliferative index (F). Postmortem examination in patient 3 demonstrates IVLBCL in many organ systems including, but not limited to, the heart (G), kidney (H), and gastrointestinal tract (I). (J) H&E-stained section of the occipital lobe in patient 4 demonstrates large atypical cells with mitotic activity contained within the vascular spaces. Tumor cells are CD20-positive (K), with a high Ki67 proliferative index (L). All photomicrograph images are taken at 400 $\times$ magnification, except for the inset in panel A, which is at 1,000 $\times$ magnification. Axial fluid-attenuated inversion recovery images of the brain (M–O) in patient 5 at different time points shows areas of increased signal intensity in the right posterior limb of internal capsule (arrow, M), right occipital cortex (arrow, N), and left cerebellum (arrow, O). Diffusion-weighted images showed evolving subacute infarcts of different ages in these regions (not shown).

IVLBCL before pursuing more invasive sampling of the brain, spinal cord, or visceral organs. Future studies in larger cohorts of patients with IVLBCL are required to systematically evaluate the frequency of skeletal muscle involvement and to better understand the utility of open-muscle biopsy for the diagnosis of IVLBCL.

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PT-F and AR reviewed the patients, collected the data, and drafted the manuscript. PJC reviewed the pathologic specimens, provided the micrographs, and critically reviewed the manuscript. RCB and SGK critically revised and prepared the manuscript.

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