Journal of Investigative Medicine High Impact Case Reports
Volume 8: 1–6

DOI: 10.1177/2324709620959997
journals.sagepub.com/home/hic
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Intravascular Large B-Cell Lymphoma Presenting as Acute Axonal Polyneuropathy: A Case Report and Literature Review

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Abstract

Intravascular large B-cell lymphoma (ILBL) is a rare and difficult to diagnose subtype of large B-cell lymphoma. The most common locations of presentation are in the central nervous system and the skin, but there are reports of other organ involvement. Due to the indolence, nonspecific symptoms, and rarity of the disease, this form of lymphoma is most often diagnosed postmortem. In this article, we describe a case of ILBL that presented as a rapidly progressive acute axonal polyneuropathy. Acute axonal polyneuropathy is a common disease process with a wide differential diagnosis, but there is limited literature on its prevalence as the presenting symptom of ILBL. This patient was treated with R-EPOCH and intrathecal methotrexate with significant improvement in his polyneuropathy after 1 cycle, and complete remission after 6 cycles. Data on chemotherapy regimens and their success rates for this disease are lacking.

Keywords

acute axonal polyneuropathy, polyneuropathy, large B-cell lymphoma, DA-R-EPOCH, intravascular large B-cell lymphoma

Introduction

Acute low back pain is a common presenting complaint in outpatient primary care. It has a large economic impact in the United States, with total costs estimated to be greater than $100 billion per year.[1] More often, low back pain is attributed to common musculoskeletal or psychological conditions, but sometimes the etiology is more obscure.

Intravascular large B-cell lymphoma (ILBL) is a rare subtype of extranodal lymphoma isolated to the small vessels with relative sparing of the surrounding tissues. This disease is difficult to diagnose due to the occult presentations and relative obscurity of the disease, and the diagnosis is most commonly made via surgical biopsy postmortem.[2]

Case Report

A 60-year-old male with a history of hypertension and diabetes who initially presented to his primary care physician for evaluation of low back pain. His only significant family history was sarcoidosis—a son and a niece both had pulmonary sarcoidosis. The patient developed acute low back pain that radiated down his legs bilaterally, with pain progressing rapidly over several days to difficulty with ambulation. His primary care physician diagnosed him with a urinary tract infection and treated him with antibiotics, believing his lower back pain to be flank pain. Approximately 2½ weeks later he developed urinary incontinence and bilateral paralysis, which were treated with a spinal steroid injection. He subsequently developed dyspnea and chest pain, prompting presentation to his local emergency department, where he was diagnosed with a pulmonary embolism by computed tomography (CT). Over a 2-week hospitalization, he underwent extensive workup, including magnetic resonance imaging (MRI) of the brain and spine, which showed abnormal foci of enhancement in the lumbar spine and T12 concerning for metastatic disease or multiple myeloma. Following the MRI, he underwent a skeletal survey, which was negative;

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Received August 12, 2020. Revised August 23, 2020. Accepted August 26, 2020.

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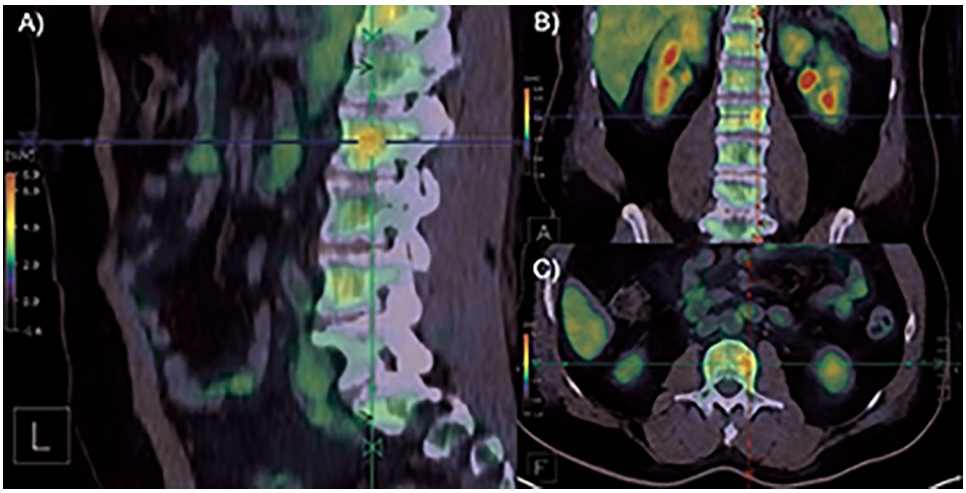

Figure 1. Whole body positron emission tomography showing patchy thoracolumbar marrow uptake, with focal increased uptake in the left lateral aspect of the L2 vertebral body seen in the sagittal cut (A), frontal cut (B), and axial cut (C).

CT-guided bone marrow biopsy, which was negative for malignancy; and a lumbar puncture (LP) that showed a cerebrospinal fluid (CSF) white blood cell count of 13 cells/mm^3 with 82% lymphocytes, red blood cell count of 10 cells/mm^3, total protein of 132 mg/dL, and negative polymerase chain reaction testing for herpes simplex virus and West Nile virus. The patient was given 1 day of intravenous steroids, after which pain significantly improved, but the bilateral weakness persisted. Steroids were discontinued due to concern for masking symptoms. Pain did not recur, but urinary incontinence persisted, and new bowel incontinence developed. He was started on a 5-day course of intravenous immunoglobulin and transferred to our tertiary care center, University of Florida Health Shands Hospital, for further workup.

At our facility, CT of the chest, abdomen, and pelvis, as well as scrotal ultrasound, did not show evidence of a solid tumor, and repeat spinal MRI showed nerve root enhancement, possibly secondary to trauma from the LP or an inflammatory process. Electromyography showed a sensorimotor polyneuropathy of axonal type. Serum studies were significant for an angiotensin-converting enzyme level of 83 U/L, positive anti-nuclear antibody (1:160 speckled) with otherwise negative autoimmune laboratory results, and lactose dehydrogenase level of 2722 IU/L. A repeat LP demonstrated resolution of previously elevated CSF white blood cell, and samples were sent for additional studies. CSF cytology showed no evidence of malignancy. A paraneoplastic panel was completely negative, and flow cytometry demonstrated no immunophenotypically aberrant cells. He was started on plasma exchange for presumed acute inflammatory demyelinating polyneuropathy; however, worsening of symptoms, including a significant decline in lower extremity strength and difficulty voiding, prompted a second repeat MRI of the spine. This MRI showed a new 3-cm focus of T2 hyperintensity within the central portion of the lower lumbar spinal cord with interval worsening of abnormal enhancement of the cauda equina nerve roots. This imaging raised concern for active worsening of an inflammatory condition, particularly neurosarcoidosis. He was given methylprednisolone 1 g intravenous daily for 5 days and completed a 5-day course of plasmapheresis. These efforts resulted in improved symptoms, and the patient was discharged on an extended course of prednisone 60 mg by mouth daily for a presumed diagnosis of neurosarcoidosis.

Following his first discharge from our facility, outpatient positron emission tomography (PET) was performed, which showed patchy thoracolumbar marrow uptake with increased focal uptake of the left lateral aspect of the L2 vertebral body (Figure 1). The patient was seen by outpatient neuroimmunology shortly after discharge and prednisone was increased to 80 mg by mouth daily and gabapentin to 600 mg by mouth thrice daily for the presumptive diagnosis of acute axonal polyneuropathy with acute central nervous system (CNS) inflammatory disease of unclear etiology. Despite these changes, lower extremity neuropathy worsened with sensory changes extending up to the umbilicus. Over the next 2 weeks, leg weakness progressed to where the patient required use of a wheelchair. He continued to have worsening bowel and bladder symptoms including constipation and urinary incontinence, ultimately forcing him to present back to the ED approximately 1 month after his initial discharge. Spinal MRI was repeated for the third time showing a new focus of hyperintensity in the lateral left cord at the T6 level, worsening hyperintensity in the anterior and lateral left spinal cord at the level of T12/L1, new diffuse myositis of the paraspinal muscles in the lumbosacral region, and subtle extra-axial linear and irregular contrast enhancement along the left side of the spinal cord at the level of T4, most likely in the leptomeningeal region. Another course of methylprednisolone 1 g intravenous daily for 5 days was given, which again resulted in mild temporary relief. A muscle biopsy of the left vastus lateralis was performed, which showed type 2 myofiber atrophy and did not have any overt myopathic features or granulomatous inflammation. He then

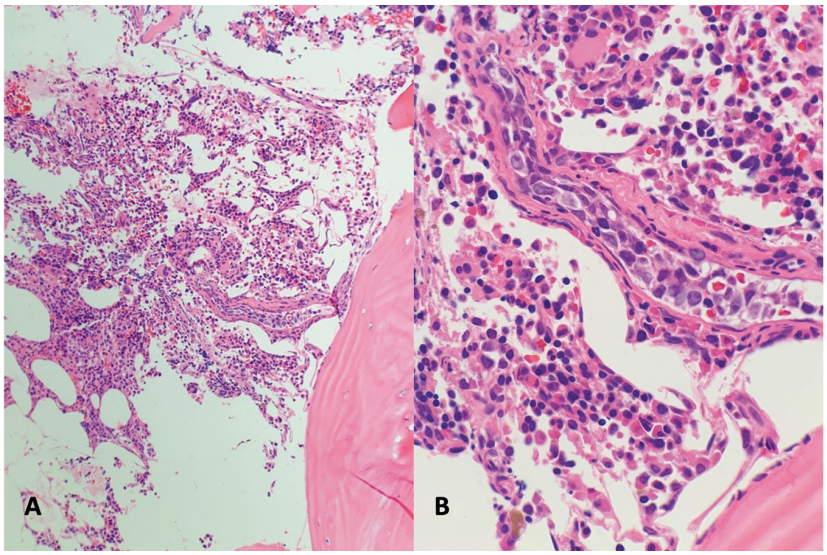

Figure 2. (A) Low-power (200× magnification) hematoxylin and eosin (H&E) section demonstrating intravascular involvement by B-cell lymphoma. (B) High-power (600× magnification) H&E section showing atypical B-cells with open chromatin and prominent nucleoli within intravascular space.

underwent a vertebral body biopsy, which was highly suspicious for involvement of a B-cell neoplasm, prompting a repeat bone marrow biopsy, which showed a large B-cell lymphoma exclusively involving the vasculature and with low level (less than 1%) marrow involvement (Figure 2).

Oncology was consulted, and the patient was started on combination chemotherapy with dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) with intrathecal methotrexate. Prior to treatment the patient was completely unable to activate any lower extremity muscles, but following treatment with his first cycle of chemotherapy, physical therapists reported activation of quadriceps muscles bilaterally. Following completion of 6 cycles of DA-R-EPOCH with intrathecal methotrexate, the patient achieved complete remission. One year after completing chemotherapy, the patient has remained in complete remission with only mild residual leg weakness.

Discussion

The differential diagnosis for low back pain is extremely broad with multiple different presentations and severities. Red flag symptoms such as bowel or bladder incontinence, saddle anesthesia, unexplained weight loss, and fever are often used as a means for physicians to assess urgency.[3] Back pain without red flag symptoms can be treated outpatient, with less concern for permanent loss-of-function or mortality. However, life-threatening etiologies for back pain exist, such as malignancies, infections, and neurological disorders. Many malignancies are readily apparent on MRI with lytic or blastic lesions, or visible masses. But there is a subset of patients with red flag symptoms, without significant imaging findings, and with inadequate response to temporizing therapies. In such cases, there remains a broad differential diagnosis, which includes atypical neoplastic diseases such as ILBL.

ILBL was first reported in 1959, as an unusual type of neoplasm that was not readily apparent on imaging and with a heterogeneous clinical presentation. ILBL most classically presents in the CNS or skin, but has been reported in almost every organ system.[2] These include the lungs, presenting with pulmonary hypertension[4]; the adrenal glands, presenting with adrenal failure[5]; the kidneys, presenting with renal failure and fevers[6]; the bones, presenting with bone pain[7]; the endometrium, presenting with vaginal bleeding[8]; the liver, presenting with fatigue and anorexia[9]; and hemophagocytic syndrome, presenting with hemolytic anemia and splenomegaly.[10] Presenting symptoms were found to differ in incidence between Asian (n = 106) and European (n = 38) cohorts, including fever (74% vs 45%), general fatigue (26% vs 16%), gastrointestinal symptoms (20% vs 2%), neurological symptoms (25% vs 34%), dyspnea (20% vs 3%), edema (10% vs 5%), urinary tract symptoms (1% vs 8%), and skin eruptions (6% vs 39%).[11] In a North American cohort (n = 29), there was similar heterogeneity of clinical presentation, with neurological symptoms (75.9%), cutaneous lesions (17.2%), pulmonary symptoms (27.6%), and gastrointestinal symptoms (24.1%).[12] ILBL involving the CNS can present with focal sensory or motor deficits, generalized weakness, altered sensorium, rapidly progressive dementia, seizures, hemiparesis, dysarthria, ataxia, vertigo, and transient vision loss.[2] While ILBL commonly presents in the nervous system, there are few reports of patients presenting with isolated acute axonal polyneuropathy. We summarized the key features of these rare cases (Table 1).

Table 1. Summary of Published Cases of ILBL Presenting With Neuropathy Including Demographics, Clinical Characteristics, Diagnostic Findings, Treatment Used, and Outcomes.

Author (year)	Onset (age)/ gender	Race	Presenting complaint	Imaging	Electromyography/nerve conduction study results	Biopsy	Treatment	Outcome
Jiang et al[16] (2010)	55/male	Hispanic	Symmetric numbness and weakness in lower extremities	Spine MRI: unremarkable Brain MRI and MRA: unremarkable	First: early demyelinating sensory and motor polyneuropathy Second: mononeuropathy multiplex	Sural nerve: mild axonal loss and mild ongoing axonal degeneration Gastrocnemius muscle: perivascular, mostly periarterial, infiltrates comprised of morphologically normal mononuclear inflammatory cells Autopsy: intravascular large B-cell lymphoma, which was widely disseminated in extranodal sites (brain, spinal cord, lung, heart, liver, kidney, adrenal, skeletal muscle, testicle, gallbladder, spleen, pancreas, esophagus, stomach, small and large bowel, bladder, and thyroid)	Not available	Patient died prior to diagnosis
Lynch et al[15] (2012)	63/Male	NA	Fatigue, malaise, left leg paresthesias, and then weakness	MRI brain and spine: degenerative vertebral changes without abnormalities or enhancement of the spinal cord, meninges, or nerve roots	Consistent with confluent mononeuropathy multiplex	Sural nerve: acute and subacute axonal neuropathy with myelin ovoids Gastrocnemius muscle: medium and small caliber vessels containing atypical large-sized lymphoid cells with muscle fiber atrophy of type-2 predominance. Atypical lymphoid cells were confined to the intravascular space.	R-CHOP, 2 cycles completed	Patient died from pneumonia following second cycle of chemotherapy
Fukami et al[14] (2020)	67/male	Not available	Acute bilateral lower extremity numbness and weakness	MRI brain and spine: multiple hyperintense white matter lesions in the brain on T2 fluid-attenuated inversion recovery sequences and a spinal cord lesion that involved more than 3 vertebral levels; nerve roots were not enlarged	Consistent with demyelinating sensorimotor polyneuropathy	Sural nerve: onion bulbs in some fascicles without infiltration by atypical cells Skin (random): no evidence of lymphomatous cells Bone marrow: no evidence of lymphomatous cells Brain: several round CD20-positive tumor cells within the lumen of small blood vessels	Cyclophosphamide pulse therapy	Patient died from pneumonia
Minish et al (2020; present case)	60/male	African American	Acute low back pain, then bilateral lower extremity pain and weakness	MRI brain and spine: abnormal focus of enhancement in the lumbar spine and T12 PET: patchy thoracolumbar marrow uptake with focal increased uptake of the left lateral aspect of the L2 vertebral body	Consistent with sensorimotor polyneuropathy of axonal type	Bone marrow (1): negative for malignancy. Muscle: type 2 myofiber atrophy and did not have any overt myopathic features or granulomatous inflammation. Bone (vertebra): occasional large CD20(+)/ PAX5(+) B-cells both singly and in some small clusters, highly suspicious for involvement of a B-cell neoplasm. Bone marrow (2): large B-cell lymphoma exclusively involving the vasculature and with low level (less than 1%) marrow involvement.	R-EPOCH with intrathecal methotrexate	Complete remission following 6 cycles of chemotherapy with residual neuropathy at 1 year

Abbreviations: ILBL, intravascular large B-cell lymphoma; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; PET, positron emission tomography.

In ILBL, there is selective growth and proliferation of clonal lymphocytes within the blood vessel lumen, with a remarkable sparing of surrounding tissue and organ parenchyma.[2,11] It has been shown that ILBL cells lack CD29 (B1 integrin subunit), which is integral for lymphocyte extravasation, as well as a decreased number of homeostatic chemokine receptors, which act on lymphocyte migration across vascular structures.[13] The exact mechanism of this disease process is largely unknown, but it has been shown that ILBL cells lack molecules for extravasation and express molecules involved in cell migration and molecules that make them capable of endothelial adherence.[13] Diagnosis requires biopsy of involved organs demonstrating clonal large B-cells within the small vessel lumina. In a retrospective review, Brunet and colleagues[12] saw patients (n = 23) diagnosed by biopsies of skin (38%), bone marrow (21%), brain (17%), kidney (12%), duodenum (4%), liver (4%), and retroperitoneal lymph nodes (4%).[12]

The rarity of ILBL has made prospective clinical trials difficult, and the majority of recommendations have been based on case reports, retrospective studies, and small subset inferences from clinical trials.[13] In 2004, the primary treatment for ILBL was anthracycline based.[17] Of the patients in this study with CNS involvement, 5 of the 6 patients received chemotherapy, with 4 dying early, and only 1 patient, who was treated with doxorubicin, cyclophosphamide, vincristine, methotrexate, bleomycin, and prednisolone (MACOP-B) followed by autologous stem cell transplantation, was alive at 19 months.[17] In 2008, a retrospective analysis of ILBL treated with rituximab containing chemotherapy was found to have a complete response rate of 82% versus 51% in those treated with chemotherapy not containing rituximab and an overall survival at 2 years of 66% versus 46%.[18] Currently, per Ponzoni and colleagues,[13] the recommended first line therapy is a combination of anthracycline-based regimens with rituximab and CNS prophylaxis with intrathecal methotrexate. Due to small sample sizes for ILBL clinical trials, these patients have been included in diffuse large B-cell lymphoma clinical trials, such as the Alliance/CALGB 50303 trial. The Alliance/CALGB 50303 trial, published 2 months after our patient was started on DA-R-EPOCH with intrathecal methotrexate, showed no improvement in overall survival, progression-free survival or response rate with the more intensive DA-R-EPOCH to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).[19]

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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