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Letter to the Editor: New Observation

Multifocal Myelitis Associated with Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is an indolent hematologic disease that rarely results in neurological manifestations. We describe an unusual case of a man who presents with subacute to chronic of progressive lower extremity weakness, urinary incontinence, with imaging correlate of multifocal myelitis as the initial presentation of CLL.

A 74-year-old otherwise healthy man developed a coronavirus disease 2019 respiratory infection and underwent a CT thorax that showed incidental pulmonary nodular opacities and enlarged lymph nodes that were consistent with postinfectious or inflammatory changes. He did not have any known past medical history or any constitutional symptoms.

Four months later, he presented with a 5 week history of progressive, asymmetric leg weakness that was worse on the right and concomitant urinary incontinence. Neurologic examination demonstrates mild spasticity in his left arm, moderate right leg spasticity and weakness in a pyramidal pattern (2/5 proximally and 4/5 distally), multiple suspended sensory levels (left C5–C6, right C8–T1, and right T8–T9), absent vibration sense up to his knees, and upgoing plantar responses bilaterally.

An MRI of the cervical and thoracic cord demonstrates multiple patchy areas of T2 hyperintensity, most conspicuous at C6–C7, T1, T3–T4, and T8 levels, reported as suggestive of a demyelinating etiology (Fig. 1). A subsequent MRI brain showed scattered nonspecific patchy areas of T2 fluid-attenuated inversion recovery hyperintensities in the supratentorial white matter, including periventricular and juxtacortical lesions (Fig. 2). Lumbar puncture revealed mildly elevated cerebrospinal fluid (CSF) protein of 409 mg/L and 16 total nucleated cells with lymphocytic predominance. Oligoclonal bands were matched in serum and CSF. Cytology did not demonstrate malignant cells in the CSF. Results of CSF polymerase chain reaction testing for herpes simplex virus (HSV), varicella zoster virus (VZV), and enterovirus were negative. Flow cytometry, serum/CSF paraneoplastic antibodies, and JC virus were not sent.

His complete blood count revealed normal hemoglobin, mild leukocytosis of 16.5×10^9 with lymphocytic predominance, and mild thrombocytopenia of 124×10^9. Electrolytes, creatinine, liver enzymes, and lactate dehydrogenase were normal. Serologies for hepatitis B/C, human immunodeficiency virus, syphilis, and lyme were negative. His vasculitis markers, aquaporin-4, and myelin oligodendrocyte glycoprotein antibodies returned negative.

The patient was empirically started on high-dose steroids for a presumed demyelinating or inflammatory etiology. This led to partial improvement of his leg weakness, but his leukocytosis rose to 44.1×10^9 with increased neutrophils and lymphocytes. Subsequently, a whole-body CT demonstrated mild intrathoracic and abdominopelvic lymphadenopathy with interval resolution of the incidental pulmonary nodular opacities. A positron emission tomography (PET) scan did not demonstrate any fluorodeoxyglucose (FDG) avidity.

Given the persistence of intrathoracic lymphadenopathy, the patient underwent an endobronchial ultrasound-guided biopsy of a subcarinal lymph node, and the results showed a B-cell type lymphoproliferative neoplasm with features consistent with CLL or small lymphocytic lymphoma. A second lumbar puncture revealed normal glucose at 3.6 mmol/L, borderline elevation in CSF protein at 417 mg/L, and 19 total nucleated cells with lymphocytic predominance. Flow cytometry of the CSF was consistent with a B-cell lymphoproliferative neoplasm with 95% CLL predominant infiltrate (positive for CD19, CD5, and dim CD 20 and negative for CD10). Cytology of the CSF revealed mostly small and mature lymphocytes. Overall, the CSF was densely infiltrated with CLL, and he was diagnosed with CLL with central nervous system (CNS) involvement. The patient was started on ibrutinib 560 mg once daily. At 8 months of follow-up, he reported stability of his neurological symptoms and his repeat CSF testing demonstrated normal protein at 386 mg/L, 4 nucleated cells, and 446 erythrocytes.

CLL is the most common hematological malignancy in the elderly with a 0.8% prevalence of clinically significant neurological manifestations.[1] Approximately half of these cases are due to Richter's syndrome in the CNS, and the other half are due to CLL infiltration into the CNS. Richter's syndrome is characterized by the sudden transformation from CLL to a more aggressive form of large cell lymphoma. Typically, neurological manifestations in CLL present with brain parenchymal or meningeal abnormalities; case reports of significant spinal cord involvement are rare.[1,2] Akdogan et al. (2020) reported an elderly man with a 2 week history of progressive tetraparesis and radiological findings of multifocal myelitis; unlike our patient, there was a leukocytosis of 131×10^9 on presentation and subacute history of intermittent fevers. CLL was confirmed on bone marrow biopsy and the patient responded to a combination of

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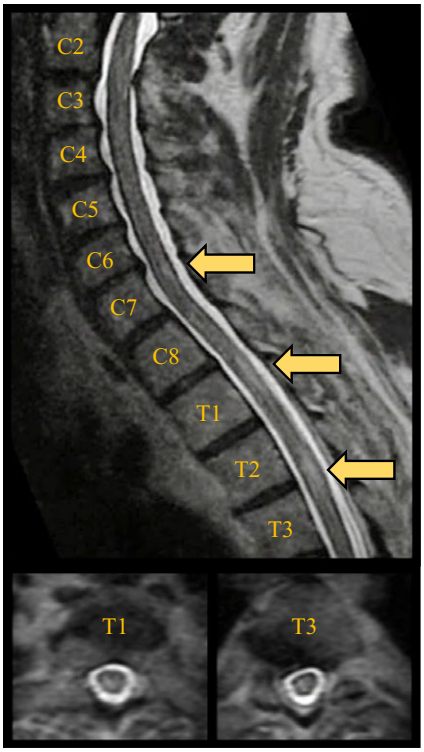


Figure 1. MRI spine demonstrates multifocal myelitis. T2-weighted images of the complete spine demonstrated patchy areas of hyperintensity throughout the cervical and thoracic cord. T2 hyperintensity involving C6–C7, T1, and T3–T4 are as shown. T2 hyperintensity at T8 was also observed (but not pictured). The short segments of hyperintensity predominantly affect the central and dorsal regions of the spinal cord and are most noticeable on the right side.

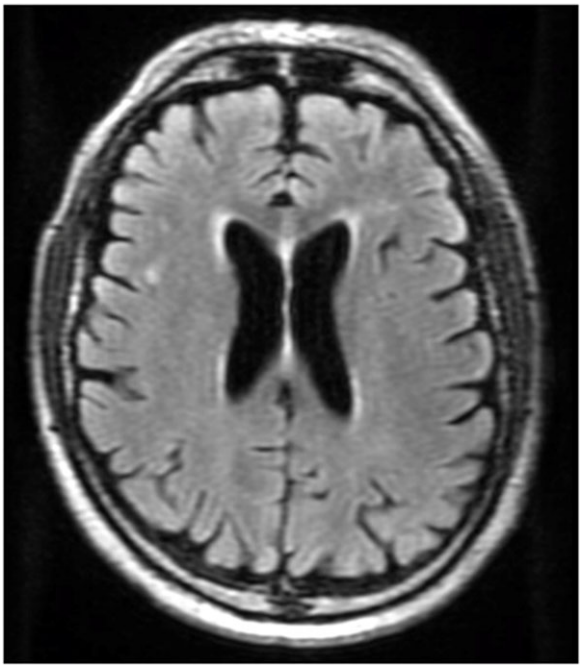


Figure 2. MRI of the brain demonstrates scattered nonspecific T2 hyperintensities. T2 fluid-attenuated inversion recovery (FLAIR) sequences of the brain demonstrate nonspecific periventricular and juxtacortical lesions. There were no areas of diffusion restriction or susceptibility weighted hypointensities.

rituximab, cyclophosphamide, and immunomodulatory therapies.[3] Although the proportion of patients with clinically significant neurological manifestations in CLL is reportedly low, postmortem analysis suggests that subclinical CNS involvement in CLL may be as high as 71%.[4]

The prognosis from onset of neurological manifestations to death in CLL patients is 12 months[5]; thus, early diagnosis and treatment are critical. FDG avidity on PET scans can be seen in multiple disorders, including neurosarcoidosis, infectious diseases (e.g., mycobacterium), and various malignancies. Similarly, PET scans have a high sensitivity for Richter's syndrome. However, there is low uptake of FDG in CLL due to its limited glycolytic activity, which can also be seen with other types of neoplasms, such as bronchioloalveolar carcinomas, carcinoid tumors, and small-sized tumors.[6] Thus, a negative PET scan does not preclude malignancy as the cause of symptoms. In a patient with sustained lymphadenopathy, clinicians should maintain a high level of suspicion for underlying malignancy and tissue biopsies should be obtained whenever possible.

CSF flow cytometry and cytology can help differentiate CLL with CNS involvement from more aggressive forms of lymphoma, such as diffuse large B-cell lymphoma. Although CSF flow cytometry has a slightly higher sensitivity than CSF cytology (13% vs. 4.5%) for CNS involvement in hematological malignancies, the diagnostic yield of both tests is low, and repeat lumbar punctures are often necessary.[7] Moreover, flow cytometry in serum can provide prognostic value. In our patient, CD49d expression was positive in the peripheral blood, which is associated with disease progression and may predict CNS involvement in CLL.[8,9]

Given the rarity of this disease, there are no standardized therapeutic regimens for CLL with CNS involvement. Recent studies showed promising data that support the use of ibrutinib and lenalidomide for CNS penetration in lymphoma.[10,11] Nakanishi et al. (2020) compiled 11 case reports that used ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor that crosses the blood-brain barrier, for treatment of CLL with CNS involvement. Of the 11 case reports, 9 patients demonstrated improvement with ibrutinib: 8/9 achieved complete remission and 1/9 achieved partial remission.[11] Since starting on ibrutinib, our patient reported stability of his neurologic symptoms. Future research will need to determine whether BTK inhibitors are truly effective in CLL patients with CNS involvement.

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