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Autoimmune Ataxia During Maintenance Therapy for Acute Lymphoblastic Leukemia

Julie Voeller, MD[1], Chrysanthy Ikonomidou, MD, PhD[2], Justin Brucker, MD[3], Carol Diamond, MD[1], Sharon Frierdich, MS, RN, BC-PNP[4], and Neha Patel, MD[1]

Abstract

Neurologic dysfunction during acute lymphoblastic leukemia treatment is commonly associated with chemotherapy. Nonchemotherapy contributions should be considered for persistent atypical symptoms. We describe a boy with acute lymphoblastic leukemia who developed recurrent fevers, diarrhea, progressive ataxia, and neuropsychiatric impairment during maintenance chemotherapy. He was found to have cytomegalovirus in his serum and colon, but not in his cerebrospinal fluid. Instead, his cerebrospinal fluid revealed oligoclonal bands not present in the serum, suggesting an autoimmune process. Prompt treatment with ganciclovir and immunotherapy resulted in marked clinical improvement. Early recognition and treatment of an autoimmune encephalitis is paramount for optimal clinical outcome.

Keywords

autoimmune ataxia, autoimmune encephalitis, acute lymphoblastic leukemia, pediatric, maintenance chemotherapy

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Vincristine and methotrexate are essential chemotherapeutic drugs in the treatment of childhood acute lymphoblastic leukemia. In addition to controlling systemic disease by oral and intravenous administration, methotrexate is given intrathecally for treatment and prophylaxis of the central nervous system, a sanctuary site for leukemia.

However, both vincristine and methotrexate can cause short- and long-term neurologic dysfunction.[1-3] Vincristine targets microtubules, therefore it can cause direct damage to peripheral nerves and induce an axonopathy which manifests as a slowly progressive sensorimotor neuropathy.[1,4,5] Symptoms include paresthesias, dysesthesias, numbness and tingling, foot drop, weakness, and gait disturbances. Methotrexate is an antimetabolite which can cause neurotoxicity through the disruption of central nervous system folate homeostasis and/or direct neuronal damage.[3,6] Patients with methotrexate-induced neurotoxicity can present with transient stroke-like symptoms, encephalopathy, seizures, or aphasia. These symptoms are often associated with leukoencephalopathy, the correlates of which are white matter hyperintensities on T2-weighted magnetic resonance imaging (MRI), though these radiographic changes can also develop in asymptomatic children receiving methotrexate.[7]

When patients present with severe chemotherapy-related neurotoxicity, dose modifications are made, including omitting doses, reducing doses, and/or replacing with alternative therapies. However, the progression of symptoms despite these changes and the presence of atypical symptoms suggest that the differential should be broadened. We describe a case of a boy with standard-risk acute lymphoblastic leukemia who developed focal motor deficits and neuropsychiatric and cerebellar symptoms during maintenance chemotherapy that

[1] Division of Pediatric Hematology, Oncology & Bone Marrow Transplant, Department of Pediatrics, University of Wisconsin, Madison, WI, USA
[2] Section of Pediatric Neurology, Department of Neurology, University of Wisconsin, Madison, WI, USA
[3] Section of Neuroradiology, Department of Radiology, University of Wisconsin, Madison, WI, USA
[4] American Family Children's Hospital, Madison, WI, USA

Corresponding Author:
Julie Voeller, MD, Division of Pediatric Hematology, Oncology & Bone Marrow Transplant, Department of Pediatrics, University of Wisconsin, 1111 Highland Ave., MC WIMR 4105, Madison, WI 53705, USA.
Email: jvoeller@uwhealth.org

progressed despite modifications to his chemotherapy. Further workup revealed presence of oligoclonal bands in his cerebrospinal fluid which raised the suspicion for an autoimmune pathogenesis.

Case Report

A 4-year-old male with standard-risk B-precursor acute lymphoblastic leukemia, CNS2a status (note 1), and history of grade 2 vincristine-related peripheral neuropathy (note 2) that improved with gabapentin and physical therapy presented with progressive neurologic symptoms during maintenance chemotherapy course. Initially his symptoms were subtle, therefore seemed consistent with chemotherapy-related side effects. Several doses of vincristine were held and intrathecal methotrexate was substituted with intrathecal hydrocortisone and cytarabine. During this time, the patient developed recurrent fevers and diarrhea. Meanwhile, his clinical status continued to worsen with symptoms atypical for chemotherapy-related neurotoxicity: asymmetric weakness, ataxia with frequent falls, and regression in fine motor skills. His mother also reported speech and language dysfunction, perseveration, and worsening oppositional defiant behavior.

Evaluation of his recurrent fevers and chronic diarrhea led to the diagnosis of cytomegalovirus viremia with a serum quantitative cytomegalovirus DNA by real-time polymerase chain reaction (PCR) of 380,000 IU/mL and cytomegalovirus colitis by tissue biopsy. Cytomegalovirus was not detected in his cerebrospinal fluid nor retinas. His fevers and diarrhea resolved after treatment with ganciclovir, and he remained seronegative for cytomegalovirus.

However, his neuropsychiatric symptoms continued to worsen. Further workup was pursued to evaluate for epilepsy, progressing leukoencephalopathy, myelopathy, and peripheral neuropathy. Electroencephalography revealed no seizure activity. Successive MRIs of the brain showed T2 hyperintensities in the white matter, which were interpreted as methotrexate-induced leukoencephalopathy, without signs of cerebellar atrophy. Magnetic resonance imaging of the spine was normal. Acute infectious encephalitis was less likely given normal cerebrospinal fluid indices, including normal protein (18) and glucose (47) and no pleocytosis (less than 1 nucleated cell). Additional cerebrospinal fluid testing revealed negative bacterial and fungal cultures and negative PCR testing for enterovirus, varicella zoster, mycoplasma, and Epstein-Barr virus. Workup for paraneoplastic and autoimmune encephalitis panels from serum and cerebrospinal fluid was negative, including neuron-specific enolase, paraneoplastic autoantibodies, and anti-N-methyl-D-aspartate (anti-NMDA) receptor immunoglobulin G. Examination of cytospin preparations of serial cerebrospinal fluid samples under light microscopy—the current gold standard for detection of central nervous system leukemia—did not reveal any blasts. Creatine phosphokinase, electromyography, and nerve conduction studies were also unrevealing for a primary myopathic or neuropathic process.

On several occasions, his cerebrospinal fluid revealed 2 or more unique oligoclonal bands not present in the serum. Despite absence of autoantibodies to neuronal and glial antigens in blood and cerebrospinal fluid, an autoimmune encephalitis was proposed. He was treated with several cycles of monthly intravenous immunoglobulin 1 g/kg, each leading to a marked improvement in his weakness, ataxia, and coordination. His symptoms continued to break through at shorter intervals and his cerebrospinal fluid demonstrated increasing numbers of oligoclonal bands, which peaked at 9, suggesting increased intrathecal synthesis of immunoglobulin necessitating escalation of immunotherapy. Rituximab induction (4 weekly infusions of rituximab 375 mg/m^2 per dose) was added to his monthly intravenous immunoglobulin infusions, and he has thus far had good clinical response. Retrospective review of his head MRIs revealed a subtle abnormality within the left basal ganglia and biparietal white matter that gradually resolved over the course of his treatment (Figure 1). His current regimen consists of intravenous immunoglobulin every 3 weeks and monthly dexamethasone pulses, in conjunction with his ongoing maintenance therapy for his underlying acute lymphoblastic leukemia. His CD19 and CD20 counts are maintained at 0.

Discussion

Gait ataxia and weakness are common side effects of chemotherapy for acute lymphoblastic leukemia caused by vincristine-induced peripheral neuropathy. Focal motor deficits and neurocognitive changes may accompany methotrexate-induced leukoencephalopathy. Here, we describe an unusual case of neurologic deficits secondary to acute noninfectious autoimmune encephalitis. Cerebrospinal fluid oligoclonal bands not found in the serum may accompany infections of the central nervous system, such as subacute sclerosing panencephalitis, cryptococcal meningitis, and neurosyphilis.[8] Cerebrospinal fluid oligoclonal bands can also be found in noninfectious diseases such as multiple sclerosis, *Behçet disease*, cerebral lupus, and paraneoplastic disorders.[9,10] In this case, intrathecal immunoglobulin G may have been triggered by an immunologic response to a systemic cytomegalovirus infection, which is a rare cause of recurrent fevers in patients being treated for standard-risk acute lymphoblastic leukemia.[11] Although no antibodies known to cause autoimmune encephalitis were identified in serum or cerebrospinal fluid, the response of this patient to immunotherapy confirmed the diagnosis of an autoimmune disorder.

Autoimmune encephalitis can manifest as a rapidly progressive disorder with subacute cognitive disturbance, memory impairment, altered mental status, psychiatric manifestations, seizures, a variety of motor deficits including focal or generalized weakness, abnormal movements, and ataxia.[12] Prompt diagnosis of autoimmune encephalitis is paramount for initiation of treatment with immunotherapy.

Antibody-associated disorders of the central nervous system can be divided into 2 broad categories: those which involve

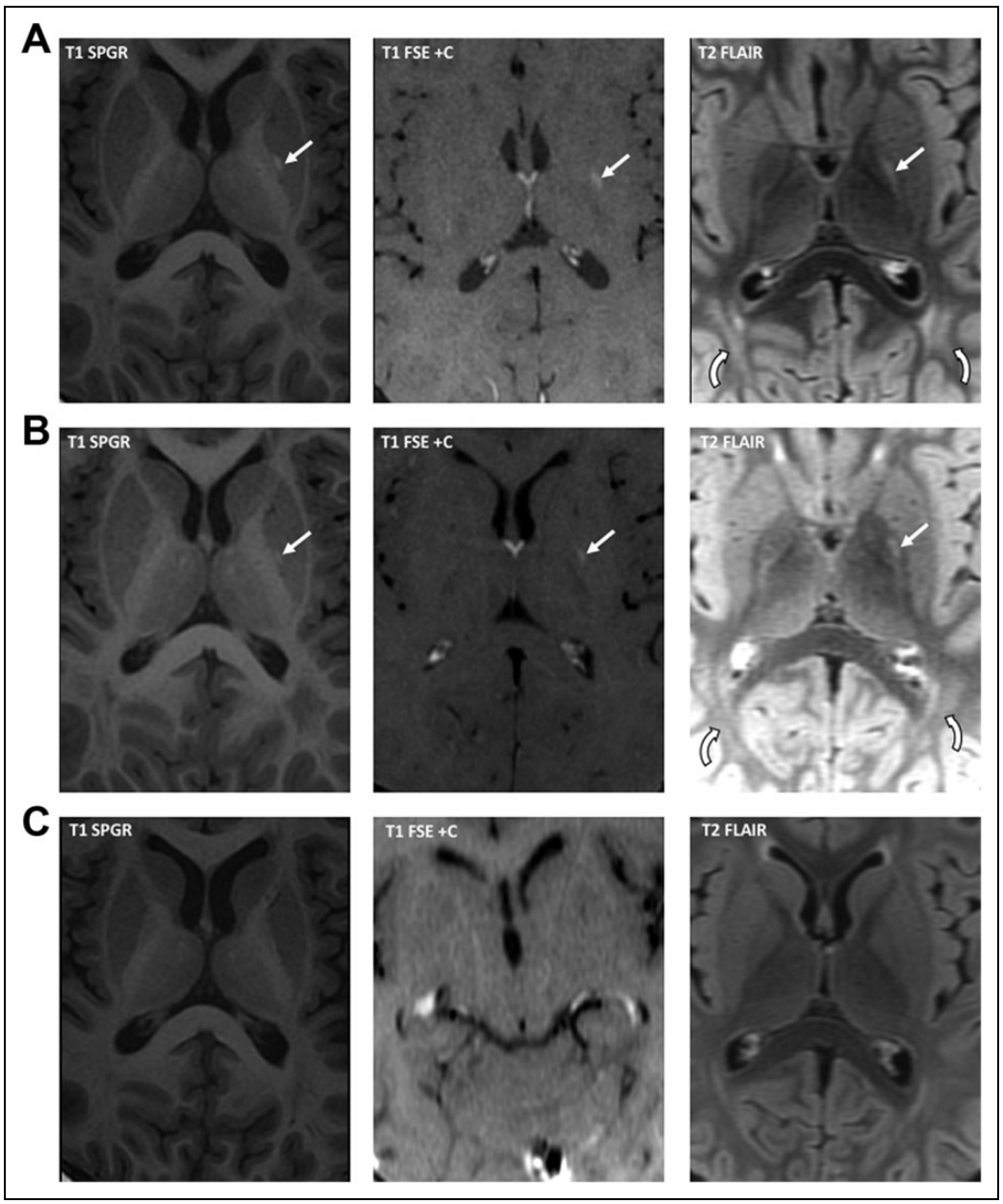

Figure 1. Successive axial images reconstructed through the level of the deep basal nuclei and ventricles, with different weightings: T1 Spoiled Gradient Recovery Echo (T1 SPGR), Postcontrast T1 Fast Spin Echo (T1 FSE +C), and T2 Fluid Attenuated Inversion Recover (T2 FLAIR). At the time of the initial magnetic resonance examination (A), there is a subtle focus of signal abnormality within the left lentiform nucleus, at the interface of the putamen and globus pallidus externa (straight arrow); this lesion is intrinsically T1 hyperintense and T2 FLAIR hyperintense, with suggested enhancement. This lesion is seen in addition to other patchy, nonenhancing T2 FLAIR hyperintense signal changes located symmetrically within the deep biparietal periatrial white matter (curved arrows); the parietal white matter signal abnormalities were initially interpreted as methotrexate-induced leukoencephalopathy. Over the course of the patient's treatment, these signal abnormalities within the left basal ganglia and biparietal white matter were gradually reduced (B), and eventually resolved (C).

pathogenic antibodies that target surface proteins and those in which antibodies target intracellular proteins with cytotoxic T cells being the main effectors of neurologic dysfunction.[13] Antibodies resulting in classic paraneoplastic disorders target intracellular neuronal antigens which mediate a cytotoxic T-cell response. Examples include anti-Hu antibody in small cell lung cancer and anti-Ma2 in testicular germ cell tumors.[14] Classic paraneoplastic disorders usually have a monophasic clinical course and limited response to treatment. In contrast, autoimmune encephalitis involving pathogenic antibodies that target cell surface and synaptic proteins, such as the NMDA receptor in ovarian teratoma and the γ-aminobutyric acid ($GABA_B$) receptor in small cell lung cancer, are much more amenable to immunotherapy.

Treatment for immune-mediated encephalitis includes immunotherapy with intravenous immunoglobulin, rituximab,

and corticosteroids. Removal of antibodies often results in neurologic improvement when target antigens are in the periphery, but additional immunotherapies are often needed to reduce intrathecal antibody titers. Prompt treatment of the tumor in paraneoplastic disorders is also a major factor contributing to the improvement in neurologic symptoms.

This case illustrates the importance of considering autoimmune encephalitis as a cause of progressive ataxia and neuropsychiatric symptoms in patients being treated for standard-risk acute lymphoblastic leukemia. Although in classic paraneoplastic disorders treatment of the primary tumor in addition to immunotherapy can improve neurologic dysfunction, resolution of autoimmune encephalitis secondary to pathogenic antibodies relies primarily on immunotherapy. Earlier initiation of treatment can result in more rapid and lasting recovery.

Author Contributions

JV, CI, JB, and NP contributed to conception and design; JV drafted the manuscript; CI, CD, SF, and NP critically revised the manuscript; and all authors agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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ORCID iD

Julie Voeller, MD https://orcid.org/0000-0001-7811-513X

Notes

1. By Children's Oncology Group (COG) criteria, this is defined as less than 10/μL red blood cells, less than 5/μL white blood cells and cytospin positive for blasts.
2. By Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Ethical Approval

Approval not necessary under institutional standards for single case reports.

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