Correlating Pathology With the Clinical Symptoms of Methotrexate-induced Leukoencephalopathy in a Child With Relapsed T-cell Acute Lymphoblastic Leukemia

Ryan J. Summers, MD,* Carlos R. Abramowsky, MD,*† and Todd M. Cooper, DO*†

Summary: Intrathecal and systemic methotrexate (MTX), as well as cranial radiation, are effective modalities to prevent central nervous system relapse in childhood acute lymphoblastic leukemia. Leukoencephalopathy is a well-described adverse effect of MTX therapy and is associated with a wide range of neurological sequelae. Most recent studies of MTX-induced leukoencephalopathy have focused exclusively on imaging findings, particularly magnetic resonance imaging. Here we report a case of severe MTX-induced leukoencephalopathy with unique magnetic resonance imaging findings and pathologic correlation from a brain biopsy taken during a period of active neurological symptomatology.

Key Words: T-cell acute lymphoblastic leukemia, methotrexate, leukoencephalopathy

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The use of high-dose systemic methotrexate (MTX) and intrathecal (IT) MTX reduce the risk of central nervous system (CNS) relapse and increase survival rates in pediatric acute lymphoblastic leukemia (ALL).1,2 However, MTX-induced leukoencephalopathy is fairly common in children with higher CNS MTX exposure, with an incidence ranging from 3% to 11%.3–5 Children with T-cell ALL (T-ALL) and high-risk B-precursor ALL (B-ALL) often receive more CNS-directed MTX therapy, and therefore are at higher risk of neurological side effects. As many T-ALL patients receive prophylactic cranial irradiation with initial therapy, salvage options for CNS relapse are limited.

Leukoencephalopathy is typically diagnosed by magnetic resonance imaging (MRI). The characteristic finding is white matter hyperintensity on T2-weighted images.3,5 The pathologic features of MTX-induced leukoencephalopathy have been described in the postmortem setting. They include the presence of hemosiderin-laden macrophages, perivascular round cells, reactive astrocytes, coagulative white matter necrosis, demyelination, and axonal swelling.6,8 Here we report a case of biopsy-proven MTX-induced leukoencephalopathy in a patient with relapsed T-ALL with recent exposure to CNS irradiation and IT chemotherapy. This case uniquely illustrates the pathologic sequelae of leukoencephalopathy during an acute neurological episode. This provides a powerful example of the challenges faced in treatment of early CNS T-ALL relapse.

CASE REPORT

A 16-year-old female presented with a 2-week history of fatigue and leg pain. Her physical examination revealed diffuse lymphadenopathy, hepatosplenomegaly, and scalp nodules. White blood cell count was 554,340/μL with 97% lymphoblasts. Peripheral flow cytometry confirmed immature T-lineage cells. Initial cerebrospinal fluid (CSF) was negative for blasts. The patient was treated with high-risk ALL therapy consisting of an augmented BFM approach with 1 delayed intensification phase, consistent with Children’s Cancer Group study 1961.9 After a 4 drug induction, the patient had no detectable minimal residual disease. She began her third course of therapy with 3 g/m² of intravenous MTX but experienced severe mucositis and opted to receive lower, escalating doses of intravenous MTX (Capozzii) for subsequent doses. She received 12 Gy of prophylactic cranial irradiation just before maintenance therapy, 9 months after her initial remission. She received IT MTX 8 weeks before and 1 week after cranial irradiation.

Three months after CNS irradiation and 12 months after initial remission, during maintenance chemotherapy, she developed encopresis, confusion, headaches, and blurry vision. CSF testing revealed a white blood cell of 2,025/μL with 98% lymphoblasts, confirming CNS relapse. Her last lumbar puncture was performed 3 months before relapse at the start of maintenance therapy. Bone marrow was negative for leukemic involvement. Brain MRI revealed abnormal T2 hyperintensity with mild enhancement and restricted diffusion in the bilateral centrum semiovale (Figs. 1A–C). These findings were consistent with subacute bilateral deep watershed territory infarctions, leukemic involvement, or demyelinating disease. Enhancement on postcontrast images and lack of recent IT MTX made treatment-related leukoencephalopathy less likely (Fig. 1B). She then received triple intrathecal chemotherapy (TIT). Given her neurological symptoms and negative bone marrow, we planned to delay systemic chemotherapy until CNS remission was achieved, as our initial agent of choice for reinduction therapy was nelarabine, which has known neurotoxicity. Her neurological status improved after her first 2 doses of TIT.

Within 10 days of beginning TIT, she presented with fever, pancytopenia, and altered mental status. Initial blood culture was positive for Escherichia coli but subsequent cultures were negative. Her neurological dysfunction progressed to bowel and bladder incontinence, delirium, agitation, and aphasia. Subsequent brain MRIs revealed new areas of T2 hyperintensity in the bilateral frontal lobes with a ring-enhancing component in the left frontal lobe. On the basis of the MRI, the differential diagnosis included treatment-related leukoencephalopathy, CNS leukemia, and infection (Figs. 1D–F). Also demonstrated were restricted diffusion in the bilateral centrum semiovale and bilateral parietal lobes (not shown). After 1 week, her mental status improved, although she had not returned to baseline. To prevent likely progression of CNS leukemia, she received IT cytarabine that resulted in worsening neurological compromise. Her CSF was negative for leukemic blasts at the time of IT cytarabine administration.
The patient was febrile and pancytopenic for 2 weeks, without evidence of leukemia in 3 bone marrow aspirates. An extensive infectious workup on both blood and CSF was negative, including adenovirus, enterovirus, fungal cultures, cytomegalovirus, cryptococcus, Epstein-Barr virus, human herpesvirus-6, human herpesvirus-8, histoplasma, herpes simplex virus, John Cunningham virus, lymphocytic choriomeningitis virus, measles, mycobacterium, parvovirus B19, rubeolla, and toxoplasma. The CSF albumin index was elevated at 18.6, indicating moderate blood-brain barrier impairment, but no oligoclonal bands were seen. CSF glucose and protein were measured several times throughout her course and ranged from 43 to 61 and 56 to 103 mg/dL, respectively.

Because of the persistent fever and pancytopenia, a biopsy of the ring-enhancing left frontal lobe lesion was performed to rule out a focal infectious process. The biopsy revealed perivascular lymphoplasmacytic inflammation, chronic inflammation of the leptomeninges, leptomeningeal vasculitis (Figs. 2A, B), focal white matter microinfarcts (Figs. 2A, C), and surface astrogliosis (Fig. 2D). All special stains for fungal, acid-fast mycobacteria, and general bacterial organisms were negative. Histologic sections showed no evidence of viral cytopathic effect, toxoplasma cysts, or leukemic infiltrates. Therefore, the clinical and pathologic findings were attributed to IT chemotherapy and radiation therapy.

Her mental status improved and she was discharged to inpatient rehabilitation where she regained much of her neurological function. She received systemic maintenance chemotherapy after discharge from inpatient rehabilitation. Five months later, and 8 months after initial CNS relapse, she presented with combined CNS and marrow relapse. Her leukemia was controlled for several months with palliative CNS radiation and single-agent nelarabine. Eventually, she passed away after experiencing septic shock and multisystem organ failure.

**DISCUSSION**

This case report is unique in that it correlates pathologic changes with a patient actively experiencing the neurological sequelae of leukoencephalopathy. The close temporal relationship between cranial irradiation and TIT necessitated by early relapse likely accelerated her clinical course. We hypothesize that radiation therapy may have caused the vasculitis, thus making the patient more susceptible to MTX-induced leukoencephalopathy. This is supported pathologically by the infarction and reactive astrocytosis (Fig. 2). The potential confounding factors contributing to her neurological sequelae—leukemic involvement and infection—were definitively ruled out by the biopsy.

The effects of radiation therapy could provide an explanation for the coincident findings of T2 hyperintensity and diffusion restriction on her initial MRI (Fig. 1). Prior reports have noted that in MTX-induced leukoencephalopathy diffusion, restriction appears simultaneously with symptom onset but before any white matter changes on
T2-weighted images. However, isolated T2 hyperintensity is a finding in early-delayed radiation toxicity. Ring-enhancing lesions are common MRI findings in CNS infection but are not seen in MTX-induced leukoencephalopathy. Our pathologic and radiologic findings suggest that MTX-induced leukoencephalopathy can produce a broader range of MRI findings than previously described.

CNS relapse occurs in 3% to 8% of children with ALL. Risk factors include T-cell phenotype and hyperleukocytosis, both present in our patient. Historically, cranial irradiation has been used as prophylaxis against CNS relapse. More recent data show that increased doses of IT MTX may obviate the need for prophylactic CNS radiation in standard-risk T-ALL. The possibility of a subsequent increase in the incidence of leukoencephalopathy has not been specifically addressed. Additional data suggest that prophylactic CNS radiation can be eliminated in all pediatric ALL patients, without an increase in IT MTX exposure, in the setting of appropriately risk-adjusted chemotherapy.

The approach to the patient with MTX-induced leukoencephalopathy is unclear and alternative treatment options are limited. Our patient relapsed 3 months after prophylactic cranial irradiation, within the time frame for early-delayed radiation toxicity. However, her symptoms worsened significantly within 10 days of beginning TIT. This is consistent with subacute MTX neurotoxicity and lends support to the hypothesis that IT MTX has direct white matter effects. Furthermore, the fact that she recovered much of her neurological function after withdrawal of MTX makes chronic necrotizing leukoencephalopathy unlikely, as this entity typically results in relentless neurological deterioration. Elevated CSF levels of myelin basic protein have been reported in patients experiencing active leukoencephalopathy but were not evaluated in our patient.

Our patient developed further neurological compromise when challenged with IT cytarabine. IT cytarabine has also been associated with leukoencephalopathy; however, it is often used after a patient experiences IT MTX-related side effects. Another proposed strategy is to include leucovorin rescue after subsequent doses of IT MTX. Other options include alternative IT cytotoxic therapies with potential activity in leukemia. IT topotecan has shown promise in patients with recurrent or refractory CNS leukemia in a phase II study. Only 1 complication of leukoencephalopathy was reported, although the study size was small. Our patient did receive IT topotecan to prevent relapse without effect. It did not, however, exacerbate her CNS symptoms.

This case demonstrates the challenges faced in early-relapse T-ALL, illustrated by both radiographic and pathologic investigations. Clearly, novel strategies are needed in both the prevention and treatment of CNS relapse.

REFERENCES


