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High-Dose Cytarabine Neurotoxicity: MR Findings during the Acute Phase

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Summary: The authors report an acute cerebral and cerebellar syndrome in a patient treated with high-dose cytarabine. Diffuse high-intensity lesions in the central white matter on T2-weighted MR completely reversed with resolution of the clinical syndrome. Although the autopsy revealed cerebellar injury, the cerebral cortex was grossly and microscopically normal, consistent with a reversible process.

Index terms: Brain, effects of drugs on; Drugs, toxicity; Chemotherapy, complications of; Brain, magnetic resonance

High-dose systemic cytarabine (HDARAC) is now widely used in postremission acute leukemia

and refractory leukemia treatment (1). The major toxic effects of HDARAC are restricted to the bone marrow, gastrointestinal tract, and nervous system. The neurologic toxicity of HDARAC ranges from a mild peripheral neuropathy to an acute cerebral and cerebellar syndrome that may be fatal. Acute cerebral and cerebellar toxicity has been described in numerous reports, but the pathophysiology is not known (2). We present a case of acute cerebral and cerebellar neurotoxicity from HDARAC and provide magnetic resonance (MR) and pathologic comparison.

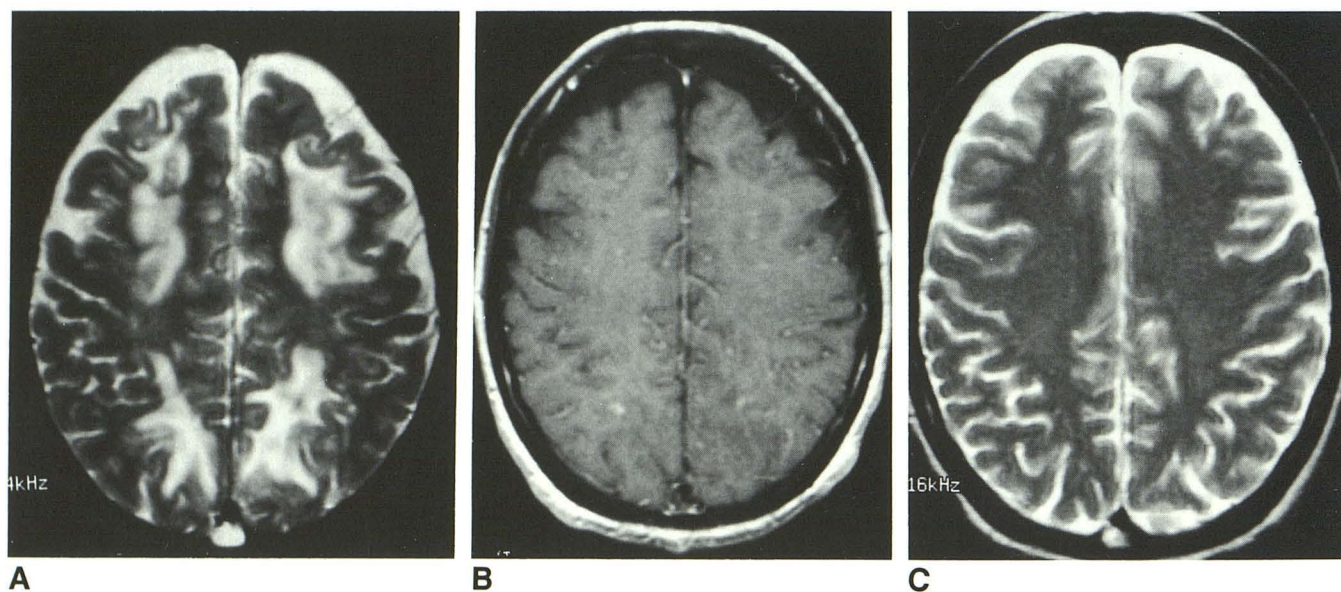


Fig. 1. A, MR imaging of the brain during an acute cerebral and cerebellar syndrome reveals patchy high intensity in the deep white matter of the frontal, occipital, and parietal lobes (2700/90/1) (TR/TE/excitations).

B, Postgadolinium image obtained at the same examination as A demonstrates punctate enhancement, most prominently in the occipital white matter (749/26).

C, MR imaging of the brain 1 month after resolution of the neurologic syndrome. No evidence of previous white matter changes is seen (fast spin echo, 3500/90).

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Case Report

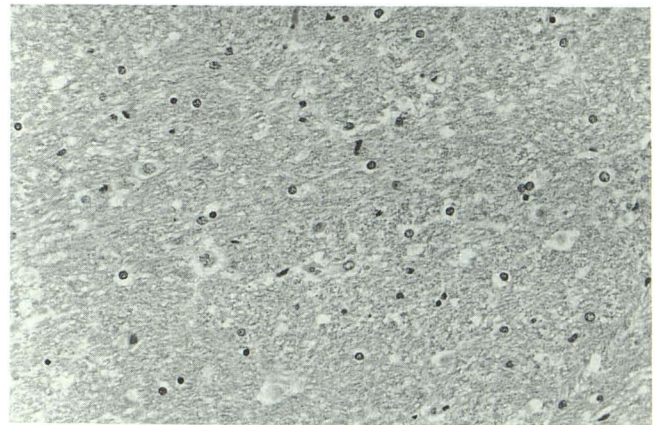
A 44-year-old woman with myelodysplasia presented with symptoms of fatigue and worsened anemia. A bone marrow biopsy revealed acute myeloid leukemia. She received induction therapy with mitoxantrone and etoposide and achieved a partial remission. Salvage therapy with HDARAC, 2 g/m² by intravenous infusion, was administered every 12 hours for 6 days. At the time of reinduction, her renal, liver, and neurologic functions were normal. She received lorazepam, prochlorperazine, and dexamethasone as antiemetic agents.

Several hours after receiving the last dose of cytarabine, the patient was disoriented. Over the next 24 hours, she became markedly ataxic. Examination revealed lethargy with poor attention and memory, dysarthria, palatal myoclonus, marked horizontal and vertical nystagmus, and dysmetria on finger-to-nose testing, and she had an ataxic gait. Her motor and sensory examination was otherwise nonfocal. Her deep tendon reflexes were symmetrically increased. The patient refused a diagnostic lumbar puncture. A MR imaging study showed patchy high intensity on the long TR images in the deep white matter of the frontal, parietal, and occipital lobes (Fig. 1A). There were punctate regions of enhancement in the occipital lobes after the admission of gadolinium (Fig. 1B). Minimal sulcal effacement consistent with edema was also seen. No cerebellar abnormalities were present. Given the clinical setting, it was felt that the white matter changes were most likely representative of an acute toxic syndrome from HDARAC and treatment was supportive.

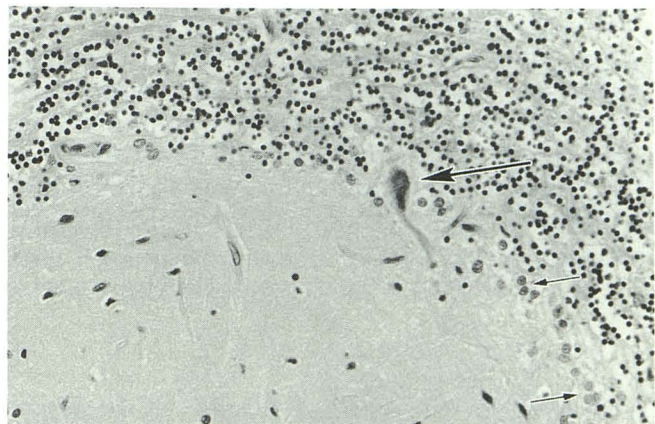
Over the next week, the patient's cerebellar dysfunction gradually improved, followed by increased attentiveness. Approximately 1 month after the acute neurologic syndrome resolved, a bone marrow biopsy documented complete remission. At the time, her neurologic examination was markedly improved, but she still had mild attention deficits and cerebellar abnormalities. One month later, her mental status and neurologic examination, including extensive cerebellar testing, were normal. A repeat MR with gadolinium enhancement revealed a complete reversal of the extensive white matter changes noted previously (Fig. 1C). The patient underwent consolidative autologous bone marrow transplantation, which was complicated by severe hemorrhagic gastritis, resulting in her death. At autopsy, the cerebral cortex and cerebellum were grossly unremarkable. Although microscopic examination of the cerebellum showed marked Purkinje cell loss and Bergmann gliosis, the cerebral white matter was unremarkable on hematoxylin and eosin-stained sections. No vascular changes or viral inclusions were identified, and special stains for fungus were negative. (Fig. 2A and B).

Discussion

Neurologic toxicity associated with cytarabine has been reported numerous times and has re-



A



B

Fig. 2. A, Microscopic examination of the cortical white matter at autopsy. No evidence of pathologic injury is noted.

B, Microscopic examination of the cerebellum shows Purkinje cell dropout (large arrow shows residual Purkinje cell) and Bergmann gliosis (small arrows).

cently been reviewed (2). The most dramatic neurologic toxicity, including seizures, cerebral dysfunction, and an acute cerebellar syndrome, has been associated with HDARAC. Patient age over 60 years, drug dose, renal and hepatic dysfunction, and the administration of neurotropic antiemetic agents have been identified as risk factors in the development of neurologic toxicity with HDARAC (2). Although other diagnoses such as progressive multifocal leukoencephalopathy, small vessel ischemia, infection, and paraneoplastic encephalomyelitis need to be considered, the onset of the typical syndrome with the administration of HDARAC, as well as the spontaneous complete clinical and radiographic resolution of the syndrome, argues for a reversible drug-related neurotoxicity.

In published reports of the acute phase of HDARAC neurotoxicity, ancillary diagnostic evaluation has often not been helpful. Electroencephalography revealing diffuse slow waves and an elevated cerebrospinal fluid protein are nonspecific findings. Computed tomography (CT) of the brain is usually normal during the acute phase of toxicity (2). A patient with cerebellar atrophy on CT performed at day 11 after the onset of dysarthria and ataxia has been reported; however, this patient had extensive pretreatment with HDARAC (3). CT and MR performed several months after the onset of symptoms may show cerebellar atrophy (4).

The patient presented here is of interest in that during the acute neurologic syndrome, an MR-documented diffuse cerebral white-matter abnormality fully reversed in the setting of normalization of the neurologic status. The unremarkable cortical pathology confirmed the reversibility of the syndrome. The cerebellum was spared radiographically despite pronounced symptoms and a

loss of Purkinje cells with reactive gliosis—the typical pathologic findings in HDARAC-related cerebellar injury (5). This case suggests that MR may demonstrate changes in patients suspected of acute neurotoxicity with HDARAC, but it needs to be studied prospectively as a diagnostic tool in patients presenting with this syndrome.

References

1. Rudnick SA, Cadman EC, Capizzi RL, et al. High dose cytosine arabinoside (HDARAC) in refractory acute leukemia. *Cancer* 1979;44:1189–1193
2. Baker WJ, Royer GL, Weiss RB Jr. Cytarabine and neurologic toxicity. *J Clin Oncol* 1991;9:679–693
3. Grossman L, Baker MA, Sutton DMC, et al. Central nervous system toxicity of high-dose cytosine arabinoside. *Med Pediatr Oncol* 1983;11:246–250
4. Miller L, Link MP, Bologna S, et al. Cerebellar atrophy caused by high-dose cytosine arabinoside: CT and MR findings. *AJR: Am J Roentgenol* 1989;152:343–344
5. Winkelman MD, Hines JD. Cerebellar degeneration caused by high-dose cytosine arabinoside: a clinicopathological study. *Ann Neurol* 1983;14:520–527