Reversible Bilateral Lateral Rectus Muscle Palsy Associated With High-Dose Cytosine Arabinoside and Mitoxantrone Therapy

GERARD J. VENTURA, MD,* MICHAEL J. KEATING, MD,* AGUSTIN M. CASTELLANOS, MD,† AND J. PETER GLASS, MD†

A patient with acute myelogenous leukemia in relapse developed reversible bilateral lateral rectus muscle palsy and cerebellar dysfunction after receiving chemotherapy with high-dose cytosine arabinoside and mitoxantrone. The differential diagnosis of this syndrome is reviewed.

Cancer **58:1633–1635, 1986.**

HIGH-DOSE CYTOSINE ARABINOSIDE (HD-Ara-C) is an effective agent in the salvage therapy of patients with relapsed or refractory acute leukemia.[1–3] Such regimens also carry a substantial risk of central nervous system toxicity. Clinically, signs of cerebellar dysfunction such as dysarthria, nystagmus, dysdiadochokinesis, and ataxia often predominate.[4–6] Mitoxantrone is a newly developed intercalating agent whose spectrum of toxicity includes myelosuppression, alopecia, stomatitis, and possibly cardiotoxicity.[7] We report a patient who developed reversible bilateral lateral rectus muscle palsy after HD-Ara-C and mitoxantrone therapy. The differential diagnosis of this lesion is reviewed and discussed.

Case Report

A thirty-four-year-old white woman, diagnosed as having acute promyelocytic leukemia in July 1983, achieved a complete remission with induction chemotherapy consisting of Adriamycin (doxorubicin), vincristine, prednisone, and Ara-C, the latter given at conventional dosage of 75 mg/m^2 daily for 7 days by continuous infusion. No acute neurological toxicities were noted. She received maintenance chemotherapy with a similar regimen until early 1985.

Relapse off chemotherapy was documented in March 1985. At that time neurologic examination revealed a mild peripheral neuropathy in the lower extremities attributed to vincristine. She received salvage therapy with Ara-C in a high-dose schedule of 3 g/m^2 over 2 hours every 12 hours for six doses, and mitoxantrone 5 mg/m^2 daily for 5 days. Intravenous fluids contained multivitamins, including thiamine.

Because of persistence of leukemia, a second course of the same regimen was administered 37 days later. On the fifth day of her second course she complained of severe dizziness, nausea and diplopia; she also had occasional episodes of positionally evoked vertigo. Neurologic examination revealed mild dysarthria with scanning and slurring of speech. There was mild confusion present on mental status examination. Moderate bilateral esotropia was present without gross nystagmus. A striking feature was bilateral weakness of the lateral rectus muscles, with inability to abduct the eyes beyond the primary position (midposition) on either side. The other cranial nerves were intact in function. Cerebellar examination revealed bilateral dysmetria and dsydiadochokinesis of the upper and lower extremities, as demonstrated on past-pointing and heel-to-shin performance. A moderate sensory-motor peripheral neuropathy of the lower extremities also was noted. Deep-tendon reflexes were within normal limits. Computerized axial tomographic (CAT) scan was normal with no evidence of leukemic parenchymal infiltration, leptomeningeal enhancement or signs of increased intracranial pressure. Cerebrospinal fluid (CSF) studies showed an opening pressure of 110 mm of water (normal, 150 mm), a protein level of 101 mg%, a glucose level of 38 mg% with a blood glucose of 88 mg%. There was one leukocyte and no erythrocytes seen on high-power field. Centrifugation and staining for malignant cells was negative. All smears and cultures for bacteria, fungus, and acid-fast bacteria were negative.

Over the next 10 days the patient's diplopia and dysmetria improved gradually. Concomitantly she demonstrated improvement and eventual resolution of the bilateral lateral rectus muscle deficit. A second lumbar puncture done 11 days after the first study showed an opening pressure of 140 mm of water, a protein level of 118 mg%, and a glucose level of 43 mg%. There were no erythrocytes or leukocytes on high-power examination, and cytologic examination again was negative. Complete remission was documented on day 28 of her second course of therapy. Neurologic examination at that time showed the pres-

From the Departments of *Hematology and †Neuro-Oncology, the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

Address for reprints: Gerard J. Ventura, MD, Department of Hematology, University of Texas M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Box 10, Houston, TX 77030.

Accepted for publication February 14, 1986.

ence of peripheral neuropathy of the lower extremities; all cerebellar signs had subsided and oculomotor function was normal.

Discussion

Although effective as salvage therapy for relapsed or refractory leukemia, regimens incorporating HD-Ara-C often produce severe central nervous system toxicity which is primarily cerebellar in character.[1,4-6] Generalized cortical dysfunction such as somnolence and mild confusion also are noted occasionally.[1,4] The dosage of Ara-C precipitating cerebellar toxicity is usually in the range of 36 g/m^2, but the syndrome has been reported with cumulative doses as low as 15 g/m^2.[2,5] Early signs of cerebellar toxicity consist of mild gait ataxia, nystagmus, or saccadic (cogwheel) pursuit movements,[6] and may progress to severe cerebellar toxicity with dysarthria, dysdiadochokinesia, and exacerbation of ataxia and oculomotor dysfunction. Although spontaneous recovery occurs within 3 weeks in most patients, some never recover.[3,4,6] Pathologically, there is a marked loss of Purkinje cells, diffuse microglial reaction, and antegrade degeneration of cerebellar corticonuclear projections.[6] Mitoxantrone is a recently developed intercalating agent, whose toxicity includes myelosuppession, stomatitis, alopecia, cardiotoxicity, and reversible abnormalities in liver function tests.[7,8] No documented neurologic dysfunction has been reported with mitoxantrone to date.

Our patient experienced severe cerebellar toxicity which was temporally related to HD-Ara-C and mitoxantrone therapy. However, in addition to well-recognized signs of cerebellar dysfunction, she also manifested bilateral esotropia with an inability to abduct either eye laterally past the primary position. Strabismus was commitant in all six cardinal positions of gaze. Clinically, the differential diagnosis of this presentation is (1) bilateral sixth cranial nerve palsy, and (2) a condition known as divergence palsy. We will briefly discuss both entities.

Paralysis of the sixth cranial nerve is the most frequent cranial nerve palsy.[9] This is thought to be due to the long and serpiginous course of the sixth cranial nerve from the brain stem to the orbit which exposes it to pathologic involvement from many contiguous structures.

Bilateral abducens palsy also is the most frequent symmetric cranial nerve deficit.[9,10] Documented etiologies of bilateral sixth cranial nerve palsy include posterior fossa tumors; aneurysms involving the posterior circulation; multiple sclerosis; toxic of inflammatory processes such as diptheria, syphilis, encephalitis, and lead poisoning; and trauma.[9,11]

Divergence paralysis or palsy, on the other hand, is a rare syndrome of paresis of conjugate gaze.[12] The classic features of this syndrome are described as sudden convergent strabismus resulting in homonymous (uncrossed) diplopia, fusion of the double image at close range to the patient, committance of stabismus on lateral gaze in either direction (the amount of esotropia remains the same), normal ocular rotations and impairment of the fusional amplitude of divergence.[12] The main characteristic differentiating the two entities is said to be the degree of committance. With divergence palsy, the amount and type of deviation of gaze observed is the same in all six cardinal directions and therefore is considered "committant." Bilateral six cranial nerve palsy, on the other hand is "noncommittant" in that the strabismus is more marked in one of the cardinal directions of gaze than it is in the other vectors. Frequently, this difference is taken as the sole differentiating diagnostic point.[11,12] However, there often is considerable overlap in the actual clinical presentation of these conditions.[12,13] The underlying causes of divergence palsy and of bilateral sixth cranial nerve palsy are similar. Therefore, some investigators believe that the two clinical entities are inseperable and that all cases of divergence palsy are in reality cases of bilateral sixth cranial nerve palsy.[11]

Although the underlying mechanism for the bilateral rectus palsy in this patient is speculative, its occurrence in the setting of cerebellar dysfunction is significant. It is well known that degenerative, neoplastic or vascular lesions in the cerebellum may be associated with a variety of oculomotor disorders, including disorders of conjugate gaze.[12-15] Divergence palsy has been documented in patients with vascular accidents who develop signs of cerebellar dysfunction.[12] A syndrome of ataxia, nystagmus and palsies of both convergence and divergence (the latter developing into a unilateral sixth cranial nerve palsy) also has been reported in patients receiving 5-fluorouracil[13] a drug known to cause cerebellar toxicity.[16,17] The occurrence of similar clinical presentations in apparently diverse etiologic settings (*i.e.*, drug toxicity, vascular accidents) may implicate as yet undetermined neurophysiologic "common pathways."

The appearance of frank bilateral lateral rectus palsy in our patient prompted a search for other etiologies, most notably leukemic meningitis or other causes of increased intracranial pressure. The only positive finding was a moderate elevation of the CSF protein content, a finding previously reported with HD-Ara-C neurotoxicity.[18] The negative neurologic work-up for malignant or inflammatory conditions, the temporal relationship between the administration of HD-Ara-C and symmetrical sixth nerve palsy, the simultaneous presence of cerebellar toxicity and the ultimate resolution of both sixth cranial nerve and cerebellar dysfunction strongly support the possible etiologic role of HD-Ara-C as a cause of the neurologic deficits. The possibility of a synergistic mechanism of neu-

rotoxicity with mitoxantrone is less likely but cannot be discounted or disproved currently.

REFERENCES

1. Rudnick SA, Cadman EC, Capizzi RL, Skeel RT, Bertino JR, McIntosh S. High-dose cytosine arabinoside (HD-Ara-C) in refractory acute leukemia. *Cancer* 1979; 44:1189–1193.
2. Early AP, Priesler HD, Slocum H, Rustum YM. A pilot study of high dose 1-B-D-arabinofuranosylcytosine for acute leukemia and refractory lymphoma: Clinical response and pharmacology. *Cancer Res* 1982; 42:1587–1594.
3. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C, Herzig GP. High dose cytosine arabinoside therapy for refractory leukemia. *Blood* 1983; 62:361–369.
4. Grossman L, Baker MA, Sutton DMC, Deck JHN. Central nervous system toxicity of high-dose cytosine arabinoside. *Med Pediatr Oncol* 1983; 11:246–250.
5. Salinsky MC, Levine RL, Aubuchon JP, Schulta HS. Acute cerebellar dysfunction with high-dose Ara-C therapy. *Cancer* 1983; 51:426–429.
6. Winkelman MD, Hines JD. Cerebellar degeneration caused by high-dose cytosine arabinoside: A clinicopathological study. *Ann Neurol* 1983; 14:520–527.
7. Nathanson L. Mitoxantrone. *Cancer Treat Rev* 1984; 11:289–293.
8. Paciucci PA, Ohnuma T, Cuttner J, Holland JF. Mitoxantrone in refractory acute leukemia. Proceedings of the 13th International Congress of Chemotherapy, part 212, 1983; 43–46.
9. Rush JA, Younge BR. Paralysis of cranial nerves III, IV and VI. Cause and prognosis in 1,000 cases. *Arch Ophthalmol* 1981; 99:76–79.
10. Schrader EC, Schlezinger NS. Neuroophthalmologic evaluation of abducens nerve paralysis. *Arch Ophthalmol* 1969; 63:84–91.
11. Jampolsky A. Ocular divergence mechanisms. *Trans Am Ophthalmol Soc* 1970; 68:730–822.
12. Cunningham RD. Divergence paralysis. *Am J Ophthalmol* 1972; 14:630–633.
13. Bixenman WW, Nicholls JV, Warwick OH. Oculomotor disturbances associated with 5-fluorouracil chemotherapy. *Am J Ophthalmol* 1977; 83:789–792.
14. Leigh RJ, Zee DS. The Neurology of Eye Movements. Philadelphia: FA Davis, 1982.
15. Gilman S, Bloedel JR, Lechtenberg R. Disorders of the Cerebellum. Philadelphia: FA Davis, 1981; 215–218.
16. Moertel CG, Reitmeier CG, Bolton CF, Shorter RG. Cerebellar ataxia associated with fluorinated pyrimidine therapy. *Cancer Chemother* 1964; 41:15–18.
17. Riehl JL, Brown WJ. Acute cerebellar syndrome secondary to 5-fluoruracil therapy. *Neurology* 1964; 14:254–257.
18. Barnett MJ, Richards MA, Ganesan TS *et al.* Central nervous system toxicity of high-dose cytosine arabinoside. *Semin Oncol* 1985; (Suppl 3) 12:227–232.