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RAPID VISION LOSS ASSOCIATED WITH FLUDARABINE ADMINISTRATION IN THREE PATIENTS

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Abstract

Purpose—The purpose of this study was to report the clinical and pathologic findings of three cases of rapid vision loss associated with fludarabine toxicity.

Methods—A retrospective, single-center case series was conducted. Autopsies of the eyes from three cases were performed.

Results—A 23-year-old man (Case 1) with systemic lupus erythematosus developed rapid and severe vision loss, generalized neurologic decline, and eventual death after administration of fludarabine before stem cell transplantation. A 48-year-old woman (Case 2) and a 60-year-old man (Case 3), both with metastatic melanoma, had similar courses after receiving fludarabine as part of a preparatory regimen before adoptive cell therapy. Fundus examination showed punctuate yellow flecks in the macula after visual decline in two cases. In all three cases, serum antiretinal antibodies were negative before and after treatment; electrophysiological testing showed markedly decreased B-waves; and pathologic analysis showed loss of retinal bipolar and ganglion cells, gliosis within the retina and optic nerve, and optic nerve atrophy.

Conclusion—Fludarabine toxicity can result in severe vision loss attributable to damage to retinal bipolar and ganglion cells. Although effective treatments are not known, care should be taken to consider fludarabine toxicity in patients who present with vision loss ~1 month after treatment.

Keywords

fludarabine; purine analog; ocular toxicity; ophthalmic pathology; adoptive cell therapy; stem cell transplantation

Fludarabine phosphate is a nucleoside analog with demonstrated antitumor activity used to treat hematologic malignancies and to achieve immunosuppression in conditioning regimens for stem cell transplantation and cancer therapy. Fludarabine toxicity to the central nervous system (CNS) has been described with moderate frequency at high doses and rarely at standard

(low) doses.¹ It presents as a diffuse, necrotizing leukoencephalopathy.² Vision loss associated with this event has been attributed to severe white matter changes in the occipital cortex.^{2,3} We describe three patients who had total vision loss after receiving standard doses of fludarabine: one with systemic lupus erythematosus and two with malignant melanoma.

Case Report

Case 1

A 23-year-old man with systemic lupus erythematosus received an autologous stem cell transplant after failing treatment with multiple chemotherapeutic agents. The preparatory regimen included rituximab (750 mg/m²), fludarabine (30 mg/m² for 4 days), and cyclophosphamide (1.2 g/m for 4 days). He had dimming vision in both eyes on day 28 posttransplant.

Evaluation revealed vision of 20/50 in the right eye and 20/32 in the left eye with normal dilated examination. Dark adaptation showed a markedly delayed rodcone break. Visual fields showed generalized depression. The vision deteriorated to 20/500 in the right eye and 20/320 in the left eye over the ensuing 3 weeks. Electroretinography showed a preserved A-wave and reduced B-wave, an “electronegative” pattern, suggesting bilateral, symmetric retinopathy with compromised bipolar cell function but preserved photoreceptor function (Figure 1).

The diagnosis of autoimmune retinopathy was entertained, and the patient's serum was analyzed for antiretinal antibodies to normal human retina, which were negative. The patient was treated with intravenous corticosteroids and plasmapheresis. Magnetic resonance imaging of the brain showed nonenhancing white matter changes in the parietal and frontotemporal regions (Figure 2A). The vision deteriorated to no light perception in both eyes during the next 3 weeks. Examination showed punctate white intraretinal flecks in the central macula of both eyes (Figure 2B). Visually evoked potentials were reduced. The patient developed confusion, which progressed to mental obtundation. Brain biopsy showed chronic demyelination and gliosis. Four months later, he was diagnosed with communicating hydrocephalus, which progressed to cerebellar herniation and death. He had completed fludarabine therapy 128 days prior.

Autopsy of the brain showed diffuse, multifocal encephalomyelopathy with demyelination. Ocular autopsy showed bilateral optic nerve cavernous atrophy (Figure 2C) in addition to retinal changes consisting of extensive loss of ganglion cells, partial loss of bipolar cells, generalized retinal edema (Figure 2D), and focal retinal hemorrhages. Figure 2E shows the retinal architecture of a normal adult macula for purposes of comparison.

Case 2

A 48-year-old woman with metastatic melanoma refractory to previous treatment entered an adoptive T-cell therapy protocol, which included 1200 cGy total body irradiation, fludarabine (25 mg/m for 5 days), cyclophosphamide (60 mg/kg for 2 days), and systemic interleukin-2. She experienced a dramatic partial response but relapsed 6 months later. She underwent another course of adoptive T-cell therapy using the same doses of fludarabine, cyclophosphamide, and interleukin-2 as tolerated without total body irradiation. Approximately 4 weeks later, she reported decreased vision measuring 20/640 in the right eye and 20/800 in the left eye. Dilated eye examination was normal. Visual fields showed generalized depression. Electroretinography showed markedly reduced B-waves and modestly reduced A-waves bilaterally (Figure 1B).

The diagnosis of melanoma-associated retinopathy was considered, and the patient was empirically treated with plasma exchange, IgG, and rituximab. During the next 2 days, she

developed lower extremity numbness and weakness. Magnetic resonance imaging of the CNS showed white matter changes in the periventricular regions (Figure 3A), the cervical spine, and thoracic spinal cord. Cerebrospinal fluid analysis was unremarkable. She received high-dose systemic corticosteroids. Vision decreased to no light perception and her neurologic deficits progressed. Repeat dilated examinations showed punctuate yellow flecks in the retina of both eyes (Figure 3B). The patient died of progressive melanoma 52 days after her last dose of fludarabine.

Brain autopsy showed diffuse vacuolation of the cerebral white matter, foamy histiocyte infiltration, and gliosis, particularly in the occipital lobe. Similar changes were observed in the splenium, brain stem, optic chiasm, and posterior columns of the spinal cord. Autopsy of the eyes showed marked gliosis of the optic nerves (Figure 3C) with infiltration by numerous macrophages (CD68-positive cells; Figure 3D), extensive loss of ganglion cells, partial loss of bipolar cells in the macula (Figure 3E), and retinal gliosis (Figure 3F).

Case 3

The sequence of events involving this 60-year-old man with metastatic melanoma mirrored those described in Case 2, including electroretinography (Figure 1C) and magnetic resonance imaging findings (Figure 4A). His treatment consisted of 1 cycle of fludarabine (25 mg/m² for 5 days) and cyclophosphamide (60 mg/kg for 2 days) in addition to cultured T cells. He received no interleukin-2 and no radiation. On ocular examination, he manifested retinal pigment mottling, which was likely present before treatment (Figure 4B). Shortly after visual decline, intravitreal and sub-Tenon Kenalog injections were administered in the left and right eye, respectively, without improvement in vision. He died of progressive melanoma 67 days after treatment with fludarabine. His last recorded vision was no light perception in both eyes. Ocular pathology resembled that of the other two cases with cavernous optic nerve atrophy (Figure 4C) and profound loss of ganglion cells and partial loss of bipolar cells (Figure 4D).

Discussion

In phases I and II trials of fludarabine, delayed CNS toxicity was identified, ranging from blindness and paralysis to coma and death.^{1,3} In solid tumor trials, 36% of patients who received doses >96 mg/m² for 5 days to 7 days experienced CNS toxicity, with no patients experiencing toxicity at doses of <80 mg/m² for 5 days.¹ In reviewing the neurotoxicity of purine analogs, Cheson et al⁴ reported the risk of neurotoxicity to be ~1% at currently recommended (low) doses. Factors that predispose patients to CNS toxicity have not been identified.

In our patients, dramatic neurologic deficits developed ~1 month after fludarabine therapy (Figure 5). These manifested initially as profound rapid vision loss and then generalized CNS dysfunction and death 1 month to 3 months thereafter. Rapid clinical deterioration correlated with the extensive CNS atrophy seen on postmortem examination. Two of the patients described here have been briefly described in a recent review of the ocular toxicity of fludarabine, which represents the only report in the literature of which we are aware illustrating the ocular pathology in this condition.⁵ Our present case series depicts the ocular pathology in greater detail and compiles the diagnostic ocular findings associated with fludarabine toxicity.

Antiretinal antibodies were tested for each of our patient's sera collected before and after administration of fludarabine using indirect immunohistochemical techniques.⁶ These were found to be negative, further supporting the diagnosis of toxic rather than cancer-, melanoma-, or autoimmune-associated retinopathy. This also suggests that irreversible blindness from fludarabine toxicity might result from direct neurotoxicity to both the CNS white matter, as previously reported, and to retinal ganglion and bipolar cells, perhaps by a similar mechanism, directly targeting central neuronal cells.⁵ This might be related to the intraretinal flecks that

developed in two of the three cases reported here, although we do not know the significance of this finding.

There is substantial evidence that fludarabine potentiates the activity of other antitumor agents such as cisplatin, cytarabine, mitoxantrone, and cyclophosphamide. The possible contribution of these agents toward toxicity has been studied. Although there are reports of a higher incidence of systemic complications with combination therapy compared with monotherapy such as increased myelosuppression, ocular toxicity is not among the complications discussed in the literature.^{5,7} Of the other agents included in our patients' conditioning regimens, only cyclophosphamide has been associated with ocular toxicity in the literature. The most commonly described findings include conjunctival chemosis and ocular surface dryness.⁸ Vision loss is seldom reported and is associated with peripheral and diffuse central neuropathies with-out mention of damage to the retinal bipolar or ganglion cells.⁹

Clinicians must consider the diagnosis of fludarabine toxicity in patients who develop abrupt loss of vision several weeks after treatment with fludarabine, even at conventional doses. Currently, we have no evidence to suggest that patient outcome would be improved by instituting an ocular or systemic screening regimen aimed at detecting neurotoxicity at its earliest stage. The incidence is low, and there is no known treatment to halt the rapidly progressive neurologic deterioration that occurs with this condition. We recommend counseling patients about the potential neurotoxic effects of fludarabine in addition to the other possible adverse effects. Further investigation into the mechanism of fludarabine toxicity and potential interventions is warranted.

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References

1. Chun HG, Leyland-Jones BR, Caryk SM, Hoth DF. Central nervous system toxicity of fludarabine phosphate. *Cancer Treat Rep* 1986;70:1225–1228. [PubMed: 2428492]
2. Spriggs DR, Stpa E, Mayer RJ, Schoene W, Kufe DW. Flu darabine phosphate infusions for the treatment of acute leukemia: phase I and neuropathological study. *Cancer Res* 1986;46:5953–5958. [PubMed: 2428488]
3. Warrell RP Jr. Berman E. Phase I and II study of fludarabine phosphate in leukemia: therapeutic efficacy with delayed central nervous system toxicity. *J Clin Oncol* 1986;4:74–79. [PubMed: 2416889]
4. Cheson BD, Vena DA, Foss FM, Sorensen JM. Neurotoxicity of purine analogs: a review. *J Clin Oncol* 1994;12:2216–2228. [PubMed: 7931492]
5. Ding X, Herzlich A, Bishop RJ, Tuo J, Chan C. Ocular toxicity of fludarabine, a purine analog. *Expert Rev Ophthalmol* 2008;3:97–108. [PubMed: 18461151]
6. Sen HN, Chan CC, Caruso RC, Fariss RN, Nussenblatt RB, Buggage RR. Waldenström's macroglobulinemia-associated retinopathy. *Ophthalmology* 2004;111:535–539. [PubMed: 15019332]
7. Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia. *J Clin Oncol* 2007;25:793–798. [PubMed: 17283364]
8. Loprinzi CL, Love RR, Garrity JA, Ames MM. Cyclophosph amide, methotrexate, and 5-fluorouracil (CMF)-induced oculartoxicity. *Cancer Invest* 1990;8:459–465. [PubMed: 2124943]
9. Rizzierin DA, Johnson JL, Niedzwiecki D, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma. *Cancer* 2004;100:1438–1448. [PubMed: 15042678]

Fig. 1. Full-field electroretinography elicited by International Society for Clinical Electrophysiology of Vision standard white flash after dark adaptation. Four superimposed tracings (**A–D**) correspond to patients 1, 2, and 3 and a control subject, respectively. Preserved A-wave and reduced B-wave are seen in the affected patients.

Top

Fig. 2. Patient 1. **A.** Magnetic resonance imaging with periventricular white matter changes. **B.** Fundus photograph showing punctate yellow deep intraretinal flecks not present on initial examination. **C.** Photomicrograph of the optic nerve showing generalized atrophy of the neural fiber bundles (seen in purple) with loss of neuronal elements, vacuolization, and thickening of the pial septae (seen in pink). **D.** Photomicrograph of the macula showing loss of ganglion cells, partial loss of bipolar cells, and edema of the inner nuclear layer. **E.** Photomicrograph of macula of healthy adult control for comparison. (**C–E.** hematoxylin and eosin, $\times 100$).

Top

Fig. 3. Patient 2. **A.** Magnetic resonance imaging with periventricular white matter changes. **B.** Fundus photograph showing punctate yellow deep intraretinal flecks not present on initial examination. **C.** Glial fibrillary acidic protein (GFAP) staining of the optic nerve showing marked gliosis. **D.** The optic nerve stains positive for CD68, indicating infiltration by microglial cells or macrophages. **E.** Photomicrograph of the macula showing loss of ganglion cells, partial loss of bipolar cells, and edema of the inner nuclear layer. **F.** GFAP staining of the macula showing retinal gliosis (**C–F.** Avidin-biotin complex immunoperoxidase, $\times 100$; **E.** hematoxylin and eosin, $\times 100$).

Fig. 4.

Patient 3. **A.** Magnetic resonance imaging with periventricular white matter changes. **B.** Fundus photograph showing macular mottling believed to predate fludarabine treatment and a small intraretinal hemorrhage (no baseline photograph for comparison). **C.** Photomicrograph of the optic nerve showing generalized atrophy of the neural fiber bundles with loss of neuronal elements, vacuolization, and thickening of the pial septae. **D.** Photomicrograph of the macula showing loss of ganglion cells, partial loss of bipolar cells, and edema of the inner nuclear layer (**C** and **D.** hematoxylin and eosin, $\times 100$).

Fig. 5.

Plot of visual acuity versus time; time zero represents completion of fludarabine treatment. Both eyes of patients 1 and 2 are shown. Patient 3 is not shown, because no baseline visual acuity data were available and the patient had experienced vision loss before our examinations. The visual acuity of a fourth patient who died of fludarabine toxicity at our institution is also shown (noted as PT4). This patient was not described here because pathology was not obtained. Note the similar timing of visual decline in all affected eyes, occurring ~30 days to 40 days posttreatment.