• Letter to the Editor •

Actinomycin D-induced bilateral optic nerve atrophy: a case report

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Dear Editor,

We report a rare case of bilateral central vision loss and color vision abnormalities after actinomycin D chemotherapy for a hydatidiform mole. Toxic optic neuropathy (TON) refers to a spectrum of disorders characterized by bilateral visual loss, papillomacular bundle damage, central or cecocentral scotoma, and color vision abnormalities[1]. The optic nerve is highly vulnerable to toxic injury from drugs, heavy metals, organic solvents, alcohols, and tobacco components. Several chemotherapeutic agents, including vincristine, cisplatin, methotrexate, cyclosporine, docetaxel, and interferon-α, have also been implicated[1-3]. The precise mechanism of drug-induced TON remains uncertain, but proposed pathways include vascular dysregulation leading to ischemic optic neuropathy and direct neurotoxic effects causing axonal injury[3].

Actinomycin D is a chemotherapeutic agent widely used in the treatment of neuroblastoma, testicular cancer, rhabdomyoma, Hodgkin lymphoma, and gestational trophoblastic disease such as hydatidiform mole[4]. Severe adverse events, including bone marrow suppression, digestive tract toxicity, and aphthous, are well recognized, whereas less common toxicities are often underappreciated. To date, optic neuropathy associated with actinomycin D has not been previously reported. Given its widespread use, raising awareness of this rare but potentially vision-threatening complication is essential. Reporting such cases not only broadens the current understanding of actinomycin D-related adverse events but also emphasizes the importance of considering TON in patients presenting with progressive, unexplained bilateral vision loss or color vision abnormalities during chemotherapy. The present case described bilateral optic nerve damage and functional loss after actinomycin D chemotherapy. Written informed consent was obtained from the patient, and this case study is in accordance with the tenets of the Declaration of Helsinki.

CASE PRESENTATION

Patient History and Clinical Examination A 32-year-old female patient presented with bilateral central vision loss and color vision abnormalities that persisted for 2mo. She presented to our hospital one month after discontinuation of 6mo of actinomycin D chemotherapy for a hydatidiform mole. Her symptoms commenced after 5mo of actinomycin D chemotherapy. Her best-corrected visual acuity (BCVA) was 20/400 both eyes (OU). Pupillary light reflexes were delayed, and the relative afferent pupillary defect was negative. Slit-lamp examination revealed no inflammation in the anterior or posterior segments. Fundus examination revealed temporal pallor of bilateral optic discs with clear margins and normal macula (Figure 1A, 1B). Visual-evoked potentials (VEP) were severely delayed with decreasing amplitudes in both eyes (Figure 1C). Ganglion cell loss at the fovea was found by optical coherence tomography (OCT; Figure 1F-1H). Humphrey visual field tests showed bilateral constricted visual fields (Figure 1I, 1J). Macular OCT (Figure 1D, 1E), ultra-widefield fundus photograph, and autofluorescence images showed no positive lesions. Electroretinography and magnetic resonance imaging (MRI) of the orbit and brain were unremarkable. Hematology, including rheumatology, infectious disease panels, retinal autoantibodies, myelin oligodendrocyte glycoprotein (MOG) and aquaporin 4 (AQP4) antibodies, and genetic testing were normal. The patient had no prior history of ocular disease, ocular surgery, or trauma. Apart from hydatidiform mole, she denied any other systemic

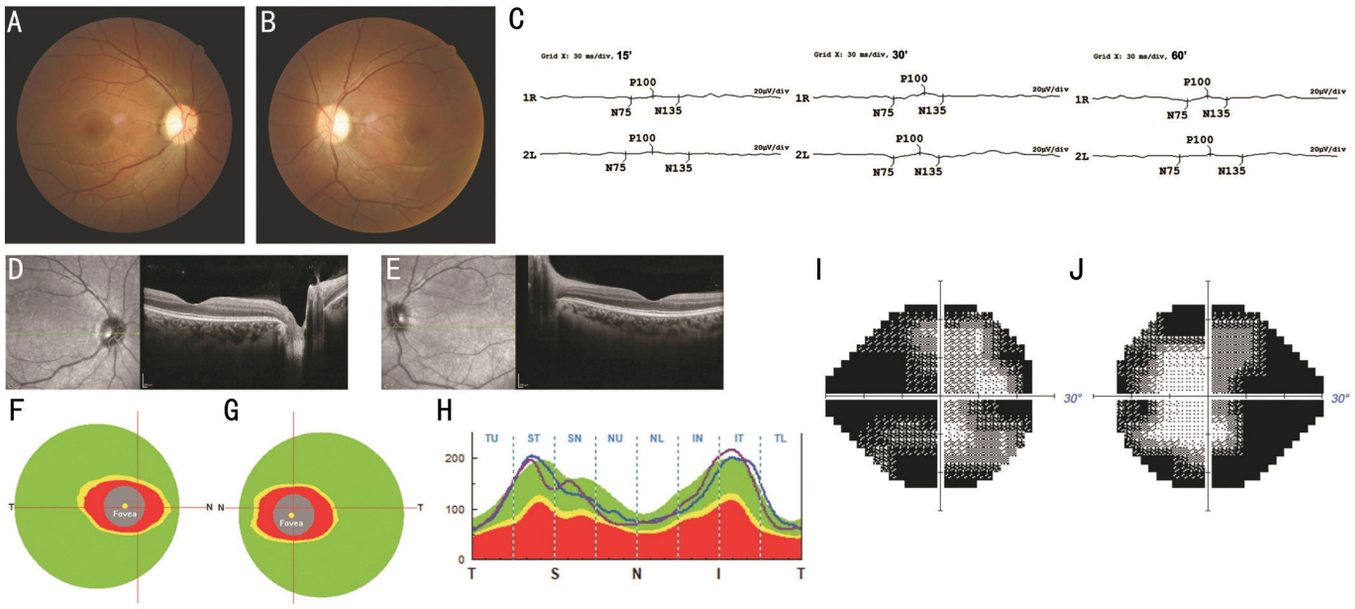

Figure 1 Structural optic nerve damage and visual function loss in both eyes after 1mo after discontinuation of 6mo of actinomycin D chemotherapy Fundus photography and macular optical coherence tomography (OCT) revealed temporal pallor of bilateral optic discs with clear margins (A, B) and normal macula (D, E). Visual-evoked potentials were severely delayed with decreasing amplitudes in both eyes (C). Ganglion cell loss at the fovea was found (F–H). Humphrey visual field tests showed bilateral constricted visual fields (I, J).

diseases, including cardiovascular, metabolic, autoimmune, or infectious conditions. Following completion of chemotherapy for hydatidiform mole, she underwent a comprehensive systemic evaluation at the general hospital, which confirmed stable overall health without evidence of active disease or systemic complications.

Management Following discontinuation of actinomycin D, the patient was initiated on neurotrophic and antioxidant therapy, including citicoline, ginkgo biloba extract, mecobalamin (methylcobalamin), and idebenone. Citicoline was administered to enhance neuronal metabolism and membrane repair, while ginkgo biloba extract was used to improve microcirculation and reduce oxidative stress. Mecobalamin, a biologically active form of vitamin B12, was given to promote axonal regeneration, and idebenone was prescribed as a potent antioxidant to support mitochondrial function and protect retinal ganglion cells. This combined regimen aimed to stabilize visual function and facilitate optic nerve recovery.

Follow-up After 8mo after discontinuing actinomycin D chemotherapy, her BCVA was 20/400 right eye (OD) and improved to 20/200 left eye (OS). Loss of superior and inferior arcuate fibers was observed on fundus photographs (Figure 2A, 2B). Thinning of retinal nerve fiber layer (RNFL), ganglion cell loss, and visual field defects were aggravated (Figure 2C-2G). After 14mo after discontinuation, her BCVA stabilized at 20/400 OU. RNFL thinning, ganglion cell loss, and visual field defects were stable with a slight decline (Figure 3).

DISCUSSION

The patient presented with bilateral optic nerve damage and functional loss after chemotherapy. Despite optic atrophy, temporal pallor of the bilateral optic discs, her normal hematology, and the lack of risk factors differentiated this case from ischemic optic neuropathy. Syphilitic optic atrophy was ruled out after examining possible infectious markers. No previous history of vision loss before chemotherapy and genetic testing could exclude hereditary optic neuropathy. Negative MOG and AQP4 antibodies and MRI excluded optic nerve and intracranial space-occupying lesions. The normal retinas and absence of retinal autoantibodies distinguished it from paraneoplastic syndrome, which often affects the outer retina. Therefore, TON was a possible cause of optic atrophy based on the patient's history of actinomycin D chemotherapy.

Bilateral constricted visual fields, visual loss, abnormal color vision, and VEP indicating optic nerve damage, but with a normal retinal appearance, have been reported in drug-induced TON. The constricted visual fields observed in our patient are similar to those seen in a 45-year-old man diagnosed with TON induced by a quinine overdose, as described in Freund *et al*'s study[2]. Rodríguez-Marco *et al*[5] presented a case of a 59-year-old woman diagnosed with multi-drug-resistant tuberculosis who developed bilateral severe concentric visual field constriction, visual loss, and color vision abnormalities induced by ethambutol and isoniazid. In Mwanza *et al*'s[6] study, thirteen patients presented with bilateral concentric constriction, the most frequent visual field defect, qualifying for the diagnosis of cyanide-induced optic neuropathy in Konzo. Pakravan *et al*[7] described a case of optic neuropathy in a patient on sirolimus, whose visual field revealed advanced

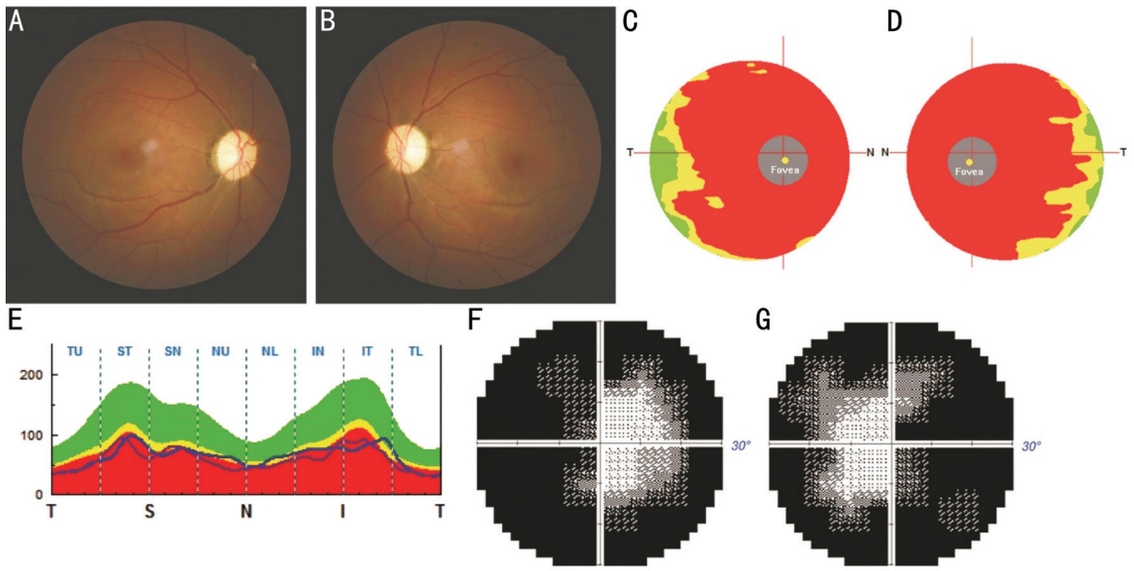

Figure 2 Worsening structural optic nerve damage and visual function loss in both eyes at 8mo after discontinuing actinomycin D chemotherapy Bilateral loss of superior and inferior arcuate fibers was observed on fundus photographs (A, B). Ganglion cell loss (C, D), RNFL thinning (E), and visual field defects (F, G) were aggravated. RNFL: Retinal nerve fiber layer.

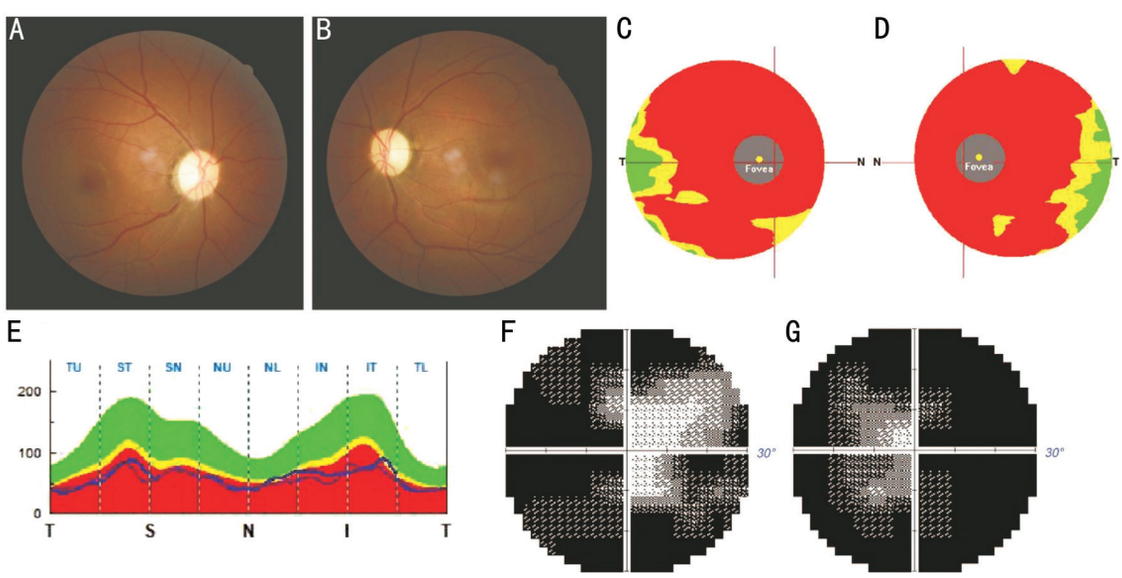

Figure 3 Stable structural optic nerve damage and visual function loss in both eyes at 14mo after discontinuing actinomycin D chemotherapy Bilateral arcuate fiber loss was stable on fundus photographs (A, B). Ganglion cell loss (C, D), RNFL thinning (E), and visual field defects (F, G) were stable with a slight decline. RNFL: Retinal nerve fiber layer.

constriction and depression in both eyes.

Actinomycin D is a chemotherapeutic agent in treating neuroblastoma, testicular cancer, rhabdomyoma, Hodgkin lymphoma, as well as hydatidiform mole[4]. It directly enters DNA base pairs to interfere with the transcription process and prevent mRNA formation[8], thereby inhibiting DNA and protein synthesis. According to the National Comprehensive Cancer Network Clinical Practice Guidelines for Gestational Trophoblastic Neoplasia, 2021, the treatment of a hydatidiform mole involves administration of actinomycin D at a dose of 10-12 μg/kg intravenously every 5d per 2wk. Four to eight cycles are usually scheduled without an absolute upper limit for clinical cumulative dose. The patient underwent 12 cycles at a safe dose (10 μg/kg). Severe adverse events associated with actinomycin D include bone marrow suppression, digestive tract toxicity, and aphthous. Common side effects included alopecia, skin rashes, liver dysfunction, and phlebitis. To our knowledge, optic neuropathy has not been reported. We report bilateral optic atrophy after 5mo of actinomycin D chemotherapy. TON represents a rare but clinically significant adverse effect of certain chemotherapeutic agents. In the present case, the close temporal association between actinomycin D administration and the onset of bilateral visual loss, followed by subsequent stabilization after drug discontinuation, strongly

suggests a causal relationship. We suspect that this was associated with the potential long exposure or sensitivity to actinomycin D toxicity, although there is no direct evidence for these possibilities. Comprehensive systemic, serological, genetic, and neuroimaging assessments effectively excluded other potential etiologies, including ischemic, infectious, hereditary, autoimmune, and paraneoplastic optic neuropathies. In addition to inhibiting RNA and protein synthesis, actinomycin D also acts as a nonspecific metabolic poison. Actinomycin D blocks the translational repressor and degrader of glutamine synthetase messenger in the embryonic neural retina, eliciting deleterious effects on oxidative respiration, adenosine triphosphate (ATP) pool size, and polyribosome content[9-10]. Furthermore, actinomycin D reduces the acid-soluble material conveyed from the optic nerve to the tectum[11]. This pronounced effect could be correlated with a higher rate of RNA synthesis in neural cells. In addition, the intracranial injection of actinomycin D elicited extensive vacuole formation and enlargement of the extracellular space within the myelin sheath of the optic nerve[12]. Myelinic vacuoles were preceded by nuclear and cytoplasmic changes in oligodendrocytes, which included nucleolar segregation, disaggregation, and diminution in number of ribosomes. These findings suggest potential pathways of actinomycin D-related neurotoxicity.

Clinically, however, actinomycin D has not previously been reported to cause optic neuropathy, making it difficult to delineate the underlying mechanism from a single case. Evidence from other chemotherapeutic agents, particularly taxanes such as docetaxel and paclitaxel, suggests two possible pathways: vascular dysregulation with vasospasm leading to ischemic injury[3], and direct neurotoxicity through microtubule aggregation that disrupts axonal transport and causes neuropathy[3]. Given that taxanes can cross the blood-brain barrier, similar axonal injury in the optic nerve appears biologically plausible[3]. Although the precise mechanism in our patient remains uncertain, these hypotheses provide reasonable explanations for actinomycin D-induced optic neuropathy.

In conclusion, actinomycin D is commonly used worldwide to treat gestational trophoblastic neoplasia. Rare conditions, such as actinomycin D-induced optic neuropathy, should be considered in the differential diagnosis of patients presenting with progressive, unexplained bilateral vision loss or color vision abnormalities during chemotherapy. Early recognition and timely ophthalmic evaluation are crucial to prevent permanent visual impairment in these patients.

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REFERENCES

1 Grzybowski A, Zülsdorff M, Wilhelm H, *et al*. Toxic optic neuropathies: an updated review. *Acta Ophthalmol* 2015;93(5):402-410.

2 Freund PR, Wright T, Margolin EA. Toxic optic neuropathy from quinine overdose. *J Neuro Ophthalmol* 2020;40(2):258-261.

3 Moloney TP, Xu W, Rallah-Baker K, *et al*. Toxic optic neuropathy in the setting of docetaxel chemotherapy: a case report. *BMC Ophthalmol* 2014;14:18.

4 Wang QY, Fu J, Hu LN, *et al*. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. *Cochrane Database Syst Rev* 2017;9(9):CD007289.

5 Rodríguez-Marco NA, Solanas-Alava S, Ascaso FJ, *et al*. Severe and reversible optic neuropathy by ethambutol and isoniazid. *An Sist Sanit Navar* 2014;37(2):287-291.

6 Mwanza JC, Tshala-Katumbay D, Kayembe DL, *et al*. Neuro-ophthalmologic findings in konzo, an upper motor neuron disorder in Africa. *Eur J Ophthalmol* 2003;13(4):383-389.

7 Pakravan P, Miri S, Lam BL. Sirolimus induced toxic optic neuropathy. *Int Med Case Rep J* 2023;16:329-332.

8 Satange R, Chang CC, Li LY, *et al*. Synergistic binding of actinomycin D and echinomycin to DNA mismatch sites and their combined anti-tumour effects. *Nucleic Acids Res* 2023;51(8):3540-3555.

9 Jones RE, Moscona MH, Moscona AA. Induction of glutamine synthetase in cultures of embryonic neural retina. Comments on the use of actinomycin D. *J Biol Chem* 1974;249(18):6021-6023.

10 Schwartz RJ. Control of Glutamine synthetase synthesis in the embryonic chick neural retina a caution in the use of actinomycin D. *J Biol Chem* 1973;248(18):6426-6435.

11 Ingoglia NA, Grafstein B, McEwen BS. Effect of actinomycin-D on labelled material in the retina and optic tectum of goldfish after intraocular injection of tritiated RNA precursors. *J Neurochem* 1974;23(4):681-687.

12 Rizzuto N, Gambetti PL. Status spongiosus of rat central nervous system induced by actinomycin D. *Acta Neuropathol* 1976;36(1):21-30.