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Sir,
Urrets-Zavalia syndrome as a complication of ocular hypotonia due to intravenous cidofovir treatment

Cidofovir (HPMPC) is widely used for the treatment of CMV retinitis and is also effective against VZV and HSV.[1]

This treatment can be responsible for two ocular side effects: anterior uveitis and severe and prolonged ocular hypotony.[1,2] Ocular hypotony can be irreversible despite specific treatment with poor visual prognosis.[1,2] The suspected physio-pathogenic mechanism of this complication is a direct toxicity of cidofovir on the ciliary body.[2,3]

Case report

A 67-year-old female was referred for ophthalmologic monitoring while receiving intravenous cidofovir treatment initiated for extensive recurrent laryngotracheal papillomatosis diagnosed in 2003. Her past medical history included hyperthyroidism, asthma, hiatus hernia, and ovarian cysts. She had no history of diabetes mellitus and did not receive any ocular therapy. Between April 2004 and October 2005, she underwent three laser excisions with intralesional injections of 2 ml of cidofovir (75 mg/ml). She was greatly improved with a normal tracheal appearance for 5 years. A recurrence occurred requiring two laser excisions with intralesional injections in 2010. In December 2011, this laryngotracheal papillomatosis caused supraglottic respiratory signs. Due to the extension of the lesion, it was decided to treat this patient with intravenous (IV) cidofovir (dose: 4 mg/kg) every two weeks instead of intralesional injections or aerosol.

She was first examined in Ophthalmology two weeks after the second IV cidofovir injection. Her best corrected visual acuity (BCVA) was 20/20 RE and 20/25 LE. There was no uveitis at this time. Intraocular pressure (IOP) was 14 mm Hg both eyes. A week later, right BCVA was unchanged but the left eye had decreased to 20/50. Mild bilateral anterior uveitis was observed without iridocapsular synechiae. IOP was still normal and the posterior segment was unremarkable. Given the effectiveness of IV cidofovir on severe respiratory symptoms, this treatment was continued. Local treatment consisted of dexamethasone eye drops three times a day and atropine eye drops 1% twice a day. The patient returned for consultation two weeks later and complained of vision decrease. Her BCVA was 20/33 RE and 20/100 LE. Bilateral Descemet's folds were present. But they were more noticeable on the left cornea. There was still bilateral anterior uveitis. IOP was 10 mm Hg RE and 8 mm Hg LE. Fundus examination of the right eye revealed macular folds. In the left eye, it found a large temporal choroidal detachment extending from the macular region to the temporal ora serrata and a left ciliary body edema of yellowish white appearance. Its extent was difficult to ascertain because of the choroidal detachment masking the periphery. Intravenous cidofovir was discontinued. Frequency of steroid therapy was increased (five times a day). However, IOP continued to decrease and stabilized at 8 mm Hg RE and 3 mm Hg LE after one week. One month later, it was possible to discontinue topical atropine therapy and to taper off topical dexamethasone as IOP improved and stabilized between 10 and 12 mm Hg both eyes. BCVA improves to 20/20 and the fundus appearance returned to normal in the right eye. In the left eye, BCVA remained reduced to 20/100 due to hypotony maculopathy. The right pupil became normally reactive when atropine was discontinued, but a mydriasis persisted on the left eye over one year. The left pupil was unresponsive to bright light, accommodation, or pilocarpine. Slit lamp examination did not reveal evidence of vermiform movement of the pupil margin and there was no area of iris transillumination or atrophy. There was no corneal anesthesia. Complete neurological examination including oculomotor testing was normal. General examination and blood testing ruled out systemic infectious disease. On the basis of these findings, the suspected diagnosis was Urrets-Zavalia syndrome (UZS).

Comment

When a unilateral fixed mydriasis appears in a patient with viral infection requiring cidofovir treatment, a neuro-ophthalmological complication should first be excluded. Other causes should be suspected, especially UZS. A fixed and dilated pupil associated with iris atrophy was initially described in 1963 by Urrets-Zavalia in patients treated with postoperative mydriatic after penetrating keratoplasty for keratoconus.[4] Since its first description, UZS has been reported after penetrating keratoplasty regardless of indication, lamellar keratoplasty, trabeculectomy, peripheral iridoplasty, or phakic intraocular lens implantation.[5,6] However, mydriatic treatments, postsurgical IOP rise, or iris atrophy are not all observed in reported cases of UZS in the literature.[5,7] A pupil with abnormal light reaction seems to be the most important sign when considering this diagnosis. Thus, UZS can be considered although our patient did not undergo any surgery and had ocular hypotonia that was not previously reported.

The pathophysiology of this syndrome is still unclear. Injury of the radial nerve fibers of the parasympathetic nerves was suspected and could explain the slow recovery observed in some cases in the literature.[5] However, currently, its most commonly accepted mechanism is iris ischemia.[6] A compression of the iris between the lens and cornea during surgery leading to this ischemia was initially suspected. IOP rise as a cause of iris ischemia has been evoked with postoperative mydriatic treatment, iridocorneal synechiae due to

severe anterior uveitis, or pigment dispersion after mydriatic therapy.[8] In addition, as a result of the anatomy of the iris vasculature, significant ciliary body disorganization can lead to an iris ischemia. In the case report, UZS occurs in the eye that is most affected by ocular hypotonia and edema of ciliary body due to cidofovir therapy. It is suspected that ocular hypotonia due to cidofovir is caused by lesion of the nonpigmented ciliary epithelium without histological damage of other structures of the eye.[3] Such lesions may exist in humans during the acute phase of cidofovir toxicity as it was reported with ciliary body detachment and choroidal effusion.[1]

Conflict of interest

The authors declare no conflict of interest.

References

1 Accorinti M, Ciapparoni V, Pirraglia MP, Pivetti-Pezzi P. Treatment of severe ocular hypotony in AIDS patients with cytomegalovirus retinitis and cidofovir-associated uveitis. *Ocul Immunol Inflamm* 2001; **9**(3): 211–217.
2 Soltau JB. Treatment of severe ocular hypotony in AIDS patients with cytomegalovirus retinitis and cidofovir-associated uveitis. *Ocul Immunol Inflamm* 2001; **9**(3): 137–139.
3 Taskintuna I, Rahhal FM, Arevalo JF, Munguia D, Banker AS, de Clercq E *et al*. Low-dose intravitreal cidofovir (HPMPC) therapy of cytomegalovirus retinitis in patients with acquired immune deficiency syndrome. *Ophthalmology* 1997; **104**(6): 1049–1057.
4 Urrets Zavalia Jr, A. Fixed dilated pupil, iris atrophy and secondary glaucoma. *Am J Ophthalmol* 1963; **56**: 257–265.
5 Espana EM, Ioannidis A, Tello C, Liebmann JM, Foster P, Ritch R. Urrets-Zavalia syndrome as a complication of argon laser peripheral iridoplasty. *Br J Ophthalmol* 2007; **91**(4): 427–429.
6 Niknam S, Rajabi MT. Fixed dilated pupil (urrets-zavalia syndrome) after deep anterior lamellar keratoplasty. *Cornea* 2009; **28**(10): 1187–1190.
7 Bourcier T, Laplace O, Touzeau O, Moldovan SM, Borderie V, Laroche L. Syndrome d'Urrets-Zavalia. *J Fr Ophtalmol* 2001; **24**(3): 303–308.
8 Mocan MC, Bozkurt B, Irkec M, Orhan M. Urrets-Zavalia syndrome following iatrogenic pupil dilation in eyes with pigment dispersion. *Can J Ophthalmol* 2009; **44**(2): 216–217.

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