Case Report

Macular Infarction following Intravitreal Clindamycin Injection : A Case Report

Alireza Hedayatfar[1], Amin Zand[1], Hooshang Faghihi[2], Arzhang Gordiz[1], Fatemeh Abdi[1]

[1]Eye Research Center, The Five Senses Institute, Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran, [2]Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Purpose: To report a case of *Toxoplasma* retinochoroiditis that was complicated by macular infarction following intravitreal clindamycin injection.

Methods: A 32-year-old otherwise healthy woman with the diagnosis of reactivation of *Toxoplasma* retinochoroiditis in her right eye, underwent intravitreal clindamycin injection. Shortly after injection, the visual acuity deteriorated, and the fundus examination revealed an extensive area of macular necrosis accompanied by vascular occlusion.

Results: The patient was observed. Unfortunately, the condition did not improve over time and resulted in a large area of retinal atrophy.

Conclusion: Macular infarction should be considered a rare but disastrous complication that can result in severe, irreversible visual loss.

Keywords: Clindamycin, Intravitreal injection, Macular infarction, Retinal toxicity, *Toxoplasma* retinochoroiditis

Address for correspondence: Fatemeh Abdi, Eye Research Center, The Five Senses Institute, Rassoul Akram Hospital, Sattarkhan-Niaiesh Street, 11335, Tehran, Iran.
E-mail: fatemeh.abdi62@yahoo.com
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Introduction

Ocular toxoplasmosis is the most common cause of infectious posterior uveitis in the world.[1] Although it is usually a self-limited disease, it can be sight threatening if it involves optic nerve or macula.[2] Once indicated, the mainstay of treatment is systemic antibiotics, which conventionally is administered by the oral route. Corticosteroids are usually prescribed shortly after antimicrobial treatment to control the inflammation. The classic triad of pyrimethamine, sulfadiazine, and corticosteroids has long been known as the standard treatment for ocular toxoplasmosis. Other regimens, including the combination of trimethoprim, sulfamethoxazole, and corticosteroid, have also been proved to be as effective as the classic triad.[1] However, these regimens may cause significant systemic adverse effects and may not be completely safe in children and pregnant women.[3] In patients with intolerance to or contraindication for systemic medication, intravitreal administration of antibiotics can be substituted. Theoretically, intravitreal administration of antibiotics delivers a higher concentration of drug to intraocular tissues and can be potentially beneficial in refractory cases.[4]

One of the most commonly used antibiotics for intravitreal injection is clindamycin. According to the previous studies, intravitreal injection of clindamycin is safe without significant side effects.[3] Here, we present an unusual complication of this treatment.

Case Report

A 32-year-old woman was referred for a progressive floater and blurred vision in her right eye. She recalled a similar but milder incident of a floater in the same eye several years ago,

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which was improved over time without specific treatment. Her medical history was unremarkable.

On examination, the best corrected visual acuity was 4/10 and 10/10 in her right and left eyes, respectively. Pupillary reactions were normal, with a negative relative afferent pupillary defect (RAPD). Intraocular pressures (IOPs) were within the normal range. The anterior chamber had a mild cellular reaction on the slit-lamp examination. Some cells were also detectable in retrolental space. On dilated fundus examination, a juxtapapillary, focal area of retinitis surrounding an old pigmented retinal scar was identified superotemporally. Sheathing of adjacent retinal vessels and a mild vitreous reaction were also visible [Figure 1a]. Macular optical coherence tomography (OCT) demonstrated focal areas of serous retinal detachments (SRDs) beneath the lesion as well as near the fovea [Figure 1b]. Fluorescein angiography (FA) showed a dense hypofluorescent area compatible with the old retinal scar with marginal hyperfluorescence corresponding to staining of the active lesion superotemporally. The pooling of dye into SRDs was evident [Figure 1c and d].

With the clinical impression of reactivation of *Toxoplasma* retinochoroiditis, systemic antibiotic (160 mg trimethoprim and 800 mg sulfamethoxazole twice daily), and shortly after that, prednisolone 0.5 mg/kg/day was initiated. Laboratory workup showed an elevated titer of immunoglobulin G against *Toxoplasma gondii*; however, anti-immunoglobulin M was negative. Other laboratory assessments for other possible infective etiologies, including tuberculin skin test, venereal disease research laboratory test, human immunodeficiency virus serology, and rheumatologic tests, were inconclusive. One week later, the patient declared that she was not compliant with systemic medications due to gastrointestinal disturbances including nausea, and requested a nonsystemic treatment. Risks and benefits of intravitreal injection were discussed, and upon her consent, intravitreal clindamycin (1000 μg/0.1 ml) and dexamethasone (400 μg/0.1 ml) were injected. For this purpose, clindamycin was obtained from a commercially available vial (clindamycin, 150 mg/ml, Zahravi Company, Tabriz, Iran) and was diluted to the desired concentration. Anterior chamber paracentesis was performed to adjust IOP. As our routine protocol, the visual acuity was checked immediately after the injection, and it was at least counting fingers. Two days after injection, the patient was referred with further visual impairment. Her vision dropped to count fingers at 5 m, with negative RAPD. Her IOP was at the normal range. On re-evaluation, widespread retinal whitening at the posterior pole with a cherry-red spot lesion was visible. Retinal necrosis in an annular configuration surrounding the fovea along with obliterated vessels was evident as well [Figure 2a]. Macular OCT showed diffuse thickening of inner retinal layers reflecting the inner retinal ischemia and recent development of a full-thickness macular hole [Figure 2b]. Fundus autofluorescence revealed the extension of macular infarction [Figure 2c]. FA showed an extensive area of the nonperfused retina at the posterior pole with an enlarged foveal avascular zone, with the normal filing of major retinal vascular arcades, which excluded retinal vascular occlusion [Figure 2d and e]. The clinical picture was consistent with macular infarction, similar to aminoglycoside-induced retinal toxicity.[5] Follow-up examination showed regression of *Toxoplasma*

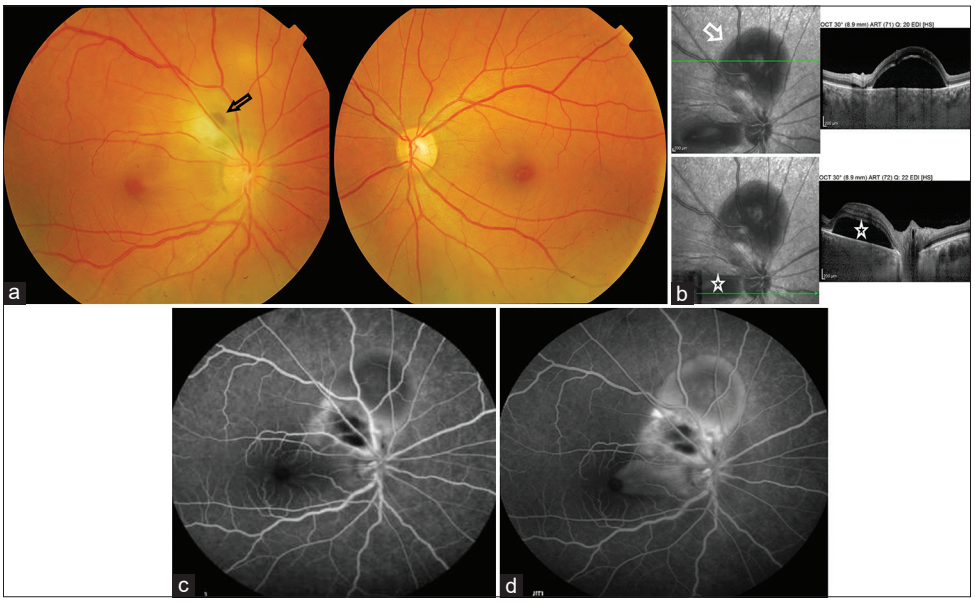

Figure 1: (a) A yellow-white retinal lesion adjacent to an old pigmented scar (black arrow) with the sheathing of neighboring retinal vessels is detected in the right eye. The fundus photograph of the left eye seems to be normal. (b) Focal areas of serous retinal detachments (SRDs) beneath the retinal lesion (white arrow) and near the fovea (asterisk). (c and d) Serial phases of fluorescein angiogram show marginal staining of retinal lesion and pooling of dye into SRDs

retinochoroiditis with the disappearance of SRDs. A well-circumscribed area of retinal atrophy remained at the posterior pole [Figure 3a]. In addition, progressive retinal thinning and atrophy was detected in serial OCTs [Figure 3b]. No further treatment was instituted, and the patient was observed. Unfortunately, the condition was not improved, and her vision remained at 4 m counting fingers at 12-month follow-up.

Discussion

Intravitreal injection of clindamycin, which is an off-label choice in the treatment of *Toxoplasma* retinochoroiditis, is effective and safe in several studies.[3,6] However, the case presented here accentuates the rare but potential disastrous side effect of such treatment: aminoglycoside-like retinal toxicity leading to macular infarction.

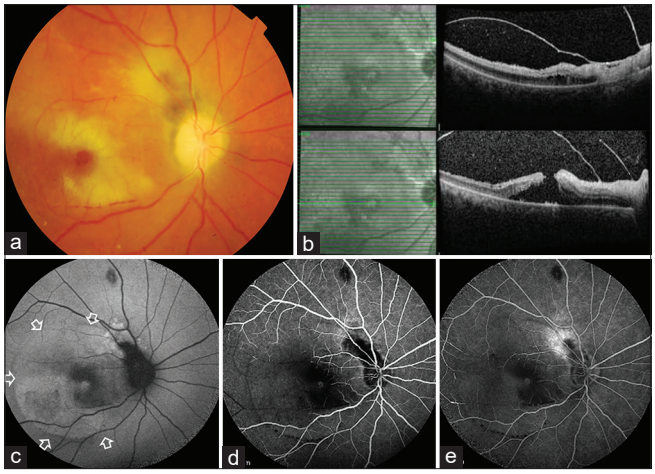

Figure 2: (a) Fundus photograph of the right eye showing perifoveal annular retinal necrosis and whitening at the posterior pole with a cherry-red spot. Note the attenuation of vessels in macula and optic disc pallor. (b) Raster spectral-domain optical coherence tomography scan revealed hyperreflectivity of the inner retinal layers indicating acute ischemia along with a partially detached epiretinal membrane with the formation of a full-thickness macular hole. (c) The well-demarcated extent of macular infarction is best visible on fundus autofluorescence image (arrows). (d) Fluorescein angiography (FA), (early phase): Abrupt termination of the precapillary arterioles and an enlarged foveal avascular zone, indicating macular infarction. (e) FA (late phase): Staining of the primary retinal lesion in addition to nonperfusion of the macula

The patient was diagnosed with ocular toxoplasmosis based on clinical findings of the presence of a focal area of retinitis near an old pigmented retinal scar, which was accompanied by vitritis. Although ocular toxoplasmosis is a clinical diagnosis, the unusual incident of multifocal SRDs adjacent to the main lesion convinced us to extend the list of differential diagnosis and exclude other probable causes. Further laboratory workups were inconclusive for other causes and were in favor of the clinical diagnosis of ocular toxoplasmosis. Choroidal ischemia has been proposed as a contributor to the development of SRD. According to previous literature, although SRD has been reported in patients with ocular toxoplasmosis, multifocal SRD is not a typical finding in these patients.[7]

Macular infarction has been reported to occur following the intravitreal injection of various kinds of drugs. Intravitreal administration of aminoglycosides is well known to cause retinal toxicity. Loss of visual function has been reported after the intravitreal administration of gentamicin, amikacin, and tobramycin.[8-10] In such cases, the retina acutely becomes opaque and edematous with superficial and intraretinal hemorrhages, cotton wool spots, arteriolar narrowing, and venous beading which is described as hemorrhagic occlusive retinal vasculitis (HORV), leading to severe visual loss.[5,11] Histopathological studies demonstrated diffuse disruption of the nerve fiber layer and the inner plexiform layers in eyes exposed to this aminoglycoside antibiotic.[12] OCT evaluation displayed macular edema, with the elevation of the neurosensory retina, and the accumulation of hyperreflective material under the neurosensory retina. In some cases, hyperreflectivity of the inner retinal layers is reported due to ischemia, similar to our patient's OCT findings.[11,13] In FA, the increased size of the fovea avascular zone due to macular ischemia is visible.[5,12] The exact cause of HORV complication

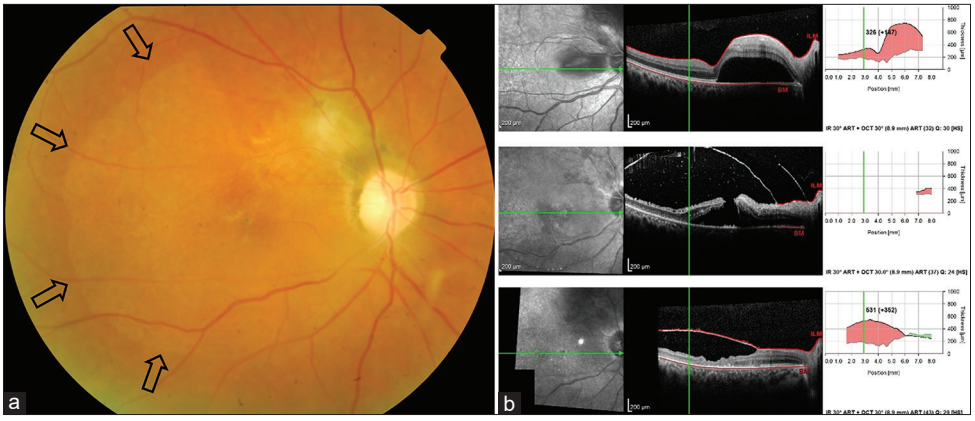

Figure 3: (a) Fundus photograph of the left eye at 2-month follow-up showing a well-circumscribed area of retinal atrophy (arrows), regression of *Toxoplasma* lesion, and temporal optic disc pallor. (b) Serial spectral-domain optical coherence tomography scans demonstrate chronic evolution of retinal thinning and atrophy

is not clear, but Witkin *et al*.[14] suggested that this complication may be a type III hypersensitivity immune reaction which is caused by immune complexes deposited in vessel walls and subsequent cellular immune response. The time course for this type of hypersensitivity is variable from hours after the introduction of the antigen to days. HORV seems to cause occlusive retinal phlebitis predominantly. Venous involvement in HORV may explain the intraretinal hemorrhages. The onset time of HORV in previous studies varies from hours to days or even weeks.[11,14] In our patient, only nonperfusion areas were revealed in the macular area without any hemorrhagic signs about 2 days after the injection. In addition, in FA, filing of major retinal vascular arcades was normal. Therefore, the diagnosis of HORV complication is less probable for our patient.

Macular infarction has also been reported following intravitreal injection of bevacizumab,[15] triamcinolone acetonide,[16] and gemcitabine/carboplatin.[17]

According to previous studies, intravitreal injection of 1 mg/0.1 cc clindamycin is safe for clinical use.[6,18] Furthermore, there are no reports of inadvertent consequences of the higher doses of intravitreal injection of the drug. However, our patient was injected by a correct calculated (1 mg/0.1 cc) dose of the drug.

The reason for macular infarct in our case could potentially be related to the toxicity of the main ingredient (clindamycin) for ocular tissue. Prior studies have investigated the retinal toxicity of various concentrations of clindamycin in nonhuman eyes. In an experimental study by Stainer *et al*.,[19] vitreous replacement fluid containing 10 μg/mL clindamycin saline was nontoxic to the rabbit retina after vitrectomy. Abnormal electroretinograms and retinal histology were only found in eyes receiving higher drug concentrations. Little is known about the toxicity of different concentrations of intraocular clindamycin in human eyes. In clinical studies, the safe and effective recommended dosage is 1000 μg/0.1 ml.[3,4,6,20-22] In practice, preparing the proper concentration of clindamycin encompasses multiple courses of dilution, a meticulous process that deserves extreme caution.

Another potential explanation may be the toxicity of preservatives in aliquots. Toxic reaction to additive preservative is another possible cause of this adverse effect. Commercially available clindamycin vials (including the brand that was used for this patient) contain benzyl alcohol (BA), which is used as a preservative in some parenteral drugs. In a study by Chang *et al*.,[23] the clinically relevant concentration of BA in Kenalog following intravitreal injection caused ultrastructural damage of retinal pigment epithelium cells. However, contrary to Kenalog, clindamycin should be diluted several times before intravitreal injection, which makes the concentration of BA much lower than Kenalog's BA. BA in clindamycin preparation is not probably the cause of the observed toxic effect.

Furthermore, a postinjection rise of IOP is another explanation. Retinal arterial occlusion secondary to a sudden increase of IOP may occur immediately after intravitreal injections as a rare but catastrophic complication.[24] However, the visual loss due to sudden rise in IOP is immediate, opposing to the current case in which the visual impairment occurred gradually following injection. Furthermore, in the fundus examination of the affected eye, she did not have any signs of major vascular arcade occlusion.

Putting together all findings and considering the timing of events, we reached the assumption that the cause of macular infarction in our case must be the direct toxicity of clindamycin, which may be accentuated by inadvertent delivery of excessive dosage. An ischemic macular hole was formed after its infarction in our patient. Although the exact cause of this process is not clarified, it is shown that after macular ischemia and its subsequent necrosis and thinning, a macular hole is established.[25,26] The fact that such a disastrous adverse reaction happened under the hand of an experienced retinal specialist emphasizes the importance of limiting the indication of intravitreal clindamycin injection to those cases who have strict contraindication for using oral antibiotics. Moreover, obsessive care must be taken to dilute the clindamycin preparation and use of appropriate concentration and dosage.

In conclusion, intravitreal delivery of clindamycin is generally considered a rather safe method of treatment in ocular toxoplasmosis; however, the rare but disastrous outcome in the case presented here, points to the fact that the safety of such a treatment should be reassessed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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