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Case Report

Use of recombinant tissue plasminogen activator for treatment of recalcitrant anterior uveitis: A case series

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الملخص

علاج التهاب القزحية الأمامية المتكرر بعد العملية الجراحية أمر صعب. نقدم هنا تقريرا عن معالجة ناجحة لحالتين بالحقن التجويفي لمنشط البلازمينوجين النسيجي المركب في حالتين من حالات التهاب القزحية الأمامية المتكرر؛ حالة التهاب القزحية الأمامية المعدي وحالة " فوت-كويناقي-هرادا". أُصيبت سيدة في الأربعين من العمر باحمرار في العينين وضعف الرؤية لمدة أسبوعين. كان لديها التهاب القزحية الأمامية، والتهاب الأوعية الدموية، والتهاب الشبكية، وتورم القرص البصري. وكانت اختبارات الأمصال لبكتريا بارتونيلا هنسيلي وتوكسوبلازما جونديأي موجبة. تم علاجها بالكورتيكوستيرويدات العامة على المدى الطويل والمضادات الحيوية المناسبة. كانت حالتنا الثانية رجلا سليما يبلغ من العمر ٣٠ عاما ظهر لديه احمرار غير مؤلم في العينين مع ضعف في الرؤية وصداع وطنين لمدة أسبوعين. كان هناك التهاب حبيبي في العينين مع التهاب السائل الثقيل والكوروويد والشبكية مع احمرار القرص البصري. وتم تشخيصه على أنه حالة " فوت-كويناقي-هرادا" وتم علاجه بالكورتيكوستيرويدات العامة. نتج لدى الحالتين إعتام ثانوي في عدسة العين والماء الأزرق الذي استدعي التدخل الجراحي. أدى الالتهاب المزمن المستمر إلى تكوين غشاء ليفي سميك أمام العدسة بعد جراحة استحلاب العدسة مع زراعة عدسة جديدة. بعد ذلك أُزيل الغشاء جراحيا وتلى ذلك الحقن التجويفي لمنشط البلازمينوجين النسيجي المركب بجرعة ٢٥ ميكروغرام. كان هناك تشافي للالتهاب المستمر وتحسن كبير في حدة البصر في غضون أسبوع من الحقن. لم تُسجل أي تأثيرات جانبية في العين أو في الجسم. الحقن التجويفي لمنشط البلازمينوجين النسيجي المركب مفيد في المرضى الذين يعانون من التهاب القزحية الأمامية المتكرر بعد العملية الجراحية. في معظم الحالات، يكون التدخل الجراحي مهما لتوفير رؤية يستفيد منها المريض. يجب أن يؤخذ الحقن التجويفي لمنشط البلازمينوجين النسيجي المركب في الاعتبار عند التعامل مع الالتهابات المستمرة من أسباب مختلفة.

الكلمات المفتاحية: التهاب البارتونيلا العيني؛ فوت-كويناقي-هرادا؛ منشط البلازمينوجين النسيجي المركب؛ التهاب القزحية الأمامية المتكرر؛ التهاب الشبكية

Abstract

Management of inflammation after surgery for recalcitrant anterior uveitis is challenging. Herein, we report successful treatment using intracameral injection of recombinant tissue plasminogen activator (rtPA) in two patients with recalcitrant anterior uveitis, due to infective uveitis and Vogt–Koyanagi–Harada disease, respectively. A 40-year-old woman presented with bilateral redness and vision reduction that had persisted 2 weeks. She also had bilateral anterior uveitis, vasculitis, retinitis, and optic disc swelling. Serology was positive for *Bartonella henselae* and *Toxoplasma gondii*. She was treated using long-term systemic corticosteroids and appropriate antibiotics. Our second case; a healthy 30-year-old man with bilateral eye redness and reduced vision without pain, and associated with headache and tinnitus for 1 weeks. He showed bilateral granulomatous inflammation with vitritis, choroiditis, retinitis, and hyperemic optic disc. The patient was diagnosed with Vogt-Koyanagi-Harada disease and treated with systemic corticosteroids. Both patients developed secondary cataracts and glaucoma that necessitated surgical intervention. Persistent chronic inflammation led to the formation of a thick fibrin membrane anterior to the intraocular lens (IOL) after phacoemulsification surgery with IOL implantation. This membrane was removed surgically, and intracameral injection of rtPA (25 μg) was carried out. The persistent

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inflammation had resolved and visual acuity had significantly improved within 1 week of intracameral rtPA injection. There were no reported ocular or systemic side effects. Intracameral rtPA is beneficial in patients with recalcitrant anterior uveitis who have undergone intraocular surgery. In most cases, surgical intervention improves the patients' vision. Intracameral rtPA should be considered in cases of persistent inflammation of varying etiology.

Keywords: Ocular bartonellosis; rtPA; Recalcitrant anterior uveitis; Retinitis; Vogt–Koyanagi–Harada

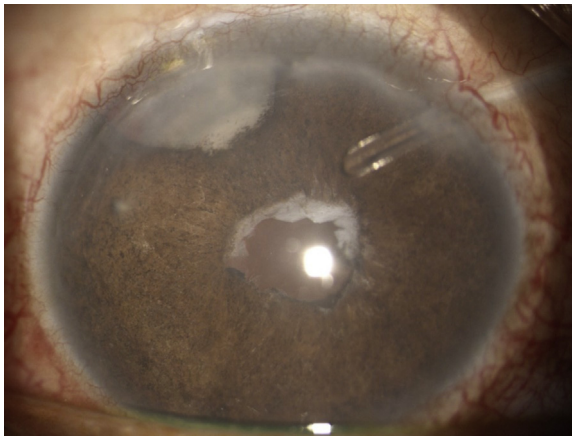

Figure 2: Case 2: 12 h after rtPA injection. Note the fibrin membrane dissolution, with minimal membrane and posterior synechiae remaining.

Introduction

Cataracts and secondary refractory glaucoma are common complications of persistent chronic uveitis.[1] In addition, extensive and severe fibrinous anterior-segment inflammation is common following cataract extraction and glaucoma surgeries in this particular condition. This sequelae is devastating for the patient and frustrating for the ophthalmologist. Topical or systemic steroid treatment can be ineffective and is often associated with unwanted side effects.[2] Tissue plasminogen activator is a serine protease that activates the pro-enzyme plasminogen to form the active enzyme plasmin, which degrades fibrin into soluble products.[3]

Many studies have shown that recombinant tissue plasminogen activator (rtPA) is effective and beneficial in the treatment of certain ocular diseases,[4–10] and several reports have stated that severe anterior chamber fibrinous inflammation responds well to intracameral rtPA injection in steroid-resistant uveitis.[6,7] Intracameral rtPA injection was reported effective to resolve fibrin in two patients with HLA27-positive uveitis[7] and post-operative endophthalmitis,[8,10] as well as in patients who have undergone cataract extraction[4,6] and glaucoma surgery.[4,5,9] Other reports have claimed that intra-arterial or intravenous rtPA injection improves acute visual loss in central retinal artery occlusion[11–13] and cilioretinal artery occlusion,[14] and that intravitreal rtPA resolves massive pre-macular hemorrhage[15] and sub-macular hemorrhage[16] secondary to age-related macular degeneration, as well as total hyphema after penetrating injury.[17] Intracameral injection is the main route of administration for treatment of anterior chamber fibrin reaction, although rtPA can also be delivered subconjunctivally.[4]

Treatment of severe anterior chamber fibrin reaction after cataract or glaucoma surgery is a challenge in patients with pre-existing persistent uveitis. Persistent inflammation may lead to the formation of an anterior chamber fibrin membrane, which can further compromise the vision. In the present study, we evaluated the effect of intracameral rtPA injection on severe post-operative inflammation in two patients with recalcitrant anterior uveitis.

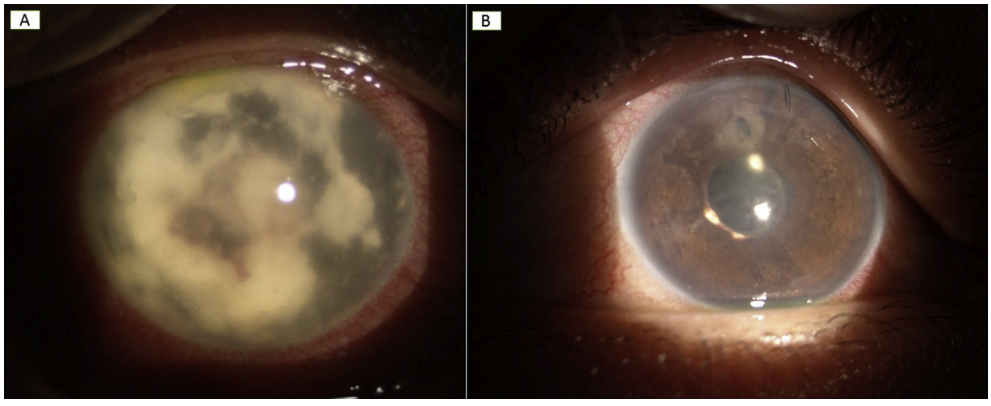

Figure 1: Case 1: (A) Day 1 after cataract extraction with PCIOL implantation, synechiolysis, and intracameral triamcinolone. Note the dense fibrin membrane, blood clot, and triamcinolone staining in the anterior chamber covering the pupil and IOL (B) After rtPA injection. Note the complete resolution of the fibrin membrane, blood clot, and triamcinolone staining in the anterior chamber.

Case reports

Case 1

A 40-year-old woman presented with a 2-week history of reduced vision, redness, glare, and discomfort in both eyes. She had no history of close contact with cats or dogs. Her best-corrected visual acuity (BCVA) was 6/7.5 in the right eye and 6/9 in the left eye. She had no relative afferent pupillary defect (RAPD). Examination revealed that both eyes had developed anterior chamber reaction, which was mild in the right eye and severe in the left eye. In both eyes, there were multiple keratic precipitates on the endothelium, as well as mild anterior vitreous cells. Both optic discs were hyperemic and swollen, showing retinitis, vasculitis, and macular edema. The intraocular pressure (IOP) was 13 mmHg in both eyes.

Investigations were conducted to establish the infectious or inflammatory causes of the patient's uveitis. Her serology was positive for *Bartonella henselae* IgM and IgG, as well as for *Toxoplasma gondii* IgG. She was treated for ocular bartonellosis and toxoplasmosis using oral doxycycline (100 mg) twice daily for 6 weeks and oral azithromycin (500 mg) daily for 6 weeks. Oral prednisolone was prescribed in a tapering dosage, with an initial daily dose of 35 mg. Topical prednisolone acetate (1%) and homatropine (2%) were administered **3 times daily**. Systemic and topical steroids were used for 2 years to treat persistent inflammation, leading to seclusio pupillae, rubeosis iridis, and secondary cataracts in both eyes.

Despite the treatment, the patient's vision had subsequently deteriorated to "counting fingers" (CF) at 2 feet in the right eye and to light perception in the left eye. Relative afferent pupillary defect (RAPD) was positive on her left eye, with iris neovascularization, and her left IOP ranged between 46 and 62 mmHg. An Ahmed valve was implanted in her left eye, and this procedure was combined with synechiolysis, peripheral iridectomy, and intracameral injection of triamcinolone (4 mg/0.1 mL). Intracameral ranibizumab (0.5 mg/0.05 mL) was injected prior to the procedures. Postoperatively, the patient's IOP was well-controlled: 12–16 mmHg during clinical follow-up.

Subsequently, even though the patient was receiving maximum medication doses, her right eye's IOP started to increase. Therefore, a right-eye lens aspiration was performed, with implantation of a posterior chamber intraocular lens (PCIOL), synechiolysis, and intracameral injection of triamcinolone (4 mg/0.1 mL). After surgery, she developed severe inflammation, with blood clot, fibrin formation, and triamcinolone staining in the anterior chamber obscuring the pupil and intraocular lens (IOL) (Figure 1A). She was given two subconjunctival injections of dexamethasone (0.8 mg/0.2 mL) and mydricaine (1 mg atropine, 012 mg adrenaline and 6 mg procaine hydrochloride), but showed no improvement. She then underwent another procedure where her right anterior chamber was washed out, peripheral iridectomy was done and intracameral injection of dexamethasone was given. However, she still showed no improvement. An intracameral injection of rtPA (25 μg) was administered on day 17 after cataract extraction to treat the recalcitrant inflammation.

The fibrin membrane, blood clot, and triamcinolone staining had resolved 1 day after this injection, and the inflammation had resolved 3 days after the rtPA injection (Figure 1B). Her right eye best corrected visual acuity (BCVA) improved to 6/12. The tapering doses of oral prednisolone, topical prednisolone acetate (1%), topical homatropine (2%; **3 times daily**), and topical moxifloxacin were continued.

Case 2

A healthy, 30-year-old man presented with reduced vision and redness without pain in both eyes, associated with tinnitus and headaches, that had persisted for 1 week. His BCVA was 6/18 in both eyes. Examination revealed bilateral conjunctival injection, granulomatous keratic precipitates, anterior chamber reaction (3+), and anterior vitreous cells (2+). Posteriorly, inferior exudative retinal detachment was noted, as were choroiditis, vitritis, Dalen–Fuchs nodules, macular edema with striae, and swollen and hyperemic optic discs. However, there was no RAPD. The patient showed mild sensorineural hearing loss in both ears. Otherwise, he had no poliosis, vitiligo, or alopecia. Serology was negative for antinuclear antibody, rheumatoid factor, toxoplasma, syphilis, toxocara, and cytomegalovirus, and the patient's renal function, complete blood count, erythrocyte sedimentation rate, Mantoux test, and chest radiograph were normal.

Based on clinical findings, he was diagnosed with Vogt–Koyanagi–Harada (VKH) disease and treated using intravenous methylprednisolone (250 mg; **4 times daily**) for 3 days, followed by tapering doses of oral prednisolone (50 mg daily), topical homatropine (2%; **3 times daily**), and prednisolone acetate (1%) for 6 years. Anterior and posterior segment inflammation persisted, leading to bilateral neovascularization of the optic discs and subretinal hemorrhage, with vitreous hemorrhage in the right eye. Bilateral panretinal photocoagulation therapy was performed in both eyes. Bilateral rubeosis iridis, steroid-induced cataracts, and secondary glaucoma had developed, and RAPD was present in the left eye. His vision had deteriorated to "hand movement" in the right eye and CF at 2 feet in the left eye.

Furthermore, he developed systemic side effects of steroids: moon facies, buffalo hump, and abdominal striae. To minimize the side effects of systemic steroid, oral cyclosporine (50 mg **2 times daily**) was started. Even though he was receiving maximum medications for elevated IOP, his IOP was persistently high—ranging between 13 and 55 mmHg. A right augmented trabeculectomy with mitomycin C administration (0.04%; 0.4 mg), was performed to control his IOP. Initially, this procedure was successful, but the patient later showed signs of failure that necessitated needling with 5-fluorouracil (10 mg/0.2 mL). Subsequently, seclusio pupillae developed, and his IOP continued to rise, reaching 34–48 mmHg. A Baerveldt valve was then implanted, combined with mitomycin C administration (0.2%; 0.2 mg), phacoemulsification, PCIOL implantation, and synechiolysis. His IOP was reduced to 8–20 mm Hg.

An Ahmed valve was then implanted in his left eye, combined with mitomycin C (0.04%; 0.4 mg), phacoemulsification, and PCIOL implantation. Due to uncontrolled IOP in the left eye, a second glaucoma drainage device was

implanted in the superior temporal region 2 years later. To reduce the complications associated with rubeosis iridis, intravitreal ranibizumab (0.5 mg/0.05 mL) was injected into both eyes 1 week prior to surgical intervention.

Inflammation persisted despite the systemic and topical anti-inflammatory drugs (oral prednisolone, oral cyclosporine, and topical prednisolone acetate [1%]), leading to seclusio pupillae and a severe anterior chamber fibrin membrane on the right eye. The fibrin membrane formation slowly progressed to cover the visual axis and IOL, causing deterioration of vision to CF at 2 feet. At this point, the patient was housebound, but still able to care for himself. Four years later, to help improve his vision, right eye synechiolysis, membrane excision, and intracameral rtPA injection (25 μg) were performed after cataract extraction and glaucoma surgery. After surgery, the membrane was completely resolved, and only minimal posterior synechiae remained (Figure 2). His BCVA improved to 6/21 in the right eye and 6/7.5 in the left eye.

Discussion

It is challenging and frustrating to deal with persistent ocular inflammation—every possible decision has a high risk of complications and a low chance of success. However, with advances in technology and drug development, the management of persistent and recalcitrant ocular inflammation has become more rewarding.

In the two cases of the present report, we observed significant improvement in visual acuity 1 week after intracameral rtPA injection. In fact, in cases 1 and 2, fibrin had completely resolved on days 3 and 1 after rtPA injection, respectively. Other studies have reported that fibrin completely resolves as early as 30 min to several hours after rtPA injection.[4,7]

However, intracameral rtPA injection is not recommended to treat anterior segment fibrin clots that have persisted for more than 20 days.[18] Moreover, rtPA should be injected 4 days to 3 weeks after surgery to ensure maximal benefit and minimal risk of bleeding from clot lysis.[4] However, in case 2, rtPA injection was performed 4 years after surgery for cataract extraction, PCIOL implantation, and glaucoma. To our knowledge, no previous studies have reported intracameral rtPA injection years after anterior chamber surgery. The patient in case 2 benefited from rtPA injection several years after anterior segment surgery in steroid resistant and recalcitrant uveitis.

In both cases, rtPA injection was carried out to reduce fibrin exudation and improve visual acuity after anterior segment surgery. To date, the dosage of intracameral rtPA injection in uveitis has not been standardized. We selected a dosage of 25 μg of rtPA based on previous studies.[5,8,10,17] Both Damji et al. and Riaz et al. reported complete fibrin resolution after intracameral rtPA injection (25 μg) in patients with pseudophakic endophthalmitis who had severe anterior chamber fibrin reaction. A lower concentration of rtPA has been reported to be equally effective. For example, Heiligenhaus et al. reported that anterior chamber fibrin resolved in a patient with uveitis after intracameral injection of 10 μg rtPA. Additionally, intracameral injection of 12.5 μg rtPA resolved a severe anterior chamber fibrin reaction in HLA27-positive uveitis patients.[7]

There were no complications related to rtPA injection in either case, although such complications are not uncommon and include anterior chamber bleeding, transient clouding of cornea, anterior chamber flattening, and hypotony.[4,5,9,19] Lundy et al. reported that hyphema was more likely to occur after intracameral injection of 25 μg rtPA to treat severe fibrin formation after glaucoma surgery with or without cataract extraction.

To conclude, rtPA injection is effective as an adjunctive treatment for severe post-operative inflammation in recalcitrant anterior uveitis. This treatment should be considered in the treatment of persistent inflammation of varying etiology.

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None.

Conflict of interest

The authors have no conflict of interest to declare.

Consent

Informed consent was obtained from all patients.

Authors' contributions

All authors contributed to patient management, literature review, and preparation of the manuscript. All authors read and approved the final manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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