Acinetobacter Baumannii Endophthalmitis Following Intravitreal Ranibizumab Injection

İntravitreal Ranibizumab Enjeksiyonu Sonrası Gelişen Acinetobacter Baumannii Endoftalmisi

Cem ÇANKAYA[1], Tongabay CUMURCU[2], Selim DOĞANAY[3]

ABSTRACT

We aimed to report a case who developed Acitenobacter baumannii endophthalmitis after intravitreal Ranibizumab (Lucentis®) injection. A 79-year-old male patient was admitted with vision loss in both eyes. Fluorescein angiography showed dry type age-related macular degeneration (ARMD) in the right eye and subretinal hemorrhage secondary to subfoveal classic type choroidal neovascular membrane in the left eye. Intravitreal injections of 3-dose Ranibizumab (Lucentis®) at monthly intervals were planned for the left eye of the patient. After the injection of the third dose of Ranibizumab, on the third day, the patient returned to the clinic with a complaint of excruciating ocular pain, red eye and vision loss in the left eye. The visual acuity of the patient was at the level of light perception. A slit lamp examination and B-mode ultrasonography revealed endophthalmitis. The patient was promptly hospitalised and medical treatment was started. After the sampling of vitreous from the left eye, vancomycin and ceftazidime were intravitreally administered. Systemic cefazolin and gentamicin, topical fortified vancomycin and ceftazidime, and topical moxifloxacin along with topical cycloplegic drops were started. Pars plana vitrectomy could not be performed due to corneal opacification. Four days after the initialisation of the therapy, the culture of the vitreous sample yielded Acinetobacter baumannii. In the following days, no regression in the clinical picture was determined and the level of the visual acuity worsened to light perception loss.

Acute Acinetobacter baumannii endophthalmitis following intravitreal Ranibizumab injection occurs rapidly and can result in severe loss of vision. Although endophthalmitis is rare, ophthalmologists should be alert to the possibility of patients having endophthalmitis caused by A. baumannii.

Key Words: Acinetobacter baumannii, endophthalmitis, Intravitreal injection.

ÖZ

Çalışmamızda, vitreus içi Ranizumab (Lucentis®) uygulaması sonrası Acitenobacter Baumannii endoftalmisi gelişen bir olguyu sunmayı amaçlamaktayız. Yetmişdokuz yaşında erkek hasta, her iki gözünde görme azlığı şikayeti ile kliniğimize başvurdu. Hastanın yapılan Fundus floresein anjiografisinde (FA) sağ gözde kuru tip yaşa bağlı maküla dejenerasyonu (YBMD), sol gözde ise subfoveal klasik tip koroid neovasküler membran ve buna ikincil subretinal hemoraji tespit edildi. Hastanın sol gözüne 3 doz birer ay arayla intravitreal Ranibizumab (Lucentis®) tedavisi planlandı. Olgumuz, 3. doz uygulamayı takiben 3. günde görme kaybı, şiddetli göz ağrısı ve kırmızı göz ile kliniğimize başvurdu. Hastanın görme keskinliği ışık hissi düzeyindeydi. Biyomikroskobik muayenesinde ve B tarama ultrasonografide endoftalmi tablosu izlendi. Hasta acil olarak hospitalize edildi ve medikal tedavisine başlandı. Sol gözden vitreus örneği alınmasını takiben intravitreal Vankomisin ve Seftazidim uygulandı. Topikal sikloplejik ajanlarla birlikte sistemik sefazolin ve gentamisin, topikal fortifiye seftazidim ve vankomisin ve topikal moksifloksasin tedavisine başlandı. Yoğun kornea opasifikasyonu nedeni ile pars plana vitrektomi uygulanamadı. Tedavinin başlangıcından 4 gün sonra vitreus kültüründe Acinetobacter baumannii üremesi olduğu bildirildi. Takip eden günlerde klinik tabloda bir iyileşme izlenmedi ve görme keskinliği ışık hissi kaybına kadar ilerledi.

Vitreus içi Ranibizumab uygulamasından sonra akut Acinetobacter baumannii endoftalmisi çok hızlı oluşabilir ve ciddi görme kaybına neden olabilir. Acinetobacter baumannii'ye bağlı endoftalmi tablosu nadir olmasına rağmen, oftalmologlar bu etyolojik ajana karşı daha dikkatli olmalıdırlar.

Anahtar Kelimeler: Acinetobacter baumannii, endoftalmi, intravitreal enjeksiyon.

1- M.D., Malatya Universal Hospital, Eye Clinic, Malatya/TURKEY
CANKAYA C., cem_cankaya@yahoo.com
2- M.D. Associate Professor, İnonu University Faculty of Medicine, Department of Ophthalmology, Malatya/TURKEY
CUMURCU T., t.cumurcu@inonu.edu.tr
3- M.D. Professor, İnonu University Faculty of Medicine, Department of Ophthalmology, Malatya/TURKEY
DOGANAY S., sdoganay@inonu.edu.tr

Geliş Tarihi - Received: 02.07.2012
Kabul Tarihi - Accepted: 31.07.2011
Ret-Vit 2013;21:59-62

Yazışma Adresi / Correspondence Adress: M.D., Cem ÇANKAYA
Malatya Universal Hospital, Eye Clinic, Malatya/TURKEY

Phone: +90 536 822 23 98
E-Mail: cem_cankaya@yahoo.com

INTRODUCTION

Once the importance of vascular endothelial growth factors (VEGF) in ocular angiogenic disorders was understood, drugs inhibiting VEGF began a new era in the treatment of diseases such as age-related macular degeneration (ARMD), diabetic retinopathy, and retinal vascular obstructions. Ranibizumab (Lucentis®) and Pegaptanib sodium (Macugen®), which are approved only for the indication of wet ARMD and Bevacizumab (Avastin®) that has been used for indications beyond its aim, are the most commonly used drugs today.[1] However, some severe complications due to intravitreal injections of these drugs were reported. Invasive procedures allowing entrance within intraocular spaces have long been accepted as potential risks for endophthalmitis.

The genus Acinetobacter is currently classified in the family Moraxellaceae and consists of bacteria that are nonmotile, oxidase-negative, gram-negative coccobacilli. Acinetobacter species have a wide habitat in the environment and are found frequently in most water and soil samples. Acinetobacter organisms have been cultured from the moist skin of healthy humans; increased colonization of the skin and the respiratory and gastrointestinal tracts occurs in individuals in long-term-care facilities and hospitals. Although this organism is associated primarily with nosocomial infections, it has also been involved in cases of community-acquired infections.[2]

The aim was to investigate an interesting case, for whom a three-dose intravitreal injection of Ranibizumab was planned because of wet type ARMD and who developed an Acinetobacter baumannii endophthalmitis in the early period following the administration of the third dose.

CASE REPORT

A 79-year-old male patient applied to our clinic with the complaint of vision loss in both eyes, which had begun in the last few years and had gradually progressed. On examination, visual acuity was found to be 1/10 with correction in the right eye and 1/20 with correction in the left eye, using Snellen charts. During a slit lamp examination, both eyes were normal. Intraocular pressure was measured as 15 mmHg in the right eye and 14 mmHg in the left eye with an applanation tonometer. During the fundus examination, an atrophic scar in the centre of macula of the right eye and subfoveal hemorrhage in the left eye was seen; therefore, a fundus fluorescein angiography (FA) was planned. FA revealed atrophic type ARMD in the right eye and subfoveal classic type choroidal neovascular membrane and consequent subretinal hemorrhage in the left eye.

Intravitreal injections of 3-dose Ranibizumab (Lucentis®) at monthly intervals were planned for the left eye of the patient, at which point an informed consent form was obtained from the patient. Applications were performed in the operating room, an environment providing completely sterile conditions. Five minutes prior to the injections, 0.5% proparacaine and 5% povidone-iodine solutions were administered topically. Eyelids and eyelashes were cleaned with povidone-iodine and the eyelashes were kept away from the area with sterile ophthalmic drapes. Thereafter, 0.5 mg (in 0.05 ml) of Ranibizumab (Lucentis®) was administered with a 30 gauge proper needle from the superior temporal pars plana region. No complications occurred during the procedure.

The injection site was applied pressure using an applicator with a sterile cotton tip and the patient was prescribed topical moxifloxacin (Vigamox) for prophylactic purposes (a topical antibiotic, hourly in the first day and subsequently four times a day for one week). After the first two-dose application, the visual acuity of the left eye reached the level of 4/10. On the first day after the injection of the third dose of Ranibizumab, the anterior segment was normal and intraocular pressure (IOP) was 12 mmHg. On the third day, the patient returned to the clinic with complaints of excruciating ocular pain, red eye and vision loss.

The visual acuity of the patient was at the level of the sense of light perception; diffuse palpebral edema, conjunctival hyperemia, chemosis and dense hypopyon hindering the fundus reflection were found (Figure). B-mode ultrasonography revealed dense condensation of vitreous. The patient was promptly hospitalised. After the sampling of vitreous from the left eye, vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml) were intravitreally administered. Systemic cefazolin (2x1g) and gentamicin (2x80mg), topical fortified vancomycin and ceftazidime hourly, moxifloxacin (Vigamox) 5x1 along with topical cycloplegic drops were started.

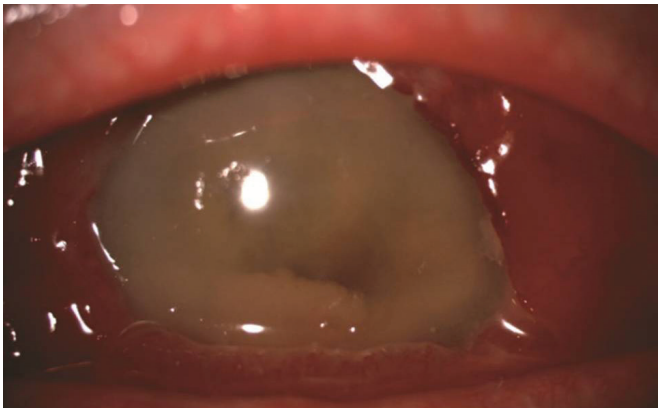

Figure: *Diffuse palpebral edema, conjunctival hyperemia, chemosis, corneal edema and dense hypopyon hindering the fundus reflection.*

Pars plana vitrectomy could not be performed due to corneal opacification. Four days after the initialisation of the treatment, the culture of the vitreous sample yielded Acinetobacter baumannii, which was sensitive to amikacin, imipenem and meropenem. Since no improvement was determined in clinical status after the initial intravitreal antibiotic injections, intravitreal amikacin (400µg/0.1ml) was given 4 days later. Topical drops were substituted with fortified amikacin and ceftazidime hourly. In the following days, no regression in the clinical picture was determined and the level of the visual acuity worsened to light perception loss. At the end of first month, B scan ultrasound revealed retinal detachment. Dense hypopyon and condensed vitreous were also detected, the cornea was opaque and serious ocular hypotony persisted.

DISCUSSION

Endophthalmitis, which is one of the most undesirable complications of ophthalmic invasive procedures, may develop after intravitreal injections.1 Intravitreal use of the drugs inhibiting VEGF has become common in recent years and an increase in the frequency of some undesirable severe complications, such as en-dophthalmitis has occured. The rate of endophthal¬mitis, which was approximately 10% in the era prior to asepsis, began to drop rapidly after the 1950s.[2] Among the causal agents of endophthalmitis, bacteria account for 90% and fungi were shown to be responsible for 10% of the cases. Earlier studies from literature 1964 and 1974 revealed a high percentage of S. aureus and Pseudomonas infections and very few anaerobic infections.

However, recent reports overwhelmingly suggest that S. epidermidis is the single most common causative agent and P. acnes is the most common cause in delayed onset endophthalmitis. Fungal etiology has been very rare.3 Bacterial endophthalmitis usually presents acutely with pain, redness, lid swelling, and decreased visual acuity as in our case. In addition, some bacteria (e.g., Propionibacterium acnes) may cause chronic inflammation with mild symptoms. This organism is a member of typical skin flora and usually inoculated at the time of intraocular surgery. Fungal endophthalmitis may manifest an indolent course over days to weeks. Symptoms are often blurred vision, pain, and decreased visual acuity.

A history of penetrating injury with a plant substance or soil-contaminated foreign body may often be elicited. In cases of postsurgical endophthalmitis, infection most often occurs shortly after surgery (e.g. in the first week) but it may occur months or years later as in the case of P. acnes.[2]

Visual loss, eye pain and irritation, headache, photophobia, ocular discharge, intense ocular and periocular inflammation and injected eye are the symptoms of endophthalmitis. Physical findings correlate with the structures involved and the degree of infection or inflammation.[1] The bacterial strains have great importance for prognosis; coagulase positive bacteria (e.g. Staphylococcus aureus) have a more devastating clinical course, whereas coagulase negative bacteria (e.g. Staphylococcus epidermidis) show a more benign course.4 Acinetobacter baumannii, which was shown to be the causative agent in our patient, has been defined as an important nosocomial pathogen in the last 15 years. It causes infections of various systems, such as bloodstream infections, urinary system infections, wound infections, ventilator-associated pneumonia (VAP), meningitis and endocarditis.[2] The importance of Acinetobacter species and in particular A. baumannii is based on its intrinsic resistance against many antibiotics. The known mechanisms of resistance against antimicrobials have been shown to be extended spectrum beta-lactamase production, aminoglycoside modifying enzymes and alterations in outer membrane porins.[5]

In the literature, there are various clinical pictures reported due to Acinetobacter species such as exposure keratitis, corneal ulceration (after penetrating keratoplasty), endophthalmitis (after trauma and cataract surgery), corneal perforation, infectious crystalline keratopathy and corneal infection due to the use of soft contact lenses.[4] According to current knowledge and research, an infectious situation caused by Acinetobacter species after intravitreal injections has not been reported. The rate of endophthalmitis developing after intravitreal injections including avastin, ranibizumab and triamcinolone was reported at various rates in studies with large series.

Bhavsar et al.,[5] reported the rate of endophthalmitis after intravitreal injections of ranibizumab to be 0.09%. It was reported that endophthalmitis rate of the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascularization) study group was 0.05% and that of the ANCHOR (anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in ARMD) group was less than 0.1%.6 In a study containing 452 ARMD patients, it was reported that the rate of endophthalmitis was 0.02% (2/128) in the ranibizumab group and 0.006% (2/324) in the avastin group.7 In endophthalmitis cases, the treatment depends on the underlying cause of endophthalmitis. The final visual outcome is heavily dependent on timely recognition and treatment, although multiple different approaches and advances in treatment have been performed, according to recent data.

The mechanism of resistance developed by the causative microorganism against multiple antibiotics is one of the challenges encountered during the treatment. At present, meropenem, imipenem and colistin (polymyxin E) are the most effective antimicrobial preparations against Acinetobacter baumannii strains.[5] The organism isolated from our patient was susceptible to amikacin, imipenem and meropenem; however, the clinical picture of endophthalmitis rapidly progressed and the visual acuity regressed to the loss of light perception, although the therapeutic protocol was applied.

Chen et al., reported two cases with endophthalmitis due to Acinetobacter baumannii; one with endogenous endophthalmitis and the other with postkeratoplasty endophthalmitis. In both patients, the clinical picture rapidly deteriorated and, despite antibiotic therapy, no remarkable improvement was observed.[8]

In conclusion, ocular infections due to Acinetobacter species, although uncommon, are challenging situations in the treatment period because of the multiple antibiotic resistance and high virulence of the bacteria. Considering the fact that they are widely present in the hospital environment, we think that these bacterial species might cause serious problems for the patients who are hospitalised for a considerable amount of time.

REFERENCES/KAYNAKLAR

1. Inan UU. Potential Toxicity with inhibitors of vascular endothelial growth factor. Ret-Vit (Special Issue) 2007;15:55-62.
2. Opazo AC, Mella SM, Domínguez MY, et al. Multi-drug efflux pumps and antibiotic resistance in Acinetobacter baumannii. Rev Chilena Infectol 2009;26:499-503.
3. Anand AR, Therese KL, Madhavan HN. Spectrum of aetiological agents of postoperative endophthalmitis and antibiotic susceptibility of bacterial isolates. Indian J Ophthalmol 2000;48:123-8.
4. Levy J, Oshry T, Rabinowitz R, et al. Acinetobacter corneal graft ulcer and endophthalmitis: report of two cases. Can J Ophthalmol 2005;40:79-82.
5. Bhavsar AR, Googe JM Jr, Stockdale CR, et al. Risk of endophthalmitis after intravitreal drug injection when topical antibiotics are not required: the diabetic retinopathy clinical research network laser-ranibizumab-triamcinolone clinical trials. Arch Ophthalmol 2009;127:1581-3.
6. Schmidt-Erfurth U. Clinical safety of ranibizumab in age-related macular degeneration. Expert Opin Drug Saf 2010;9:149-65.
7. Fong DS, Custis P, Howes J, et al. Intravitreal bevacizumab and ranibizumab for age-related macular degeneration. a multicentre, retrospective study. Ophthalmology 2010;117:298-302.
8. Chen KJ, Hou CH, Sun MH, et al. Endophthalmitis caused by Acinetobacter baumannii: report of two cases. J Clin Microbiol 2008;46:1148-50.