การเกิดเลือดออกจำนวนมากใต้ชั้นคอรอยด์หลังการฉีดยา bevacizumab เข้าน้ำวุ้นตา ในคนไข้โรคหลอดเลือดโป่งพองใต้จอประสาทตา: รายงานผู้ป่วย

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บทคัดย่อ

การฉีดยา bevacizumab เข้าน้ำวุ้นตา เป็นการรักษาที่นิยมใช้กันอย่างแพร่หลายสำหรับโรคของจอประสาทตา ภาวะแทรกซ้อนที่พบได้มีหลายอย่าง รวมถึงภาวะเลือดออกใต้ชั้นคอรอยด์

วัตถุประสงค์ของการศึกษาเพื่อรายงานการเกิดเลือดออกจำนวนมากใต้ชั้น คอรอยด์ (choroid) หลังการฉีดยา bevacizumab เข้าน้ำวุ้นตา ในผู้ป่วยโรคหลอดเลือดโป่งพองใต้จอตา (Polypoidal Choroidal Vasculopathy; PCV)

ผู้ป่วยรายที่1 ผู้ป่วยหญิงอายุ 75 ปี เป็นโรคหลอดเลือดโป่งพองใต้จอประสาทตา มีอาการปวดตาและมัวลงหลังรับการรักษาด้วยการฉีดยา bevacizumab เข้าน้ำวุ้นตา เป็นเวลา 1 เดือน

ผู้ป่วยรายที่ 2 ผู้ป่วยหญิงอายุ 53 ปี มาด้วยอาการเลือดออกใต้จอประสาทตา ได้รับการรักษาด้วยการฉีดยา bevacizumab เข้าน้ำวุ้นตา หลังจากนั้น 1 สัปดาห์ มีอาการปวดตาและมัวลงจนมองไม่เห็นแสง

รายงานผู้ป่วยนี้เป็นการรายงานผู้ป่วยที่สองที่พบภาวะเลือดออกรุนแรงใต้ชั้นคอรอยด์หลังการฉีดยาbevacizumab เข้าน้ำวุ้นตา ดังนั้นจึงควรจะต้องระวังการเกิดภาวะแทรกซ้อนที่รุนแรงนี้จากการฉีดยา bevacizumab เข้าน้ำวุ้นตาในคนไข้โรคหลอดเลือดโป่งพองใต้จอตา

คำสำคัญ: bevacizumab, เลือดออก , ภาวะแทรกซ้อน

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Massive Choroidal Hemorrhage after Intravitreal Injection of Bevacizumab in Polypoidal Choroidal Vasculopathy: Case Report

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Abstract

Purpose to report two cases of massive choroidal hemorrhage after intravitreal injection of bevacizumab for PCV (Polypoidal Choroidal Vasculopathy).

A 75 years olds woman with known case of PCV who had sudden ocular pain and loss vision after intravitreal bevacizumab injection in her right eye.

A 53 years olds woman with massive subretinal hemorrhage who had severe ocular pain and no light perception one week after intravitreal bevacizumab injection in her left eye.

Conclusion: This is second document report of massive choroidal hemorrhage after intravitreal bevacizumab. We suggest to warning about this serious complication after intravitreal injection bevacizumab in patient who had massive subretinal hemorrhage before injection.

Keywords: bevacizumab, hemorrhage, complication

Introduction

This is second document report of massive choroidal hemorrhage after intravitreal bevacizumab. There was one male case report of massive choroidal hemorrhage after intravitreal administration of bevacizumab for AMD from Greece[1] with onset for massive hemorrhage was ten days. Dose injection was 1.25 mg same as this case report.

Polypoidal choroidal vasculopathy (PCV) as a disease has yet to be comprehended completely. The clinical features consisting of huge serosanguineous retinal pigment epithelial and neurosensory layer detachments, although unique may closely mimick neovascular age-related macular degeneration (AMD).[2] Various treatment modalities, such as direct thermal laser photocoagulation, tissue plasminogen activator (t-PA) injection with gas displacement, submacular surgery and macular translocation surgery have been proposed.[2] Photodynamic therapy (PDT) with verteporfin has shown good results for PCV, but extensive subretinal hemorrhages and exudation limits its application.[3] Favorable results have been reported with combined therapy, including PDT and intravitreal bevacizumab (IVB), to treat PCV.[3]

Standard treatment of PCV now is PDT and/or intravitreal antivascular endothelial growth factor (Anti-VEGF). The most commonly reported complication of PDT for PCV is subretinal hemorrhage, estimated to be around 10%–30%.[4] Other complications of full fluence PDT include massive suprachoroidal hemorrhage, Retinal pigment epithelium (RPE) tears and micro rips, choroidal ischaemia, RPE atrophy, secondary Choroidal neovascularization (CNV) and fibrous scarring.[4] Although a lot of work[3,5] has been done on the role of photodynamic therapy (PDT) in PCV, the sequence of events leading to the resolution of the polyps is not clearly understood. PDT with verteporfin utilises selective endothelial uptake of photoactivated compound into PCV lesions.

Effect of anti-VEGF therapy; the anti-permeability property of anti-VEGF agents probably plays a role in reducing the exudation from abnormal choroidal vessels and polyps, thereby decreasing the subretinal fluid and preserving vision.[6-13] Four such drugs are now available in the world, one of them off-label (bevacizumab, in use since 2005) and three that have been approved for use in Europe: ranibizumab (approved 2007), aflibercept (approved 2012), and brolucizumab (approved 2020). The three approved drugs each cost approximately 1000 euro per injection, while bevacizumab costs only approximately 40 euro.

Intravitreal administration of bevacizumab (Avastin; Genentech, Inc., San Francisco, CA, USA.), tumor-starving (anti-angiogenic) therapy, Avastin was designed to block a protein called vascular endothelial growth factor (VEGF). Intravitreal anti-VEGF injection has become the standard therapy for many retinal disease.[14] The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%).[4] Serious systemic adverse events was arteriothrombotic event, cerebrovascular accident, transient ischemic attack.[4] It was found that a single intravitreal bevacizumab (IVB) significantly reduced the plasma VEGF levels for up to 1 month compared to no significant systemic effects of an intravitreal injection of ranibizumab on plasma VEGF in patients with diabetic macular edema and AMD.[15]

Case report

First case: A 75-year-old woman with no underlying disease presented with known case of PCV both eyes (BE) since 2017 and history of

breakthrough vitreous hemorrhage in her left eye (LE) in 2018. She had been treated with several time of intravitreal bevacizumab injections in her both eyes since 2017 and Pars plana vitrectomy in her left eye in 2018. Her Best corrected visual acuity (BCVA) was 20/40 in the right eye and 20/30 in the left eye. This episode she had new submacular hemorrhage (SMH) in the right eye then she had an intravitreal injection of 1.25 mg bevacizumab (Avastin) in the right eye (RE).

one month after injection before day of follow up, she had sudden ocular pain and loss vision in her right eye so she came to the hospital before date of appointment. On presentation, her BCVA was no light perception (NLP) in the RE. The conjunctiva was ciliary injection, the cornea edematous, and the anterior chamber (AC) was flat. Ultrasound of the eye showed massive choroidal hemorrhage. The intraocular pressure in the patient's RE was 48 mmHg. The oral administration of carbonic anhydrease inhibitor and hyperosmotic agent which is standard treatment of acute severe increase intraocular pressure was performed, then she had treated by laser cyclophotocoagulation. After treatment the pressure gradually decrease and six months later, the RE became to phthisis bulbi.

Second case: A 53 years old female with no underlying disease who had present with massive subretinal hemorrhage (SRH) with macular involvement in her left eye (Figure 1). Her BCVA was 20/20 in her right eye and 20/400 in her left eye. She had been treated with intravitreal bevacizumab 1.25 mg. One week after injection she had came to hospital because of symptom of severe ocular pain. Her best corrected visual acuity of left eye was no light perception with more than 60 mmHg of intraocular pressure. Conjunctiva of left eye was marked injection, the cornea was swelling and bullous keratopathy was found. Anterior chamber was shallow grade 3 (Figure 2). Ultrasound of the left eye showed massive choroidal hemorrhage and haziness in vitreous cavity. Treatment was oral glycerine and oral acetazolamide but one hour after treatment the ocular pressure still over 60 mmHg. Because of severe pain that has not got better, so she was treated by suprachoroidal drainage by 23G port (Figure 3). The pain was dramatic relief after surgical treatment but BCVA was still no light perception.

Figure 1A. Preinjection fundus picture showed massive subretinal hemorrhage in the left eye.

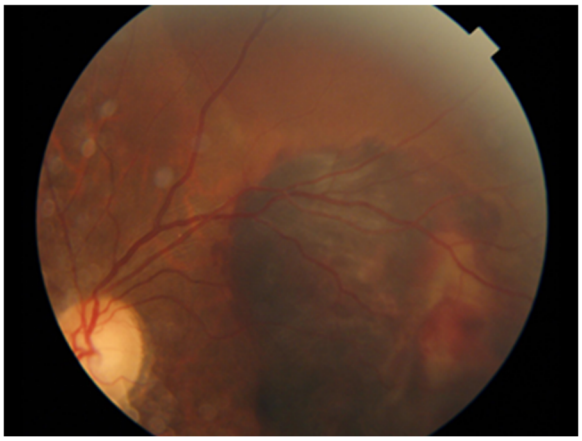


Figure 1B. Optical coherence tomography (OCT) showed massive hemorrhage under the retina

Figure 2A. Marked conjunctival injection with corneal edema in the left eye. The anterior chamber was shallowed

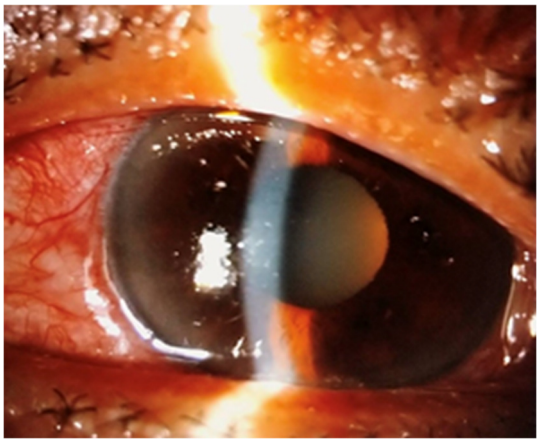


Figure 2B. Ultrasound showed intraocular massive hemorrhage.

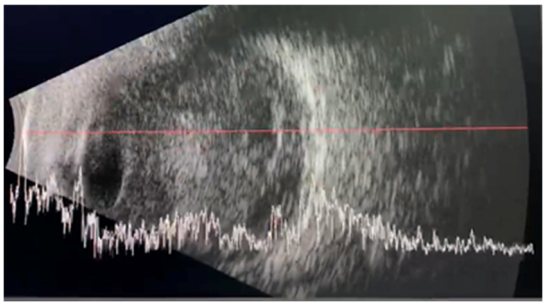
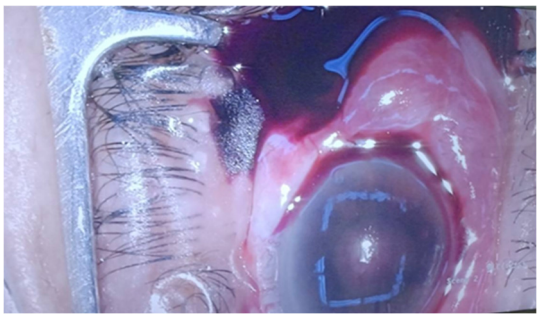


Figure 3. Large amount of blood by 23 gauge port intraoperative suprachoroidal drainage of the left eye



Discussion

It has been reported that the aqueous humor level of vascular endothelial growth factor (VEGF) was higher in the eyes with PCV than in the eyes with AMD[16], revealed an association between VEGF and PCV. Bevacizumab, a humanized monoclonal antibody that inhibits all VEGF isoforms, has shown promising results against CNVs that were secondary to AMD.[17-20] Gomi, et al[21] reported that intravitreal bevacizumab (IVB) was effective in reducing the fluid from PCV but not for diminishing choroidal vascular changes. In addition, they reported that a single IVB was insufficient for the treatment of PCV and that regular injections might maintain vision over a longer time because of the anti-leakage effect of bevacizumab on the exudative changes due to PCV.

Systemic administration of bevacizumab causes serious adverse event that serious and sometimes fatal adverse reactions included: gastrointestinal (GI) perforation, GI bleeding, arterial thromboembolic events, hemorrhagic complication. The ocular complications of intravitreal injection included lens injury, ocular inflammation, retinal pigment epithelial tear, endophthalmitis and acute vision loss.[22]

Although the mechanism of massive hemorrhage after bevacizumab injection remains unclear, the robust effect of bevacizumab on abnormal choroidal vessels could contribute to the hemorrhage. So the researcher suggest to injection slowly in patient who have large subretinal hemorrhage.

One study reported that a significantly higher rate of submacular hemorrhage occurred following intravitreal bevacizumab for ≥15 ml occult CNV than following intravitreal ranibizumab because bevacizumab has a longer half-life and more strongly influences contraction of the CNV

membrane, resulting in rupture of blood vessels.[23]

SRH after anti-VEGF injection for wet AMD or PCV may occur as a consequence of the natural history of the disease. In particular, patients with PCV sometimes develop spontaneous massive SRH.[24] But we had to consider about the hemorrhagic complication of Anti VEGF intravitreal injection.

The 5 years experience of researcher had performed injection for 2552 eyes and had found only 2 cases who have massive choroidal hemorrhage (0.08%). After clinical review, no significant pitfall was found in these two cases. However tightly control blood pressure and hold anticoagulant drug before injection may be decrease risk of hemorrhage.

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