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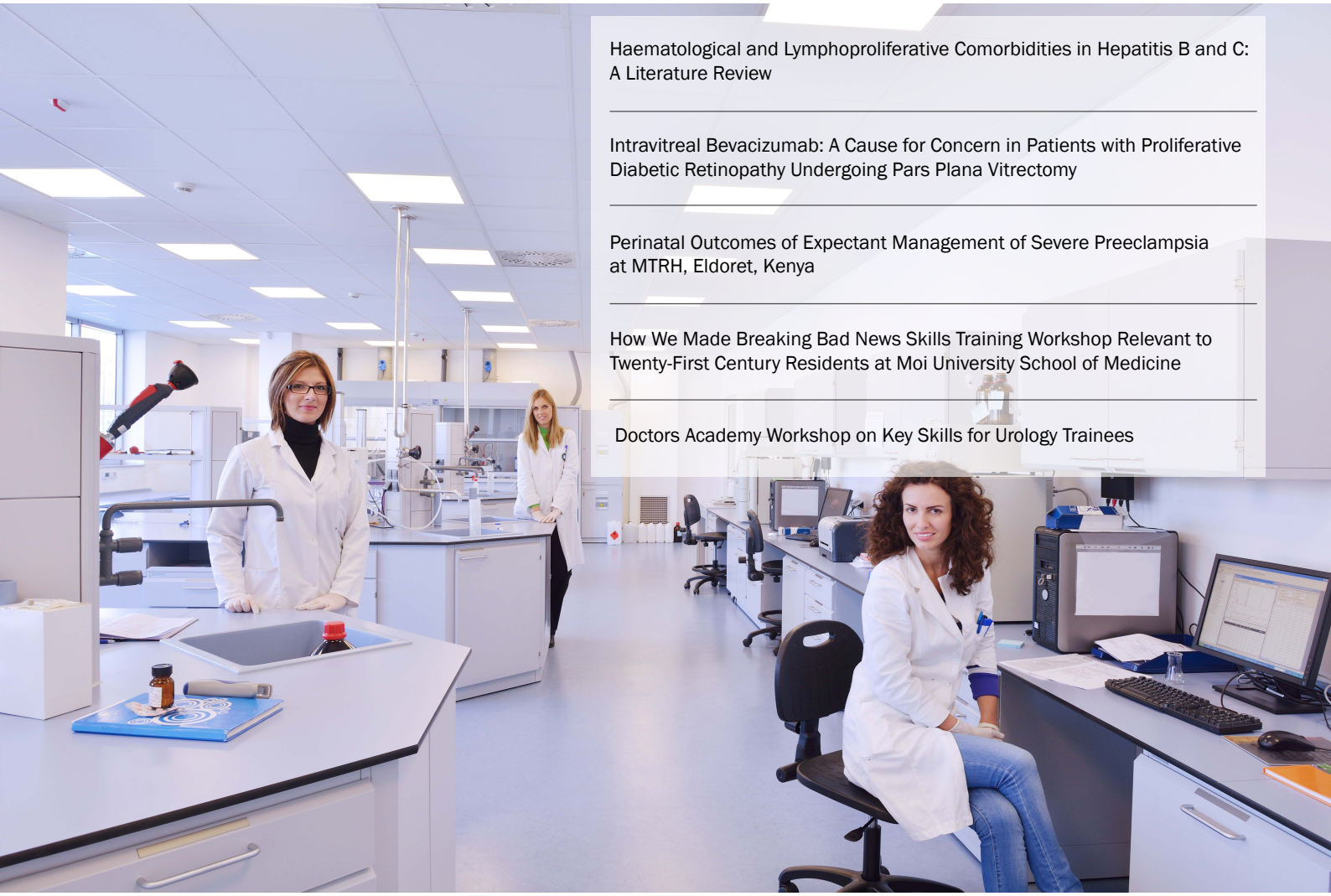

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Case Report
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Intravitreal Bevacizumab: A Cause for Concern in Patients with Proliferative Diabetic Retinopathy Undergoing Pars Plana Vitrectomy

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Abstract
Aim: To report: 1. Development of no light perception (NLP) in the left eye (OS) one day post pars-plana vitrectomy (PPV) with pre-operative intravitreal bevacizumab. 2. Progression from extra-foveal tractional retinal detachment (RD) to combined fovea threatening rhegmatogenous and tractional RD in the contralateral untreated right eye (OD) five days post-surgery.
Observations: A 53-year-old female with 20-year history of insulin dependent diabetes presented with a gradual drop of vision over a four-month period. A diagnosis of tractional RD threatening the fovea was made OS, and extra-foveal tractional RD OD. Pre-operative best corrected visual acuity (BCVA) was 4/200 OS and 20/50 OD. The patient was treated with 25-gauge PPV, gas tamponade and pre-operative intravitreal bevacizumab OS. Day 1 post-op, BCVA was NLP OS. Day 5 post-op, BCVA was hand-motion OD with a diagnosis of combined rhegmatogenous and tractional RD threatening the fovea.
Conclusions: The reasons for development of NLP on day one post-PPV in the treated eye are inconclusive. We propose that progression to fovea threatening combined rhegmatogenous and tractional RD in the untreated eye is due to the systemic absorption of the pre-operative intravitreal bevacizumab to the treated eye leading to increased fibrous contracture, causing retinal breaks.

Key Words
Intravitreal Bevacizumab; Proliferative Diabetic Retinopathy; Combined Rhegmatogenous and Tractional Retinal Detachment; No Light Perception

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Introduction

Pars plana vitrectomy (PPV) is known to improve anatomic features as well as functional visual acuity.[1] In the majority of cases, visual improvement is seen. However, there remain to be intraoperative (intra-op) and postoperative (post-op) complications that may hinder visual outcome.[2] Intra-op complications include retinal breaks and choroidal haemorrhage. Post-op complications include recurrent vitreous haemorrhage and retinal detachment (tractional, rhegmatogenous or combined).[3] In terms of best corrected visual acuity (BCVA): one study of 124 patients found that five of these patients developed light perception (LP) vision on the first post-operative day (pre-op BCVA were counting fingers (CF) – light perception LP)). two of these five developed no light perception (NLP) by the second and fourth week post-operatively while LP for the other patients persisted during the first month post-op.[4]

Another study of 100 eyes requiring vitrectomy for proliferative diabetic retinopathy (PDR) had eight individuals with a pre-operative diagnosis of macula detached tractional retinal detachment (RD). One of those individuals progressed to NLP vision at 12 months follow up. However, there was no data to show what their BCVA was on first day post-op.[1]

The use of intravitreal anti vascular endothelial growth factor (Anti-VEGF) drugs such as bevacizumab (avastin) is indicated no more than one week pre-vitrectomy due to vitreous haemorrhage. It has been shown to reduce post-op vitreous haemorrhage.[5] Some studies however, have linked it to the development of tractional RD in patients with PDR.[6,7,8] Intraoperative avastin has also been reported to cause progression to tractional RD involving the macula in the untreated eye.[7]

We report an eye developing NLP on day one post PPV pre-treated with avastin, followed by the contralateral eye developing combined tractional and rhegmatogenous RD after five days.

Case Report

A 53-year-old female with a past medical history of uncontrolled type 2 diabetes on insulin replacement therapy, hypertension and past ocular history of two sessions of bilateral pan-retinal photocoagulation (PRP) for PDR presented to King Khaled Eye Specialist Hospital with gradual worsening of vision over a four-month period. Examination revealed a BCVA of 20/50 in the right eye (OD) and 4/200 in the left eye (OS). Intraocular pressure (IOP) was 16 bilaterally. Both eyes had nuclear sclerotic (NS) cataract, and neither had iris neovascularization (NVI). Fundal examination OD showed extra-foveal tractional RD, posterior hyaloid proliferation, inferior vitreous haemorrhage and old retinal laser scars with a normal optic nerve head. Fundal examination OS showed tractional RD involving the fovea, old retinal scar and a healthy optic nerve head. Fluorescein angiography (FA) OS showed a variable degree of macular ischaemia and good optic nerve perfusion.

The right eye was treated with PRP. The left eye was treated with intravitreal avastin followed by a 25-gauge PPV with membrane segmentation and delamination, panretinal endolaser photocoagulation (EL), fluid air exchange and 20% sulfur hexafluoride (SF6) gas tamponade three days later. A guarded prognosis was discussed with the patient. Days 1-4 post-PPV: The patient was not in pain. OD BCVA was 20/50 and fundal examination was unchanged. OS BCVA was NLP, IOP was 30, the cornea was clear, the lens remained mild NS and retina was flat under 90% gas with a healthy appearing disc. Day 5 post-PPV: OS remained unchanged. OD BCVA was hand motion with a new combined rhegmatogenous and tractional RD involving the fovea. The right eye was then treated with PPV with membrane segmentation and delamination, EL, fluid air exchange and silicone oil tamponade.

Visual acuity OD improved to 20/300 on the subsequent visits and continues to show progress. Visual acuity OS improved to 2/300 after resolution of 40% of the gas bubble and has complete anatomical success. Removal of silicon oil was performed on the right eye and the vision remained stable.

Discussion

No light perception following pars plana vitrectomy is uncommon. As discussed above, one out of 100 patients in one study (1%) and two out of 124 patients (1.6%) in another developed NLP.[1,4] We have, however, not found any patients developing NLP on day one post-op such as this patient we described. Many significant risk factors have been identified. Common in both mentioned studies is post-op vitreous haemorrhage and NVI.[1,4] Pre-operative NVI and post-op macular ischaemia are others.[4] It is important to note that on the contrary, post-op rise in IOP and pre-op TRD and PRP therapy are not significant risks.[1,4] With this in mind, after thorough examination and analysis of our patient, we could not adequately explain why they developed NLP one day post-PPV.

The use of Anti-VEGF medications such as avastin has been linked to tractional or combined rhegmatogenous and tractional RD shortly after vitrectomy due to inducing more fibrous contracture leading to breaks.[9] The risk of RD is increased with a longer time interval between injection and vitrectomy in patients with uncontrolled diabetes, VH and PDR resistant to PRP.[6]

A few pharmacokinetic studies have identified a potential contralateral effect of avastin.[10,11] Avastin was injected unilaterally through an intravitreal route in eyes of rabbits; levels were measured in the vitreous and serum and were found to be raised to a lesser extent in the contralateral eye. This suggests systemic absorption and distribution.[10] In patients with wet age related macular degeneration, serum pharmacokinetics and plasma free VEGF were evaluated and showed after the first week of injection, plasma levels of avastin were raised above its half inhibitory concentration (IC_{50}) and led to a significant reduction in plasma free VEGF, further demonstrating systemic exposure.[11] A study by Matsuyama et al, on patients with PDR who received unilateral intravitreal avastin showed that at day 7, the level of VEGF in the contralateral eye was also significantly reduced. Thus we need to be observant of the fellow eye when injecting avastin.[12]

Therapeutic response of intravitreal injection of avastin (1.25mg/0.05ml) on the contralateral eye has been reported in the treatment of PDR and macular oedema. This also suggests adverse effects should also be anticipated in the contralateral eye.[13,14,15]

To summarise, avastin has been linked to development of rhegmatogenous and tractional RD.[9] It has also been linked to cause progression of tractional RD involving the macula in the contralateral eye[7], and has been shown by various studies to affect the contralateral eye.[10,11,12,13,14,15]

With this in mind, we hypothesise that, in our patient, the development of contralateral combined rhegmatogenous and tractional RD five days post-PPV is due to the avastin given three days pre-PPV. We cannot absolutely rule out the possibility that the progression to combined rhegmatogenous and tractional RD involving the fovea in the right eye is a coincidental event

resulting from natural disease pathology. We, however, deem this unlikely given that it occurred five days post-PPV and eight days post-injection of avastin in the contralateral eye. To the best of our knowledge, this is the first reported case of developing NLP one day post-PPV and the first reported case of progression of the contralateral eye to combined rhegmatogenous and tractional RD involving the fovea.

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