Case Report

The Challenges in Managing Proliferative Diabetic Retinopathy with Neovascular Glaucoma

Putri A Idham, Elvioza, Andi Victor, Gitalisa Andayani, Aridjatikusumo, Anggun Ramayudatha
Department of Ophthalmology, Faculty of Medicine Universitas Indonesia
Jakarta

ABSTRACT

Background: *The aim of this study is to emphasize the importance of close monitoring of the disease progression, minimize late complication, and knowing the important parameters of succesful treatment.*
Methods: *A 52 years old woman with proliferative diabetic retinopathy was referred to Vitreoretina division. Patient came with chief complaint blurry vision of the left eye. Patien was diagnosed with diabetes melitus type 2 since 10 months ago. At ophthalmological examination, there was iris neovascularization on the left eye. Due to this finding, patient was given treatment for the proliferative diabetic retinopathy and neovascular glaucoma.*
Results: *The patient undewent intravitreal injection of bevacizumab and Kehki Meta implant surgery after panretinal photocoagulation laser. Neovascularization of the iris was regressed and the intraocular pressure was controlled.*
Conclusion: *This patient underwent laser panretinal photocoagulation, bevacizumab injection and Keiki Mehta implant surgery. The result was good. The neovascularization was regressed. Closed monitoring should be continued to evaluate the progression of the disease and control the intraocular pressure to prevent further visual loss*

Keywords: *Proliferative diabetic retinopathy, neovascular glaucoma, diabetic macular edema*

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus.[1] The prevalence of all types of diabetic retinopathy ini diabetic population increases with the duration of diabetes and patient age.[2] Data from Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) indicate that 1.07 and 1.3% of persons with diabetes will develop PDR and DME.[1] Proliferative diabetic retinopathy (PDR), a more advanced stage of DR, is characterized by neovascularization at or near the optic disc, retina, and/or iris.[3,4] This neovascularization occured as a result of some cellular event which include wide retinal hypoxia, elaboration of factors that stimulate endothelial cell proliferation, macrophages, and vitreous contraction.[3]

Based on the extent of proliferation, PDR is graded into early, high-risk, or advanced categories.[2] Diabetic Retinopathy Study (DRS) defined high risk characteristics patients by the presence of preretinal or vitreous hemorrhage, eyes with NVD equalling or exceeding one-quarter to one-third disc area with or without hemorrhage, and NVE equalling more

than a half disc area with hemorhage.[2, 4] Untreated patients with high risk characteristics had between 25.6% and 36.9% chance of severe visual loss within 2 years depending on the size and location of the new vessels and whether or not hemorrhage was present.[4]

Potential visual loss in patients with diabetic retinopathy can be associated with macular edema, macular ischemia and sequelae from ischemia-induced neovascularization. Retinal edema involving the macula is an important visual consequence of abnormal retina vascular permeability in diabetic retinopathy.[2] Based on Early Treatment Diabetic Retinopathy Study (ETDRS) definition, diabetic macular edema was defined as retinal thickening within 1 disk diameter of the center of the macula or definite hard exudates in this region.[5]In the United States, diabetic macular edema (DME) is the most common cause of visual loss in those with diabetic retinopathy.[5] Suggestive data have been reported that the prevalence of DME relative to PDR may vary by race with rates of DME relatively low in Native Americans.[6]

Neovascularization of the iris may occur in PDR patients as a result of retinal ischemia and had a close relationship with the extent of retinal ischemia.[7, 8] In an unselected diabetic population, the incidence of iris neovascularization ranged from 1% to 17%. In eyes with PDR, the incidence of iris neovascularization increased to 65%.[8] Study by Bonnet et al[9] shows that 49% of the eye with optic disc new vessels was have iris neovascularization. Among eyes affected with iris neovascularization, 93.8% had also optic disc neovascularization.[9] Neovascularization of the iris frequently begins at the superior pupillary border of the iris and trabeculum due to convection currents in the anterior chamber. This condition can leads to neovascular glaucoma state because of angle block[7]

Neovascular Glaucoma (NVG) is a secondary glaucoma resulting from severe ocular ischemia and is most commonly associated with posterior segment conditions such as proliferative diabetic retinopathy.[10] Formation of tiny dilated capillary tufts on the pupillary margin is typically associated with neovascular glaucoma. If left untreated, the new blood vessels may proceed to join the circumferential angle vasculature. Iris neovascularization develops in about 33% to 64% of patients with PDR.[11] .

The principal goal in the management of diabetic retinopathy with neovascular glaucoma is the delay and prevention of complications. These goal can be achieved by implementing both systemic and local treatment that influence the progression of neovascularization in PDR.[2] Scatter panretinal photocoagulation (PRP) treatment is almost always recommended for patients with high-risk PDR. [2, 4]

This article reports a case of high risk proliferative diabetic retinopathy with neovascular glaucoma. Panretinal photocoagulation (PRP) of both eyes and anti VEGF intravitreal injection of the left eye were performed, and followed by Keiki Mehta implantation surgery of eye. The problem in this case is that although the treatment was given as soon as the patient was diagnosed, the outcome of treatment was poor due to the wide ischemia of the retina. The aim of this case report is to emphasize the importance of close monitoring of the disease progression, minimize late complication, and knowing the important parameters of succesful treatment. This case report offers additional knowledge of knowing the holistic treatment and succesful parameter of treatment in diabetic patient with proliferative diabetic retinopathy.

CASE ILLUSTRATION

A 52 years old woman came to Cipto Mangunkusumo Hospital Kirana on February 11, 2014 with chief complaint blurry vision of left eye (LE) since 8 months ago. The patient felt that the blurry vision slowly worsened and was progressive. There were no floaters or photopsia, no history of spectacles, and no red eyes, watery eyes, discharge, and pain. Patient was diagnosed with diabetes melitus type II by a general practitioner since 10 months ago. She was treated with metformin 500 mg twice a day but she did not took the medicine regularly. There was no history of hypertension and insulin therapy.

Visual acuity (VA) of right eye and left eye were 6/60 uncorrected. Intra ocular pressure (IOP) of right eye was 19.3 mmHg and left eye was

43.7 mmHg. There was iris neovascularization on left eye. Fundus examination of right eyes showed round papil with cup disc ratio 0.3-0.4, arterivenous caliber 2/3, hard exudates, dot blot hemorrhages, microaneurysms at 4 quadrants, and decreased macular reflex. Fundus examination of left eye showed round papil, neovascularization of the disc with cup disc ratio 0.4 - 0.5 and normal arteriovenous caliber. There were Weiss ring, cotton wool spots, hard exudates, dot blot hemorrhages, flame shaped hemorrhages, microaneurysms, but there were no neovascularization elsewhere (-), with decreased macular refllect.

Patient was diagnosed with Proliferative diabetic retinopathy (PDR) on the left eye and posterior vitreous detachment with severe non-proliferative diabetic retinopathy (NPDR) on the right eye, bilateral immature senile cataract, clinically significant macular edema (CSME) and neovascular glaucoma of the left eye. The Patient was planned to have laser pan retinal photocoagulation (PRP) on her left eye then right eye, and Anti-VEGF injection of left eye. She was also planned to have ancillary testings including fundus photography and fundus fluorescein angiography (FFA). Patient then was given some medicines for the left eye includes timolol eye drop 0.5% twice a day, acetazolamide three times a day, and potassium 300 mg tablets one time a day.

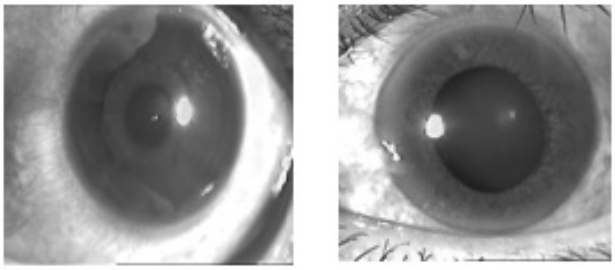

Figure 1. (A) Picture of the right eye. (B) Left eye. Iris neovascularization at lateral pupillary margin (black arrow)

Patient underwent bilateral macular OCT and fundus photography examination on February 13, 2014 and underwent FFA on February 14, 2014. Fundus photography of right eye showed hard exudates, cotton wool spots, flame shaped and dot blot hemorrhages in 4 quadrants (picture 3.A) while left eye showed neovascularization on the disc and dot blot hemorrhages in 4 quadrants (picture 3.B)

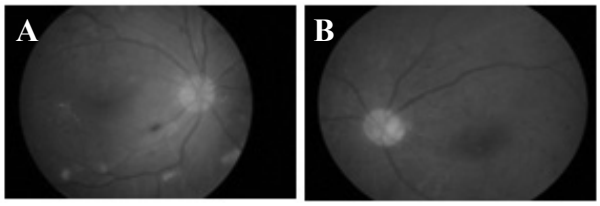

Figure 2. Fundus photography. (A) Fundus photography of the right eye shows hard exudates (white arrow), cotton wool spots (black arrow), flame shaped and dot blot hemorrhages in 4 quadrants. (B) Fundus photography of the left eye shows neovascularization on the disc (black arrow) and dot blot hemorrhages at 4 quadrants.

On February, 18 2014, one week after given medications, patient complained about headache, nausea and sometimes pain in the left eye. There were no red eyes following the complaint. VA of the right eye was 6/60, and 1/60 for the left eye with intra ocular pressure of the right eye: 15.3, OS 53.7. Retinal clinic planned to consult the patient to glaucoma division, and scheduled the patient to underwent laser PRP of left eye. Glaucoma division assest the patient with neovascular glaucoma of left eye, bilateral immatur senile cataract, PDR on the left eye, and severe NPDR on the right eye. Patient was scheduled to underwent Keiki Mehta implantation and phacoemulsification with IOL insertion of left eye join operation with retina division to do intravitreal injection of bevacizumab. Patient was given Acetazolamide three times a day, Potassium twice a day, and timolol 0.5% twice a day. Patient came back on March 3, 2014 and underwent laser PRP of left eye.

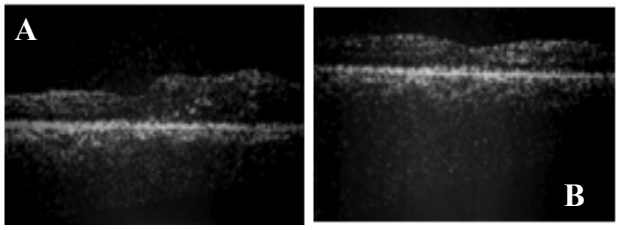

Figure 3. Stratus OCT (A) Stratus OCT of the right eye shows retinal thickening temporal from the macula. (B) Stratus OCT of the left eye shows normal macula

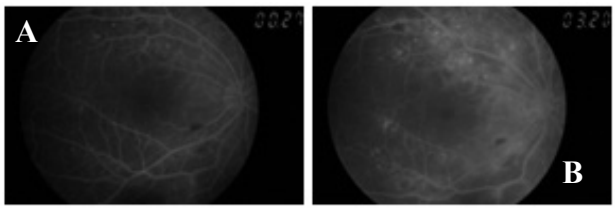

Figure 4. Fundus fluorescein angiography (FFA) of right eye shows hypofluorescence area. Prove any capilary leakage.

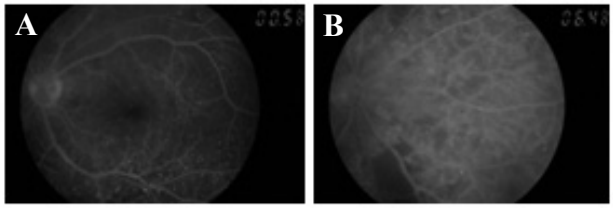

Figure 5. Fundus fluorescein angiography (FFA) of left eye (A) It shows capilary leakage on the disc (B) The picture shows hypofluorescen area and nonperfusion area

On March, 6 2014, Patient underwent Keiki Mehta implantation, phacoemulsification with IOL insertion and bevacizumab injection of left eye. One day post operation, VA of right eye was 6/60 and left eye was light perception. Intraocular pressure were 10 mmHg on right eye and 3 mmHg on left eye (with portable non-contact tonometer). There were eyelid edema and spasm, conjunctival and ciliary injection, and subconjunctival bleeding on superior part. There was corneal edema with Descemet folds, 2 sutures on superior at 1 o'clock position. Anterior chamber was VH1 temporal and VH2 nasal site, and there was inferior blood clot, dispersed hyphema with cells +2, and no flares. Posterior chamber with tube at 2 o'clock position. Pupil round, central, dilated, light reflex decreased. The lens with IOL implantation, vitreous and fundus were hard to be evaluated. Patient was given diclofenac potassium 50 mg tablet three times a day, levofloxacin eye drop six times, prednisolone eye drop six times, and atropine sulphate 1% three times a day on the left eye.

Seven days after surgery, on March, 14 2014, patient came back. She still complaint about her blurry vision. Patient felt that the blurry vision of left eye was worsened. VA of right eye : 6/60 and 1/300 for the left eye. Intra ocular pressure of right eye : 13.6 mmHg while intra ocular pressure of left eye: 8.7 mmHg. The eyelid was still spasm with minimal edema, conjunctival and ciliary injection with subconjunctival bleeding. There were minimal Descemet fold. Anterior chamber was VH 1 at temporal site, VH 2 at nasal site, blood clot with hyphema. Pupil round, central, dilated, light reflex decreased, implant at posterior chamber of the left eye at 1 o'clock position, V/F hard to be evaluated because of blood clot. The medications was still continued from the last visit.

Two weeks after surgery on March, 25 2014 patient came back. VA of right eye was 3/60 and left eye was 1/300, intra ocular pressure of right eye : 13.7 and left eye was 20.8. The cornea was clear. Other ophthalmological conditions was still remaining the same. The medications were still continued.

April, 11 2014 **:** VA of right eye and left eye were 3/60 with intra ocular pressure of the right eye was 13.2 mmHg and the left eye was 28.1 mmHg. There was edema of the eyelid. Conjunctival and ciliary injection, cornea was clear, iris pigmen at endotel, 2 sutures at 2 o'clock position. Anterior chamber was VH1 at temporal site, VH2 at nasal site, peripheral anterior synechia at 2 and 6 o'clock position, posterior chamber : tube shifting to the front, Lens with IOL and coagulum and PCO. Fundus was hard to be evaluated. Patient was diagnosed with neovascular glaucoma of the left eye post Keiki Mehta implantation + phacoemulsification with IOL insertion. Patient was planned to have synechia release and peripheral iridectomy of the left eye. Patient was given Levofloxacin four times, prednisolone four times, and artificial tears six times a day on the left eye.

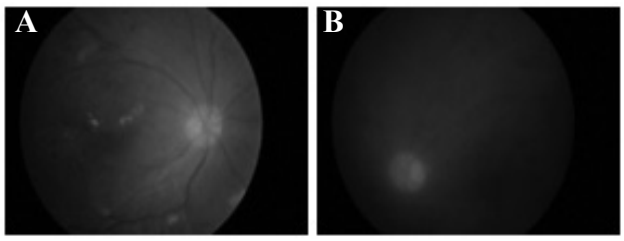

Figure 6. Fundus photography about 1 months after Keiki Mehta implantation and bevacizumab injection (A) Fundus photography of right eye. (B) Fundus photography of left eye.

DISCUSSION

Diabetic retinopathy is the leading cause of blindness among adults aged 20 to 74 of age in US. It is estimated that more than 10.000 individuals become legally blind from diabetic macular edema (DME) and/or Proliferative diabetic retinopathy (PDR) each year.[12] Proliferative diabetic retinopathy (PDR) is an advanced stage of diabetic retinopathy and marked by neovascularization on the retina, iris, and/or optic disc.[3, 4] Neovascularization on the disc (NVD) is defined as new vessels growth on the retina in locations greater than one disc are of the optic nerve head. Neovascularization elsewhere (NVE) is defined as new vessel growth on the retina in locations greater than one disc area from the optic nerve head.[13]

The duration of diabetes is a strong risk factor for the development of retinopathy. The natural history of diabetic retinopathy is progressive. Over 60% of patient with type 2 diabetes develop some degree of retinopathy over the course of 20 years.[12] American Academy of Ophthalmology[14] launched a new clinical severity scale for diabetic retinopathy in 2003. The scale was based on data from important clinical studies such as ETDRS and WESDR. This international clinical diabetic retinopathy disease severity scale was classify diabetic retinopathy into 5 level. The first level is "no apparent retinopathy". The second level is "mild Non Proliverative Diabetic Retinopathy (NPDR)" which describes any microaneurysms in retina. The third level is "moderate NPDR". The fourth level is "severe NPDR" which the most ominous prognosis for relatively rapid progression to PDR. The criteria for this category was the presence of lesions with "4:2:1 rule". This include four retinal quadrant containing extensive retinal hemorrhages (approxiomately 20 per quadrant), two quadrants containing definite significant venous beading or any single quadrant containing definite Intraretinal microvascular anomalies (IRMA).[12,14] In evaluations performed on the ETDRS data, IRMA and venous beading were very predictive of the risk of developing proliferative diabetic retinopathy. The fifth level,"PDR" includes all eyes with definite neovascularization.[12] Vascular proliferation in diabetic retinopathy appears because of ischemia of the inner retinal layers secondary to closure of segments of the retinal capillary system. This process has subsequent production of vessel stimulating growth factors by the ischemic retina. One vessel stimulating growth factor currently being studied is VEGF. VEGF is a group of protein that initiates angiogenesis and increases permeability at blood-tissue barriers. VEGF is produced by the retina, choroid, and retinal pigmen epithelium. Levels of VEGF are greatly increased in the aqueous and vitreous fluid of persons with diabetic retinopathy.[13]

In patients with Diabetes Melitus (DM), the prevalence of any form of diabetic retinopathy is approximately 24%.[15] Diabetic Macular Edema (DME) is the major vision-threatening complication of DR. The Wisconsin Epidemiologic Study has reported that the prevalence of DME in diabetic of 15 years duration is approximately 20% in patients with type I DM and 25% in patients with type II DM that are on treatment. [16] Up to 3% of patients whose diabetes is first diagnosed at age 30 or later will have CSME or high-risk characteristics at the time of the initial diagnosis of diabetes.[17] Macular edema develops secondary to microaneursym formation, breakdown of the blood-retinal barrier, increased vascular permeability and leakage of fluid and exudate. ETDRS defined macular edema as retinal thickening from accumulation of fluid within one disc diameter of the macula. Macular edema is defined as clinically significant macular edema (CSME) if any of the following three features are present : (1) thickening of the retina at or within 500 microns of the center of the macula, (2) hard exudates at or within 500 microns of the center macula, if associated with thickening of the adjacent retina, (3) a zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula. Chronic macular edema may progress to macular retinoschisis and partial or complete macular hole formation.[13]

Vascular occlusion and ischemia can lead to local tissue hypoxia condition. These conditions can induce vascular endothelial growth factor (VEGF) and other host growth factors.[18] Vascular

endothelial growth factor is thought to be a key factor in the pathogenesis of DME[19] and is a vasoactive cytokine that both induces vascular permeability and stimulates angiogenesis. It is approximately 50.000 fold more potent in inducing permeability than histamine.[20] Vascular endothelial growth factor concentrations are elevated in both the vitreous fluid and aqueous humor of patients with active proliferative diabetic retinopathy.[21] Recent studies showed the role of anti VEGF agents in human with diabetic macular edema. Regarding this circumstances, certain research studies concerning anti VEGF in diabetic macular edema patient report and support the benefit of anti VEGF treatment. American Academy of Ophthalmology (AAO)[22] reports the safety and efficacy of 4 major anti VEGF agents that have been evaluated in treating DME. These agents include pegaptanib sodium (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), and anti VEGF trap-eye (Aflibercept® and Eylea®). The study shows that anti-VEGF pharmacotherapy, delivered by intravitreal injection is a safe and effective treatment over 2 years for DME. Study by BOLT study[23] also support the efficacy of bevacizumab. It was reported that bevacizumab injection in clinically significant macular edema patient decrease center macular thickness better than macular laser therapy. Bevacizumab, a full-length humanized monoclonal neutralizing antibody against VEGF designed for intravenous administration and approved for the treatment of metastatic colorectal cancer, in the management of patients with DME associated with severe cappilary loss.[24] DA VINCI study[25] also reported the efficacy of anti VEGF. They show that significant best corrected visual acuity (BCVA) from baseline achieve at week 24 maintained or improved at week 52 in all VEGF Trap-Eye groups compared with laser treatment groups. Patients without macular edema can still maintain good vision even if they have advanced stage of the disease. Hence, management of DME has become important for ophthalmologist in preventing vision loss to their diabetic patient. The Diabetes Control and Complication Trial[26] showed that intensive blood glucose control can reduced the risk of development of DME by 23%.

Our patient on her first visit complained about blurry vision of left eye. Blurry vision occured gradually and progressive. There were no history of trauma, floaters, and fotopsia. Patient was diagnosed diabetes melitus type II by general practitioner since 10 months ago. On ophthalmological status, there were iris neovascularization on the left eye, neovascularization on the disc, weiss ring, cotton wol spot, hard exudate, dot blot hemorrhage, flame shaped hemorrhage, microaneurysm, but there were no neovascularization elsewhere (-) and there were decreased macular reflex. With this finding, we can assume that this is a proliferative diabetic retinopathy with clinically significant macular edema. On ophthalmological status of the right eye, there were hard exudate, dot blot hemorrhage, flame shaped hemorrhage, microaneurysms at 4 quadrants, and decreased macular reflex. This clinical finding meets the criteria of severe nonproliferative diabetic retinopathy. Although the left eye has shown neovascularization on the disc, which was more advanced stage of the diabetic retinopathy and show further wide ischemia, its manifestation do not show any neovascularization elsewhere and also do not have hemorrhage, hard exudates, cotton wool spot as much as the right eye. Patient then underwent fundus photography of both eye (OU) and macular optical coherence tomography (OCT) OU. The fundus photography supports the clinicial findings of fundus examination. The macular OCT show increased thickness of central macula for the left eye. This result support the diagnosis CSME of the left eye. Then, we planned to perform fundus fluorescein angiography to identify nonperfusion areas, increased vascular permeability, and any neovascularization. Due to elevated intra ocular pressure, patient was given timolol eye drop 0.5% twice a day, acetazolamide three times a day, and potassium one time a day.

Fundus photography, fluorescein angiography and ultrasonography are valuable tools in the management of diabetic retinopathy. These modalities enable clincians to document pathology, monitor progression, and guide treatment.[27, 28] Fundus photography plays an important role in monitoring progression of diabetic retinopathy.

Photographs can be used to monitor progression of disease, particularly when following subtle changes in the posterior pole. Color fundus photos can be taken in stereoscopic or nonstereoscopic mode and can be performed in the traditional seven stereoscopic 30^0 fields or wide angel 60^0 fields. Fundus photography is becoming a popular method of screening large population for diabetic retinopathy.[27]Optical coherence tomography (OCT) is a noninvasive test that evaluates diabetic retinopathy both quantitatively and qualitatively.OCT is useful to monitor the clinical course as well as the response to treatment of laser photocoagulation, intravitreal pharmacotherapies, and vitreoretinal surgery.[28, 29]

Fluorescein angiography (FA) plays an important role in the diagnosis and treatment of retinal and choroidal vascular pathology. It is useful to guide laser treatment of clinically significant macular edema and also to identify areas of nonperfusion, increased vascular permeability, and neovascularization. These characteristics make fluorescein angiography a valuable tool in managing the vascular complications commonly associated with diabetic retinopathy. Fluorescein angiography is not typically indicated for management at early and moderate stage of NPDR unless the level of visual loss seems to surpass the degree of diabetic retinopathy seen clinically. FA is not also indicated for severe stage of NPDR. It may be helpful to follow disease progression with color fundus photographs. Wide-angle fluorescein angiography can be directed to detect peripheral capillary nonperfusion.[27, 28] Study by Terasaki et al[30] has found that peripheral angiography may be useful in identifying patients likely to develop anterior segment neovascularization. Correlation of clinical examination, fluorescein angiography, and OCT findings can provide a comprehensive assessment and understanding of visual dysfunction in patients with diabetic retinopathy.[29]

Our patient's right eye fundus photography showed much apperance and signs of ischemic areas but there were no neovascularization whether the left eye showed some intraretinal hemorrhages but with neovascularization on the disc. Our patient then planned to have fluorescein angiography examination to identify nonperfusion areas, increased vascular permeability, and the possibility of neovascularization elsewhere OU. The fundus fluorescein angiography of right eye showed much wide ishemia at the right eye as well as the left eye but there were no neovascularization. This condition makes a new remarkable question wheater wide ischemia has a correlation with neovascularization or developed new vessels can grow anywhere independently. Optic disc neovascularization is evidence of severe retinal ischemia in diabetic retinopathy and significantly followed by capillary occlusion in the temporal raphe and radial peripapillary capillaries.[8] Study by Hamanaka et al[8] reports that retinal nonperfusion in the midperiphery, capillary occlusion in the radial peripapillary capillaries and temporal raphe and optic disc are the risk factors for angle neovascularization. Niki et al[31] later found a positive correlation between the initial site of capillary nonperfusion and progression of retinopathy. Progression was more rapid when nonperfused areas were, in ascending order: peripheral, midperipheral, central, and generalized. Shimizu et al[32] demonstrated that the peripheral retina was much more likely to undergo capillary nonperfusion than posterior retina.

Visual morbidity and blindness can be combated effectively if treatment of retinopathy is intituted in a timely fashion. Diabetic Retinopathy Study (DRS) and ETDRS, demonstrated that effective treatment for retinopathy could reduce vision loss by 90%.[12] Clinical trials provide evidence regarding the safety and efficacy of various management options for treatment of diabetic retinopathy. In patients with proliferative diabetic retinopathy (PDR) or severe nonproliferative diabetic retinopathy (NPDR), scatter laser photocoagulation can reduces the rate of severe visual loss by 50%. In patients with clinically significant macular edema, focal/grid laser photocoagulation reduces the rate of moderate visual acuity loss by 50%. Clinical trial data have documented the value of vitrectomy in eyes with very severe PDR or severe vitreous hemorrhage.[33] Preffered Practice Pattern (PPP) by American Academy of Opthalmology irecommend laser photocoagulation surgery as

the standard technique for treating diabetic retinopathy. In general, it is advised for patients with high-risk PDR, CSME, neovascularization of the anterior chamber angle.

Laser photocoagulation techniques can be classified as panretinal (also referred to as scatter photocoagulation), focal, or grid laser. For many years, neovascularization conditions in diabetic retinopathy have been treated by panretinal photocoagulation (PRP) of the retina, which causes regression of the abnormal new vessels on the iris and angle.[34] PRP laser is the treatment of choice as demonstrated in several clinical trials for severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. Beside of its advantages, PRP laser exhibit scarring and loss of function in the area that were treated.[35] In eyes of patients with DME, corticosteroid inhibit the expression of VEGF and decrease angiogenesis.[35]

Primary interventions of diabetic retinopathy include glycemic control, blood pressure control, and lipid-lowering therapy. A consistent relationship between glycated hemoglobin (HbA1c) levels and the incidence of diabetic retinopathy has been confirmed in large randomized clinical trials (RCT). Several RCT demonstrating that tight glycemic control reduces both the incidence and progresion of diabetic retinopathy.[36] Secondary interventions of diabetic retinopathy include medical intervention such as antiplatelet agents, protein kinase C inhibitors, aldose reductase inhibitors, growth hormone/ insulin-like growth factor inhibitors. The outcome measures of the interventions included progression of diabetic retinopathy, changes in visual acuity and macular thickness, and rates of legal blindness and adverse effects. There were significant variations between the studies to define the progression of the disease.[36] The Diabetes Control and Complications Trial (DCCT)[37] defined progression as at least three steps worsening from baseline, while the United Kingdom Prospective Diabetes Study (UKPDS)[36] defined progression as a two-step change from baseline. Other studies used increases in number of microaneurysms or the need for laser photocoagulation as indicators of progression.

There is strong evidence that panretinal laser photocoagulation (PRP) is useful for treating severe nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. Focal laser photocoagulation should be considered for all patient with clinically significant macular edema (CSME). Laser re-treatment sessions may be necessary for macular edema. Scatter (panretinal) photocoagulation treatment is performed promptly for proliferative diabetic retinopathy (PDR) with high-risk characteristics and may be considered for severe nonproliferative retinopathy.[38]

Iris neovascularization develops in about 33% to 64% of patients with PDR. The onset of the condition seems to be directly related to the duration of the diabetes.[39] When fully developed, this condition can lead to neovascular glaucoma. Neovascular Glaucoma (NVG) is a secondary glaucoma resulting from severe ocular ischemia and is most commonly associated with posterior segment conditions such as proliferative diabetic retinopathy.[10] NVG typically associated with the formation of tiny dilated capillary tufts on the pupillary margin. If left untreated, the new blood vessels may proceed to join the circumferential angle vasculature. In the latter stages of NVG, radial contraction of fibrovascular tissue causes closure of the angle.[111¼] As with PDR, PRP is used to eliminate production of the vasoproliferative stimulus by the peripheral retina hence, diminish or eliminate anterior segment neovascularization due to PDR. Management of established NVG requires aggresive pressure treatment when beginning PRP. This includes topical and oral glaucoma therapy. Chronic medical treatment for NVG includes topical beta-blockers and alpha agonist and etiher topical or oral carbonic anhidrase inhibitors. Cholinergic agents may be less efective if the anterior chamber angle is already closed. Adjunctive treatment includes topical steroids to help control inflammation, slow proliferation of the fibrovascular membrane, and improves the outcome of subsequent filtration surgery. PRP and recent advances in filtration surgery with antimetabolites and valve implantation have markedly improved the prognosis of NVG. Allowing time for resolution of the neovascularization before surgery enhances the long-term success of filtering surgery.

Our patient was planned to have laser PRP OS to decreased oxygen-starve areas and bevacizumab injection for CSME. Patient also planned to have laser PRP of the right eye. Patient then underwent laser PRP OS. Before laser treatment, patient was underwent headache, pain, and nausea. Intra ocular pressure of the right eye was high. Patient consulted to glaucoma division and was planned to underwent Keiki Mehta implantation. The tube implantation surgery was done no so long after laser PRP. Intraoperatively, patient also given intravitreal injection of bevacizumab. After operation, visual acuity for the right eye is 6/60 and light perception for the left eye. The intra ocular pressure was 10 for the right eye and 3 for the left eye. There were edema and spasm of the eyelid, conjunctival and ciliary injection, subconjunctival bleeding, corneal edema. Anterior chamber was VH1 at temporal site and VH2 at nasal site and there were blood clot with dispersed hyphema. Tube was positioned behind the iris at 2 o'clock position. Posterior pole was hard to be evaluated. Patient then back to policlinic, 1 week later. Visual acuity of the left eye was 1/300 with IOP 20.8. The condition was still the same with postoperative condition at day 1. One month after the surgery, visual acuity for the left eyes was still the same with IOP 28.1. There were peripheral anterior synechia. The posterior pole was still hard tobe evaluated. Patient then underwent OCT scan and fundus photography. The fundus photography of left eye was obscured. It maybe caused by the coagulum that adhere to the lens. It showed that the neovascularization on the disc was start to regress. Glaucoma division was planned to do synechia release and iridectomy perifer of left eye.

The management of proliferative diabetic retinopathy with neovascular glaucoma needs comprehensive treatment and evaluation. The evaluation includes regression of neovascularization and monitoring of diabetic macular edema also the intraocular pressure. The result of the treatment in this patient is fair enough but still needs to be improved and monitored.

CONCLUSION

Proliferative diabetic retinopathy is an advanced stage of diabetic retinopathy that needs immediate management and also closed monitoring with short interval follow up. The management should be performed as soon as the patient was diagnosed to hold up the disease progression and the development of further complication such as neovascular glaucoma. Proliferative diabetic retinopathy with neovascular glaucoma need aggresive treatment to control intra ocular pressure and prevent further visual loss.

REFERENCES

1. Bhavsar AR, Emerson GG, Emerson MV, Browning DJ. Epidemiology of Diabetic Retinopathy : . In: Browning DJ, editor. Diabetic Retinopathy : Evidence-Based Management. USA: Springer; 2010. p. 53-76.
2. Staff AAO. Diabetic Retinopathy. In: Skuta GL, Cantor LB, Weiss JS, editors. Retina and Vitreous. San Fransisco: American Academy of Opthalmology; 2011. p. 109-32.
3. Gardner TW, Aiello LP. Pathogenesis of Diabetic Retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. 2nd ed. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 49-70.
4. Scanlon PH. Stage R3 : Proliferative diabetic retinopathy and advanced diabetic retinopathy. In: Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR, editors. A Practical Manual of Diabetic Retinopathy Management. United Kingdom: Wiley-Blackwell; 2009. p. 109-32.
5. Browning DJ. Diabetic Macular Edema. In: Browning DJ, editor. Diabetic Retinopathy : Evidence-Based Management. USA: Springer; 2010. p. 141-202.
6. Wolfe JA, Horton MB, McAteer MB, Szuter CF, Clayton T. Race, Macular degeneration, and Diabetic maculopathy. Arch Ophthalmol 1993;111:1603-4.
7. Pautler SE. Treatment of Proliferative Diabetic Retinopathy. In: Browning DJ, editor. Diabetic Retinopathy : Evidence-Based Management. USA: Springer; 2010. p. 227-304.
8. Hamanaka T, Akabane N, Yajima T, Takahashi T, Tanabe A. Retinal Ischemia and Angle Neovascularization in Proliferative Diabetic Retinopathy. Am J Ophthalmol 2001;132:648-58.
9. Bonnet M, Jourdain M, Francoz-Taillanter N. Clinical correlation between rubeosis iridis and optic disc neovascularization. J Fr Ophthalmol 1981;4(5):405-10.
10. Yazdani S, Hendi K, Pakravan M. Intravitreal bevacizumab (Avastin) injection for neovascular glaucoma J Glaucoma 2007;16:437-9.
11. Ohrt V. The frequency of rubeosis irids in diabetic patients. Acta Opthalmol 1971;49:301.
12. Wilkinson CP. Classification of Diabetic Retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. 2nd ed. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 13-24.
13. Guess M, Dubovy SR. Histopathology of Diabetic Retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. New York: Oxford University Press in

cooperation with the American Academy of Ophthalmology; 2010. p. 25-48.
14. Wilkinson CP, Ferris FL, Klein RE. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677-82.
15. Heriot WJ, Borger JP, Zimmet P, King H, Taylor R, Raper LR. Diabetic retinopathy in a natural population. Aust J Ophthalmol 1983;11(3):175-9.
16. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy.IV.Diabeteic Macular Edema. Ophthalmology 1984;91(12):1464-74.
17. Klein R, Klein BE, Moss SE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II.Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1984;102:520-6.
18. Nguyen QD, Shah SM, Anden E. Supplemental oxygen improves diabetic macular edema : A pilot study Invest Ophthalmol Vis Sci 2004;45:617-24.
19. Khurana RN, Do DV, Nguyen QD. Anti-VEGF therapeutic approaches for diabetic macular edema. Int Ophthalmol Clin 2009;49:109-19.
20. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
21. Funatsu H, Yamashita H, Noma H. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. Am J Ophthalmol 2002;133:70-7.
22. Ho AC, Scott IU, Kim SJ, Brown GC, Brown MM, Ip MS, et al. Anti–Vascular Endothelial Growth Factor Pharmacotherapy for Diabetic Macular Edema : A Report by the American Academy of Ophthalmology. Ophthalmology 2012;119:2179-88.
23. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT Study). Ophthalmology 2010;117:1078-86.
24. Bonini-Filho M, Costa RA, Calucci D, Jorge R, Melo LAS, Scott IU. Intravitreal bevacizumab for diabetic macular edema associated with severe capillary loss : One -year results of a pilot study. Am J Ophthalmol 2009;147:1022-30.
25. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-Year Outcomes of the DA VINCI STudy of VEGF Trap-Eye in Eyes with Diabetic Macular Edema. Ophthalmology 2012;119:1658-65.
26. Group TDCaCTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes melitus. N Engl J Med 1993;329(14):977-86.
27. Lam A, Anderson NG, Regillo CD, Brown GC. Photography, Angiography, and Ultrasonography in Diabetic Retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. 2nd ed. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 123-38.
28. Regillo C, Holekamp N, Johnson MW, Kaiser PK, Schubert HD, Spaide R, et al. Diagnostic approach to retinal disease. In: Skuta GL, Cantor LB, Weiss JS, editors. Retina and Vitreous. Singapore: American Academy of Opthalmology; 2011. p. 19-31.
29. Moshfeghi AA, Scott IU, Flynn HW, Puliafito CA. Optical Coherence Tomography in the management of Diabetic Retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. 2nd ed. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 139-60.
30. Terasaki H, Miyake Y, Mori M. Fluorescein angiography of extreme peripheral retina and rubeosis iridis in proliferative diabetic retinopathy. Retina 1999;19:302-8.
31. Niki T, Muraoka K, Shimizu K. Distribution of capillary nonperfusion in early-stage diabetic retinopathy. Ophthalmology 1984;91:1431-9.
32. Shimizu K, Kobayashi Y, Muraoka K. Mid-peripheral fundus involvement in diabetic retinopathy. Ophthalmology 1981;88:601-12.
33. Ferris FL, Davis MD, Aiello LM, Chew EY. Clinical studies on treatment for diabetic retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. 2nd ed. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 161-82.
34. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. Am J Ophthalmol 2006;142(1):155-8.
35. Gupta N, Mansoor S, Sharma A, Sapkal A, Sheth J, Falatoonzadeh P, et al. Diabetic Retinopathy and VEGF. The Open Ophthalmology Journal 2013;7:4-10.
36. Mohamed Q, Wong TY. Management of Diabetic Retinopathy : Evidence-based Systematic review. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. 2nd ed. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 265-300.
37. Group TDCaCTEoDIaCR. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381-9.
38. Goff MJ, McDonald HR, I EA. Photocoagulation for Diabetic Macular Edema and Diabetic Retinopathy. In: Scott IU, Flynn HW, Smiddy WE, editors. Diabetes and Ocular Disease : Past, Present, and Future Therapies. New York: Oxford University Press in cooperation with the American Academy of Ophthalmology; 2010. p. 183-206.
39. Wasik A, Song H-F, Grimes A, Engelke C, Thomas A. Bevacizumab in conjunction with panretinal photocoagulation for neovascular glaucoma. Optometry 2009;80:243-8.