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Case Series

Changes in Intraocular Pressure Influence Macular Edema

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Abstract

Four cases with advanced diabetic retinopathy are presented here. Eyes with normal intraocular pressure (IOP) showed marked macular edema which responded partially to repeated intravitreal anti-vegf. When some of these eyes developed high intraocular pressure; macular edema disappeared even without anti-vegf. This confirms the effect of IOP on macular edema.

Keywords: *Glaucoma; IOP; Macular Edema; AntiVEGF (Lucentis, Aflibercept)*

Introduction

The eye is a specialized organ responsible for vision. It takes a shape of a ball which is maintained in this shape by well regulated intraocular pressure (IOP). The eye wall consist of three major layers; outer fibrous layer (sclera, cornea), vascular layer in the middle (choroid, ciliary body, iris) and nervous tissue layer in the inner layer (retina). Retina is a multilayers located between the vitreous and the choroid. The macula is an oval shaped pigmented area in the posterior part of the retina temporal to the optic nerve head which is responsible for detailed vision. Macular edema is due to excess accumulation of fluid within the macular tissue causing disturbance of vision. Large number of local and systemic conditions contributes to the development of macular edema including diabetes mellitus, age-related macular degeneration, retinal vien occlusion resulting from dehydration [1] and abuse of some drugs [2], Hypertension [3], vascular telangiectasia [4] and ocular inflammation [5] and others; by altering the blood retinal barrier. A comprehensive review of diabetic retinopathy, macular edema and blood retina barriers were reported recently [6-8]. Diabetes Mellitus is a major cause of macular edema which reflects the changes in different parts of the body [9]. What might happen to the macular edema in these cases if IOP is elevated which is the subject of this report.

Cases History

Case #1: A 61 year old female with history of poorly controlled ddiabetes mellitus and hypertension. She had an irregular follow up between Sept 2015 and Feb 2023. Early on the follow up She was pseudophakic in both eyes. Visual acuity was 0.8 in in the right eye (OD) and 0.5 in the left eye (OS) and tension was 15 mm Hg in both eyes (OU) with mild non proliferative diabetic retinopathy (non PDR). Optical coherence tomography (OCT) at that time revealed no macular edema (Central macular thickness (CMT) in OD 213 and in OS 228). On May 2021 she was found to have severe non-PDR in both eyes and macular edema OD > OS (CMT OD 431 and in OS 370) and IOP was 21 mmHg OU and decreased in visual acuity OU. She refused to have any thing done but her relatives convinced her and she received an intravitreal anti-vegf injection in OD. On June 2021 her OCT macular edema improved in OD but macular edema increased in OS (CMT in

OD 285 and in OS 474). On Sept 2021 she was found to have recurrence of macular edema in OD and persistent of macular edema in OS (CMT OD 623 and 494 in OS). Rubeosis was noted in OS at this stage and IOP was 16 mm Hg in OD and 44 mm Hg in OS. She was started on maximal glaucoma therapy for OS including diamox. Intravitreal anti-vegf was given to both eyes. She refused to have any surgical or laser procedures. On 27/10/2021 her OCT showed marked improvement on the macular edema OU. On 28/11/2021 IOP 15 mm Hg OD and 32 mm Hg OS, and the rubeosis regressed in OS. On 29/12/2021 OCT showed extensive macular edema in OD and no macular edema in OS and IOP was 38 mm Hg on max treatment in OS and NVI re-appear in OS. Patient still did not want to have the intravitreal injection of anti-vegf or any surgical procedure including laser for OS in spite of the deterioration of the vision. On 13/02/2022 she had IOP 14 mm Hg in OD and 41 mm Hg in OS. She received Anti VEGF in both eyes (OD for edema - OS for rubeosis). On 20/03/2022 her follow up OCT showed marked decrease in macular edema OD and no macular edema in OS and IOP was still elevated in OS. During the period of the follow up from March 2022 till Feb 2023 no macular edema and no anti-vegf injections in OS with uncontrolled elevated IOP while the IOP was normal in OD and the macular edema persist requiring repeated intravitreal injections of anti-vegf to control it. She received total of 2 intravitreal injections of anti-vegf in OS and 9 injections in OD (Table 1).

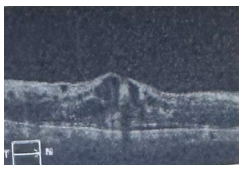
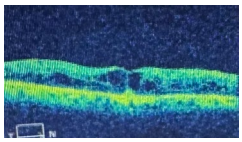
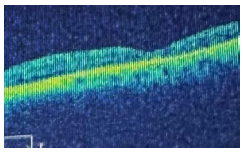
	OD		OS	
Case 1	**OCT**	**IOP**	**OCT**	**IOP**
At onset. Sept 2021		21		21
Late in follow up sept 2023		18		44
Anti-vegf	9 times		2 times	
Follow up	3 years			

Table 1: *Case 1 showing the relation between OCT changes and IOP and antivegf injections. Note with elevated IOP minimal edema present as in OS late in the follow up.*

Case #2: A 54 year old male known to have history of poor controlled diabetes mellitus. Follow up was irregular. He was seen first in February 2021. He was pseudophakic in both eyes with proliferative diabetic retinopathy and macular edema ou and NVI in OS. Visual acuity was 0.2 in both eyes. His OCT showed macular edema in OD (CMT 651) and minimal edema in OS (CMT 254). IOP was 15 mm Hg OD and 47 mm Hg OS on maximal anti-glaucoma therapy in OS. He received Anti VEGF OU and PRP OU and he received glaucoma valve implant in OS. On April, 2022, OCT showed macular edema on OD and no edema in OS (CMT OD 472 and CMT OS 239). Extensive rubeosis was noted in OS, IOP 12 mmHg OD and 24 mmHg OS on maximal topical therapy. On April 2023 rubeosis start to develop in OD. He had glaucoma Valve implant to control IOP in OD. Repeated OCT revealed minimal edema ou. He received Anti VEGF total of 3 times in in OS and 5 times in OD. Note that with high IOP in OS minimal edema macular edema while edema re-occur in OD with normal IOP at the beginning once the effect of anti-vegf disappear (Table 2).

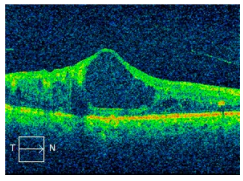
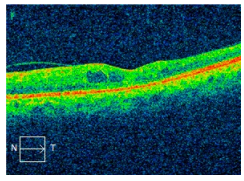
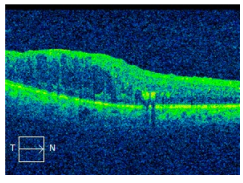
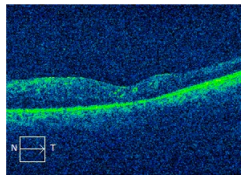
	OD		OS	
Case 2	**OCT**	**IOP**	**OCT**	**IOP**
At onset March 2021		15		47
Late in follow up June 2023		12		24
Anti-vegf	5 times		3 times for rubeosis	
Follow up	2 years			

Table 2: *Case 2 showing the relation between OCT changes and IOP and antivegf injections. Note with elevated IOP minimal edema present as in OS.*

Case #3: A 66 years old male was known to have poor control of diabetes mellitus and hypertension for many years had PRP in both eyes. He was followed between Sept 2018 and May 2023. He was pseudophakic in Both eyes his VA OD 0.4 and count fingers at 1 meter in OS and IOP OD was 17 mm Hg and OS was 15 mm Hg. Fundus examination revealed regressed proliferative diabetic retinopathy OU and laser marks of PRP in both eyes and optic atrophy and retinal ischemia in OS. OCT OS always had no edema (CMT 267) but OD had extensive macular edema (CMT 515) at the beginning; which responded to repeated antivegf injections. On Feb 2021 rubeosis was noted in OD and IOP was 38 in OD and 18 in OS the macular edema marked improved in OD. He received glaucoma valve implant to control the pressure in OD. In spite of the fact that he had glaucoma implant the IOP continue to be elevated (In upper 20) on topical glaucoma therapy, the edema markedly improved in OD (CMT 276). He received total of 19 intravitreal injections of anti-vegf in OD mainly to control rubeosis. The resolution and the mild recurrence of the macular edema in this case is due to the effect of the antivegf and elevated IOP (Table 3).

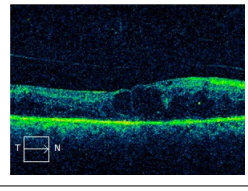
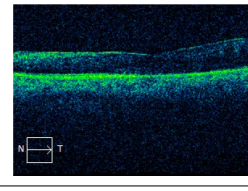
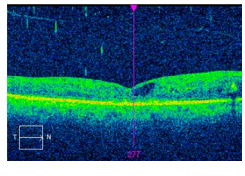
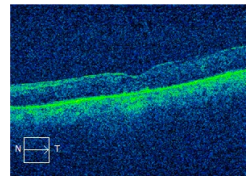
	OD		OS	
Case 3	**OCT**	**IOP**	**OCT**	**IOP**
At onset Jan 2018		17		17
Late in follow up Feb. 2021		38		14
Anti-vegf	19 times		None	
Follow up	4 years			

Table 3: *Case 3 showing the relation between OCT changes and IOP and antivegf injections. Note with elevated IOP minimal edema present as in OD.*

Case #4: A fifty six years old female known to have diabetes mellitus, and hypertension under control at the time of presentation. She was pseudophakic in both eyes. She was followed between July 2020 till June 2023. At the time when she was first seen; her vision was 0.4 in OD and 0.25 in OS. Tension was 14 mm Hg in OD and 16 mm Hg in OS. Fundus exam revealed severe non-PDR with retinal hemorrhages both eyes and macular exudate in OD. Her OCT at that time revealed extensive macular edema ou (CMT OD 592 and in OS 634). Patient received multiple intravitreal injections of anti-vegf. She had focal laser in OD. During the period of follow up patient demonstrated marked improvement of the macular edema; but with some recurrence. On October 2021 her VA was 0.63 OU and her OCT demonstrated marked improvement but still had some macular edema persisting OU (CMT OD 381 and in OS 368). On Feb 2022; she received intravitreal Ozurdex in the left eye and repeated anti-vegf in the right eye. She was given azarga bid for the left eye. The pressure was found to be normal in OD and elevated in OS (30 mm Hg) her OCT on march 2022 the macular edema in OS resolved while OD re-occurred and anti-vegf was given to OD. On June, 2022 the macular edema in OD improved after anti-vegf, but some persist (CMT improved from 463 to 361 while OS CMT increased to 531). She was off glaucoma medication and IOP was 20 mm Hg in OS and 14 mm Hg in OD. she continued to receive repeated intravitreal injection of antivegf ou on monthly bases. Last OCT revealed resolution of macular edema CMT in OD 256 and in OS 249. Till the last seen; she received a total of 23 intravitreal injections of anti-vegf in OD and 20 in OS. Note with normal IOP macular edema in this case continue to reoccur requiring repeated intravitreal injection of anti-vegf on monthly bases (Table 4).

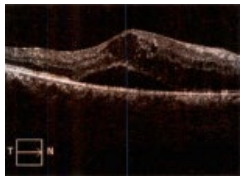
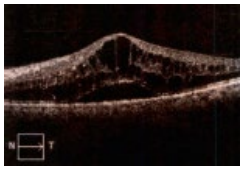
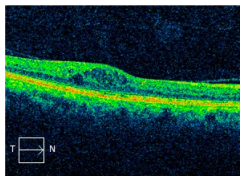
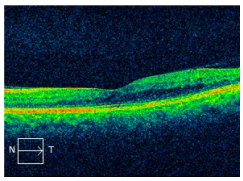
	OD		OS	
Case 4	**OCT**	**IOP**	**OCT**	**IOP**
At onset July, 2020		15		15
Late in follow up June 2023		16		16
Anti-vegf	23		20	
Follow up	40 months			

Table 4: *Case 4 showing the relation between OCT changes and IOP and antivegf injections. Note with normal IOP required more frequent anti-vegf injections in both eyes.*

Discussion

Macular edema is defined as an abnormal increase of fluid volume in the macula, which could be in the extracellular space infiltrating the retinal layers, or collected in the subretinal space or intracellular [10,11]. Frequent noticing accumulation of fluid in the macula probably related to the special structure of the macula. Add to that; it might be related to the fact that macular edema effect central vision; therefore, patients seek medical care more frequent leading to frequent recognition. In physiologic conditions, in the retina; fluid entry and exit are tightly regulated to maintain a balanced hydration state compatible with retinal homeostasis, necessary for tissue transparency and light transmission. Changes in retinal hydration state causes structural changes which interfere with light transmission and disturb vision [12-14]. Long-standing macular edema may lead to permanent retinal structural damages.

The retinal hydration is controlled by different factors that prevent the development of macular edema. These factors include: 1) Blood retinal barrier which includes the capillary endothelial cells tight junctions and the retinal pigment epithelium tight junctions, and to lesser extent the healthy external limiting membrane, 2) Balance between capillary hydrostatic pressure (= blood pressure) and tissue hydrostatic pressure (= intraocular pressure), 3) Balance between plasma osmotic pressure (= plasma protein level) and tissue osmotic pressure (= tissue protein level) 4) Efficient drainage system of the waste products by retinal pigment epithelium and glial cells. The balance between above mentioned factors are needed for retina hemostasis and transparency. These factors can be altered by aging changes, oxidative stress, inflammation and chronic hyperglycemia, hypertension and age-related macular degeneration among others; leading to the development of macular edema. Diabetic retinopathy is a major etiology of macular edema affecting up to 80% of the individuals who has poor control of diabetes mellitus for more than 20 years [15]. So, it seems that an increase in tissue osmotic pressure or decrease in plasma osmotic pressure and increase in capillary pressure or decrease in tissue hydrostatic pressure or combination of any of these encourage the development of macular edema when blood retinal barriers are disturbed. Therefore; it seems that intraocular pressure contributes to the hemostasis in the retina; therefore if the intraocular pressure is elevated the balance is altered; which may reduce or prevent movement of fluid from vascular lumen to the retinal tissue interfering with the development of macular edema. The opposite may hold true; so if the IOP is low it might encourage the development of macular edema.

Case 1: Early in the follow up (first 24 months) IOP was normal in both eyes and there was no edema ou; probably due to the fact that blood retina barriers were intact. In the following 20 months the IOP was normal in both eyes and edema start to appear in OS then in OD. In the left eye; later in the follow up; edema persist and IOP start to rise due to the development of neovascular glaucoma (NVG) which was not responding to maximum treatment. During the following period of the follow up between Oct 2021 and Feb 2023; the IOP continued to be very high on maximum treatment and there was no edema in OS (only 2 anti-vegf injections). While in OD during the follow up in the same period; IOP was always normal; edema was present but responded partially to repeated anti-vegf therapy (9 injections). In this case it seems that high IOP contributed to the prevention and resolution of macular edema in OS while normal IOP allowed the edema to persist in OD requiring repeated anti-vegf.

Case 2: NVG in OS with partial control of intraocular pressure on maximal topical therapy OCT no edema (CMT 264). He had 3 anti-vegf injections in OS for the rubeosis during the 2 years of follow up. In OD with normal IOP extensive macular edema was present which responded to repeated anti-vegf as shown in OCT (CMT 651 => 275 after 5 intravitreal injections of anti-vegf during the 2 years of follow up). This case again support the idea that high IOP contributed to the prevention of macular edema and normal intraocular pressure encourage the development of macular edema.

Case 3: In OD during the first 20 months of follow up the IOP was normal significant macular edema was present (CMT OD 508) which responded partially to repeated anti-vegf injections (7 injections). In the following 24 months of follow up NVG developed in OD edema disappeared but at the same time he had repeated anti-vegf for rubeosis (12 injections). Macular edema almost disappeared probably due to combination of repeated intravitreal injections of anti-vegf and elevated IOP. No edema was present in OS due to retinal atrophy and retinal ischemia. So comparing the response to anti-vegf in OD before the development of NVG and after revealed that rise in IOP contributed in part to the resolution of macular edema.

Case 4: During the early part of follow up (July 2020 - Dec. 2021) IOP was normal in both eyes and extensive edema was present ou (CMT 562 in OD and 634 in OS) with partial response to repeated anti-vegf. During the period between Jan. 2022 and April 2022; IOP was normal in OD and edema persist in spite of repeated anti-vegf while the IOP was elevated (30 mm Hg on Rx) in OS after Ozurdex implant edema disappeared which is due to the anti-inflammatory effect of steroid and may be due to some effect of the elevated IOP. During the period of follow up between May 2022 and June 2023 IOP was normal in ou (18 in OD and 15 in OS) the edema re-occur in OS and continue to be present in OD; they responded to repeated anti-vegf treatment. At the end of follow up CMT improved in OD from 592 to

254 and in OS from 634 to 263 on frequent anti-vegf on monthly bases. So again this case demonstrated that with normal IOP macular edema developed and may be the brief elevation of IOP in OS may add to the resolution of macular edema. The persistent of the macular edema might be in part due to the extent of the damage to the blood - retinal barriers and to the accumulation of large amount of large protein molecules in the retinal tissue that can't move easily causing the tissue osmotic pressure to be elevated and therefore attract fluid to the retinal tissue.

As we can see from the present cases; the eyes with normal intraocular pressure (case 1 ou at the beginning of the follow up and continue in OD, case 3 OD at the beginning and case 4 OU) developed macular edema; while the eyes with high intraocular pressure their macular edema disappeared (case 1 OS and case 2 OS and at later stage of the follow up case 2 OD and case 3 OD later in the follow up). These findings suggest that elevated IOP contributed to the resolution and prevention of macular edema. It seems that lower normal IOP may increase the chances of developing macular edema when the blood retinal barriers are disturbed.

Conclusion

The findings suggest that elevated IOP contributed to the resolution and prevention of macular edema. This may also suggest that lower normal IOP may increase the chances of developing macular edema when the blood retinal barriers are disturbed.

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