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Case Series

Vitelliform Macular Dystrophy; Treat or Observe Literature Review of Treatment

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Abstract

We are reporting two cases with vitelliform macular dystrophy; one represents Best's disease with marked changes during the observation for 3 years. The second case represents the adult onset of the vitelliform macular dystrophy who demonstrated improvement after anti-vegf therapy.

Keywords: *Vitelliform Macular Dystrophy; Therapy; Best's Disease*

Introduction

Vitelliform dystrophy is a slowly progressive hereditary disease with onset generally in childhood and sometimes in later teenage years and late in adulthood. They include Best's disease, adult onset vitelliform macular dystrophy and multifocal fundus vitelliform lesions. Affected individuals initially have normal vision followed by metamorphopsia and gradual decreased central visual acuity. They might be complicated by sub macular neovascularization. Individuals retain normal peripheral vision and dark adaptation. The treatment of this condition is still evolving. This report presents progression of Best's disease during 3 years of observation in one case and the response of a case of adult onset of vitelliform form condition with sub macular fluid to anti-VEGF therapy and reviewing the literature for the management.

Cases History

Case #1

Ten years old boy was seen on April 2014 because of defective vision. He was product of full-term normal pregnancy. At that time his vision was 0.8 in the right eye and 1.0 in the left without correction. Anterior segment was normal in both eyes. Fundus examination revealed normal disk and blood vessels in both fundi. There was an elevated round about 1 disk diameter egg yolk like lesión both foveas (Figure 1, 1st row). At that time the OCT revealed marked elevation of the center of the macula in both eyes with hyperreflectivity beneath the retinal pigment epithelium (RPE) in both maculas; suggesting presence of sub RPE fluid (Figure 1, 2nd row). On April 2015; he came back because of decreased vision in both eyes at this time it was found to improve his vision with glasses to 1.0 in both eyes (refraction OD + 0.25 - 1.50 X170 and OS + 0.5 - 1.50 X 05). On June 2017; he was seen because of decreased vision in both eyes. At that time his best corrected vision was 0.6 in the right eye and 0.7 in the left eye. Findings limited to the fundus again OD revealed mottling in the center of the macula in the right eye and the egg yolk like lesion in the center of the macula in the left eye (Figure 1, 3rd row). At this time the OCT in the right eye revealed decreased in the central thickness and increased in the hyper reflectivity beneath the RPE while the left OCT appear to have little change (Figure 1, 4th row). Last seen on May 2019; he came back because of decreased vision in both eyes. Vision with glasses was 0.7 in OD and 0.6 in the left eye.

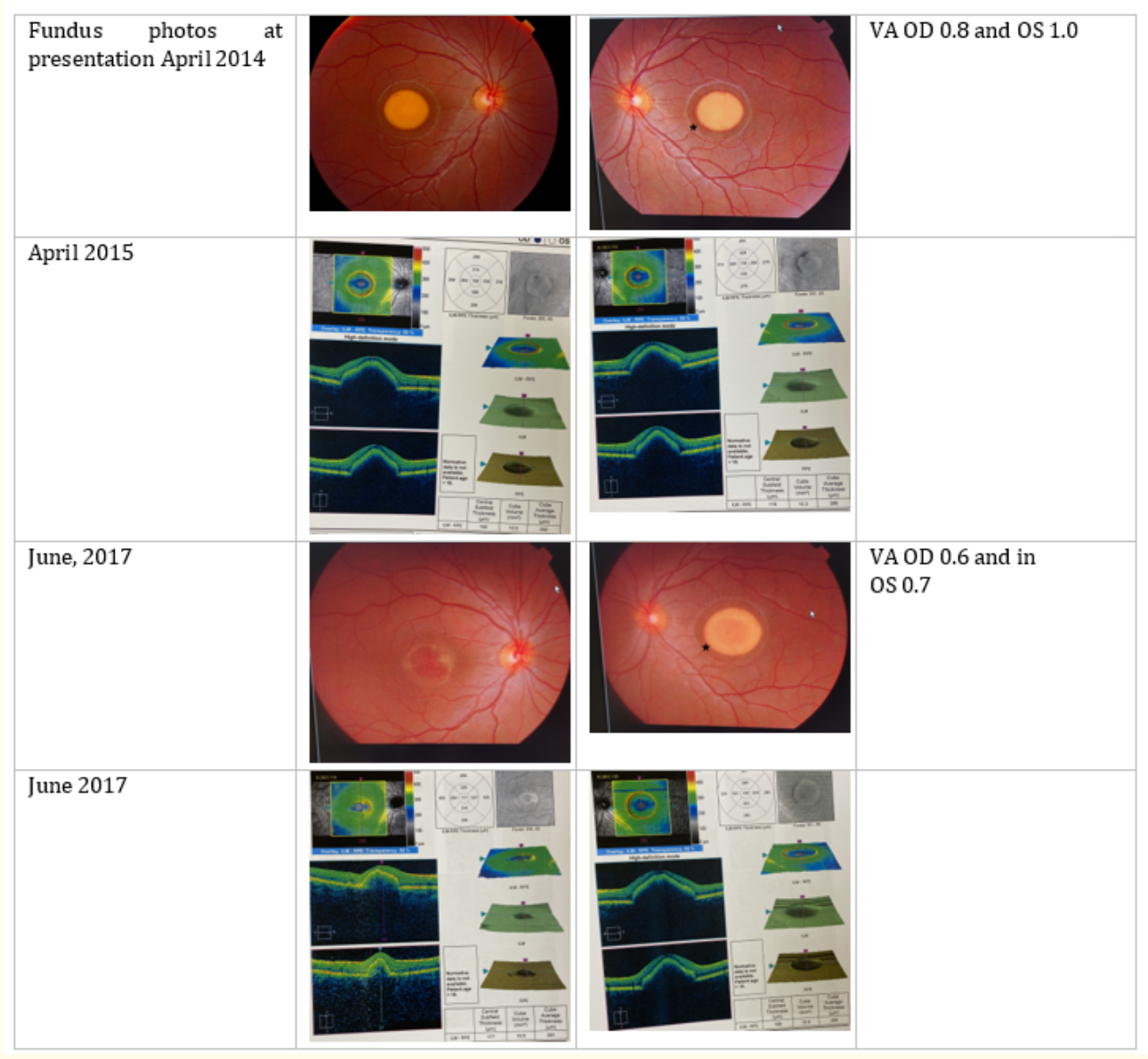

Figure 1: *Showing fundus photos and OCT from both eyes. 1st row shows the fundus photos of both eyes at presentation showing the egg yolk lesion in the center of both maculas. The second row showing the OCT from both eyes at presentation there is elevation of the center of the fovea in both eyes with accumulation of fluid and some material beneath the retinal pigment epithelium. Third row showing the fundus photos from both eyes 3 years after the initial visit. Note the mottling changes in the center of the macula in the right eye and there slight enlargement in the diameter of the lesion in the left eye as compared with photos at presentation (stars indicate the changes in OS). The 4th row showed the corresponding OCT from both eyes. Note the changes in the OCT in the right eye as compared with OCT at presentation.*

Case #2

Fifty-two years old male who was referred because of decreased vision in both eyes during the last 12 months. According to patient he was okay till about 1 year before. His parents were not related, and they were okay. His 4 brothers and his 5 sisters all were not affected.

Two of his brothers and 3 of his sisters were older than him. His best corrected vision was 0.25 in the right eye and 0.2 in the left eye. His anterior segment examination was unremarkable except for minimal lens changes. The tension was 12 mm Hg in both eyes. Fundus examination revealed bilateral sub foveal yellowish lesions measuring about one disk diameter (Figure 2, 1st row). OCT revealed elevation of the fovea region in Both eyes with hyper and hypo reflective material beneath the retinal pigment epithelium (RPE) suggesting of Sub-retinal fluid (Figure 2, 3rd row). Patient received 2 intravitreal injections of 2 mg of aflibercept in each eyes one month apart. Two months after the injections; his vision improved to be 0.32+2 in both eyes. Tension was normal in both eyes. OCT revealed some improvement in central macular thickness as compared with pre-injections study left more than right. Post treatment OCT revealed decreased central macular thickness in the right eye from 252 um to 239 um and in the left eye from 301 um to 251 um (Figure 2, 3rd, 4th rows) with increase in hyper reflective material in both eyes. The post treatment fundus photos revealed shrinkage the size of the lesion in both eyes as compared with photos at presentation (Figure 2, 1st and 2nd rows).

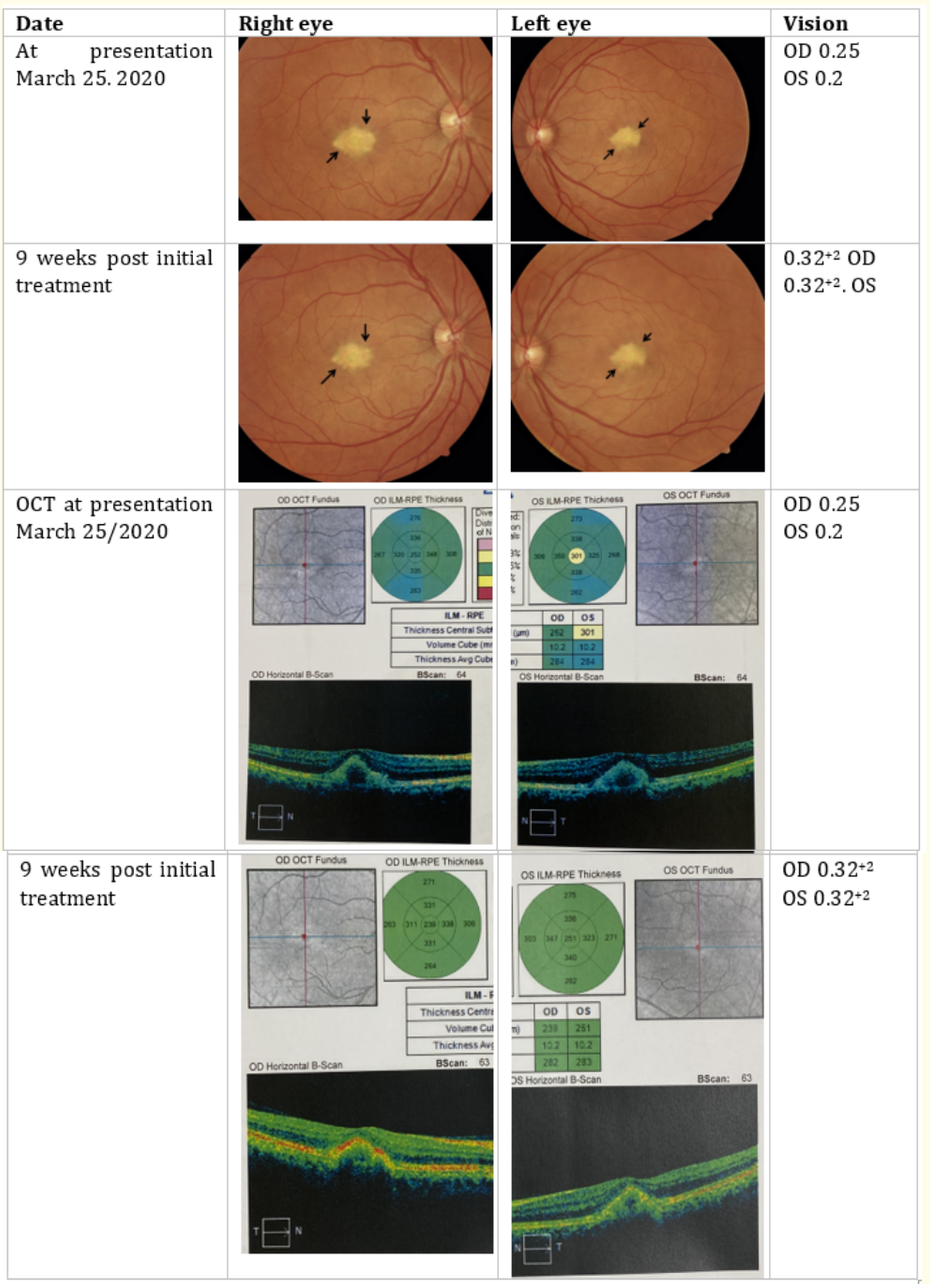

Figure 2: *Shows the fundus and the OCT photos from both eyes. First row shows the fundus photos of both eyes at presentation showing bilateral symmetrical, oval whitish lesion with sharp borders. The second row shows the fundus photos of both eyes note (arrows) the shrinkage of the lesion in Bothe eyes as compared with photos at presentation. 3rd row shows the OCT pictures of Both eyes at presentation showing accumulation of both hyper-reflective and hypo reflective materials sub RPE in the foveal region in both eyes suggesting presence of sub retinal fluids and dense materials. The 4th row shows the OCT of Both eyes after two intravitreal injections in both eyes showing reduction of the retinal thickness more in the left eye.*

Discussion

Best Vitelliform macular dystrophy (BVMD) is a hereditary retinal dystrophy involving the retinal pigment epithelium (RPE) and leads to a characteristic bilateral yellow "egg-yolk" appearance in the center of the macula due to accumulation of photopigments end products. It was First described by Adams in 1883 [1], but it was named after Dr Friedrich Best, who presented a detailed pedigree of the disease in 1905 [2]. Best disease is an autosomal dominant (also recessive form exist) maculopathy caused by mutations in the BEST1 gene (VMD2) located on the long arm of chromosome 11 (11q13) [3,4]. This gene encode bestrophin protein which is localized to the plasma membrane of the RPE and functions to regulate the trans-membrane calcium ions and chloride ions movement across the retinal pigment epithelium (RPE) membrane through the calcium Chanels, which initiate the visual signals. Mutation of this gene was found to be associated with both Best disease and to a lesser extent in adult onset of vitelliform macular dystrophy. The mutation will lead to production of defective protein; which leads to impaired function of calcium channels and therefore impaired conduction of visual signals. The appearance of the macula vitelliform lesion usually occurs between 3 - 15 years of age but can be seen in the later decades of life as in case #1. Some patients may have extrafoveal vitelliform lesions in the fundus. The vitelliform resulted from accumulation of un-phagocytized photoreceptor outer segments in the sub retinal space as in case #1 (Figure 1, 1st row). The vitelliform lesion eventually breaks down, leaving a mottled geographic atrophic appearance (Figure 1, 3rd row right eye). Late in the course of the disease, the geographic atrophy may be difficult to distinguish from other types of macular degeneration or dystrophy. The evolution of the disease will go through six clinical stages: Stage I (Previtelliform): normal vision, normal or only subtle RPE changes such as tiny, central honeycomb structure centrally with abnormal EOG. Stage II (Vitelliform): classic "egg-yolk" lesion in the center of the macula with normal vision or mild vision loss as in case # 1. The size of the lesion may increase as in case #1 left eye (Figure 1). Ectopic vitelliform lesions may be present. Stage III (Pseudohypopyon): characterized by layering of lipofuscin. Vision might be normal or mildly decreased. Stage IV (Vitelliruptive stage): there are breakup of material giving "scrambled egg" appearance. Vision might be normal or mildly decreased. The right eye in case #1 might be a reflection of this stage. Stage V (Atrophic): Central RPE and retinal atrophy. Vision may range from 20/30 - 20/200. Stage VI choroidal neovascular membrane (CNV): This complication occurs in about 20% of patients. Vision often decreased to 20/200 or worse. Case number #1 represents the classic presentation and progression of Best's disease. It demonstrated decline in visual acuity in both eyes and disappearance of the egg yolk material and mottling of the RPE as seen in the right eye (Figure 1, 3rd row).

Case #1 was observed for 3 years. At the beginning the decrease in his vision in part was due to the elevation of the fovea which was compensated for by glasses and/or by his accommodation. At that stage; the photoreceptors were still healthy. But after 3 years of elevation of the central RPE and photoreceptors; the damage became more obvious as shown by decrease in visual acuity and the fundus findings specially in the right eye and the increase diameter of the vitelliform lesion in the left eye. The elevation of RPE with the fluid and other material caused decrease in their nourishment and therefore they may die at a later stage. The question to be raised here if the sub RPE fluid is removed; can the damage be slowed down or prevented. The answer probably yes.

Case #2 represents the adult onset of the vitelliform macular dystrophy who had sub macular fluid and responded to anti-vegf therapy. Adult-Onset Vitelliform lesions presents with symmetric yellow deposits that resemble Best disease may develop in the macula of older adults. It is characterized by yellow sub-foveal lesions that are bilateral, round or oval, and typically one-third disc diameter in size but in present case it is slightly larger. This dystrophy generally appears in the fourth to sixth decades in patients who either are visually asymptomatic or have mild blurring and metamorphopsia. Eventually, the lesions may fade, leaving an area of RPE atrophy, but most patients retain reading vision in at least one eye throughout their lives but not in the present case. The most common causative gene for this condition; is PRPH2 (RDS) mutation, and there is evidence of genetic heterogeneity for this phenotype. This gene encodes Peripherin-2 glycoprotein which act as adhesion molecules involved in stabilization and compaction of the outer segment disks. Defect in this gene will cause disturbance of the normal arrangement of the disks in the outer segment. This disease also had been associated with Best-1 gene as indicated earlier. Genetic study was not available for both cases. Table 1 summarize the differences between the pediatric form and the adult form of vitelliform dystrophy. The main differences between the two are based on the genetic bases and the time of onset. Vitelliform macular dystrophy may be complicated with sub retinal neovascularization at late stage which will lead to macular degeneration and poor vision if not treated early.

Findings	Best's vitelliform	Adult onset vitelliform
Vitelliform	+	+ but smaller
Genetics	Best1 gene on chromosome 11q13 => Bestrophin protein essential for RPE function Also Best 2, Best 3 and Best 4 genes were isolated	PRPH2 on chromosome 6 location 6q21.1 => peripherin2 protein essential for photoreceptor function. Best1 gene
Age of onset	Childhood	4th to 6th decades
Bilateral	+	+
Vision	Asymptomatic early deteriorate late => RPE atrophy	Asymptomatic early deteriorate late => RPE atrophy
Hereditary	Autosomal dominant can be autosomal recessive	Autosomal dominant. Heterogeneity exist
Choroidal NV	+	+
EOG	Abnormal Arden ratio less than 1.5	normal or slightly abnormal
Full field ERG	Normal	Subnormal
Color vision	Abnormal	Abnormal
Abnormal OCT	+	+

Table 1: *Comparing best vitelliform disease and adult onset of vitelliform.*

Several modes of therapy were used during the last few years directed toward the complicated form of the disease with sub retinal neovascularization. Among these therapeutic modalities; photodynamic therapy, steroid and anti- vascular endothelium growth factor (anti-vegf) and possible genetic therapy in the future. Photodynamic therapy (PDT); which involves administration of a porphyrin-based medication that is absorbed by abnormal sub-retinal vessels. The drug is then activated by wavelength-specific, low-energy, non-thermal infrared laser exposure. Activation of the photosensitizing compounds produces localized vascular damage. Theoretically, its action is local, thereby sparing the overlying sensory retina while destroying abnormal neovascularization. Eight PDT reports for the treatment of complicated vitelliform disease consisting of 53 cases the overall benefit was not encouraging regarding visual gain (Table 2 and 3) [25-32]. Intravitreal steroid was seen in 2 reports with total of 2 cases. Dexamethasone inserts was given to one case and no benefit was noted [33]. While in the second report they used intravitreal triamcinolone acetate in one case with encouraging result [22] (Table 2 and 3). Intravitreal anti-vegf was used with encouraging results. The Vascular endothelial growth factor (VEGF) is a protein produced by the cells in the body, Normally which initiate formation of new blood vessels during normal development or during repair e.g. after trauma. But sometimes they may cause growth of abnormal leaking blood vessels as in diabetic retinopathy and cancer. Anti-VEGF medications (antibody based) blocks the VEGF function lead to slowing the growth of blood vessels as in the eye. This will slow or stop the damage from the abnormal blood vessels and slows down vision loss. Sometimes it can even improve vision as in macular edema. At present the common anti-vegf medication include Bevacizumab (Avastin), Ranibizumab (Lucentis) and Aflibercept (Eylea). The use of Bevacizumab had been reported in 12 reports in 42 cases with over all encouraging result (Table 2) [5-15]. The use of Ranibizumab had been reported in 6 reports in 34 cases with encouraging result (Table 2) [16-21]. Aflibercept was seen in 2 reports with 4 cases with encouraging results [23,24]. Genetic therapy had been tried in animals and they are setting the stage to proceed to transfer their positive findings to human [36]. Table 2 and 3 summarize the response of the reported cases to different modes of treatment from different reports. From table 2 it seems that steroid and photodynamic therapy prove of little value. Note that in steroid only 2 cases were reported. While the anti-VEGF proved to be effective. The present case received 2 intravitreal aflibercept in each eye one month apart. He demonstrated improvement in his vision by 2 lines in both eyes and decreased macular thickness in both eyes as compared with pre-treatment OCT and shrinkage of the size of the lesion on the clinical picture.

Reports	No of cases	Dx	Type of therapy	Response	Comment
Montero JA., *et al*. 2007 [5]	1 eye	VMD	Bevacizumab	Morphology and stable vision	
Tiosano L., *et al*. 2014 [6]	11 eyes		Bevacizumab	Morphological improvement	
Velazquez VD., *et al*. 2014 [7]	1 with NV		Bevacizumab	Responded well	
Celea C., *et al*. 2015 [8]	1pt and NV 8 y	Best	Bevacizumab	Improved	
Tiosano L., *et al*. 2014 [6]	11 eyes NV	Vitelliform	Bevacizumab	Improved	
Cinnamon G., *et al*. 2012 [9]	2 eyes	VMD and NV	Bevacizumab	VA improved	5 y o
Leu J., *et al*. 2007 [10]	1 eye	Best	Bevacisumab	Improve function and anatomy	13 y o m
Chhablani J., *et al*. 2012 [11]	1 eye with NV	VMD ou 6y old	Bevacizumab	Improved functional anatomy	6 y o
Perol J., *et al*. 2011 [12]	1 eye and NV	VMD	Bevacizumab	Improved	9 y o M
Richi E., *et al*. 2010 [13]	1 eye	VMD and NV	Bevacizumab	Improved both F and Anatomy	23 y o m
Lee JY., *et al*. 2009 [14]	1 eye	VMD and NV	Bevacizumab	Good anatomy modest vision improvement	
Iannaccone A., *et al*. 2011 [15]	2 eyes	VMD and NV	Bevacizumab	Improved	5 y o
Galigo PR., *et al*. 2011 [16]	6 F		Ranibizumab	Vision improve	
Kandula S., *et al*. 2010 [17]	1		Ranibizumab	No response	72 y o
Mimoun G., *et al*. 2013 [18]	24 eyes	VMD	Ranibizumab	Stabelized vision	
Prieto-Calvo E., *et al*. 2012 [19]	1 eye NV	VMD	Ranibizumab	Functional morphology improve	
Queries G., *et al*. 2013 [20]	1 eye	VMD	Ranibizumab	Morphological improvement modest VA	
Heidary F., *et al*. 2011 [21]	1 eye	VMD and NV	Ranibizumab	Improved	6 y o
Scupola A., *et al*. 2014 [33]	1		Dexamethasone insert	Nonresponse	
Barbazeto I., *et al*. 2018 [22]	10 M and 8 F	AEPVM	1 pt had triamcinolone	1 pt improved	
Gündüz K., *et al*. 2017 [23]	2		Aflibercept	Morphology and stable vision	
Braimah IZ., *et al*. 2017 [24]	2	Best	Ziv-flibercept	Modest VA improvement	
Ergun E., *et al*. 2004 [25]	8 eyes	VMD no NV	Photodynamic therapy	Negative impact on vision	
Andrade RE., *et al*. 2003 [26]	1 eye	Best and NV	Photodynamic therapy	Improved vision and anatomy	43 Y O

Murro V., *et al*. 2018 [27]	1 NV	Best	Photodynamic therapy	Improved	
Richi P., *et al*. 2009 [28]	3 eyes		Photodynamic therapy	Stabelized with fair vision recovery	
Viola F., *et al*. 2010 [29]	1	VMD and NV	Photodynamic one eye observe the other eye	Observed and treated eye similar	Young boy
Sodi A., *et al*. 2015 [30]	30 pts	Best with NV	Photodynamic therapy	Va Improved slowly	
Frennesson CI,., *et al*. [31]	5 pts	Best VMD	Photodynamic therapy in 1 pt	Improved	
Ozdek S., *et al*. [32]	4 cases	VMD with NV	Photodynamic therapy	Improved	Children
Murtagh P., *et al*. [34]	1	AEPVM	No	Worsen	

Table 2: *Summarise the therapy of the reported cases of Best's disease and its complications.*

Mode of therapy	# of reports	# of cases	Response
Steroid	2	19	Only 1 patient had triamcinolone improved
Photodynamic therapy	8	53	11 improved 9 negative impact 33 fair improvement
Bevacisumab	12	34	All improved to different degrees
Runibisumab	6	34	9 improved 25 stabilised
Aflibercept	2	4	All Improved

Table 3: *Summarise the result of different modes of therapy vitelliform dystrophy and complications illustrated in table 1.*

Conclusion

In conclusion from the literature reports and the response of the present case; it seems that anti-VEGF is promising mode of therapy in the complicated conditions at present. The anti-vegf therapy may be of some benefit for patients with sub macular fluids.

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Volume 11 Issue 8 August 2020