International Journal of Retina (*IJRETINA*) 2022, Volume 5, Number 2.
P-ISSN. 2614-8684, E-ISSN.2614-8536

IJRETINA
International Journal of Retina

CHOROIDAL NEOVASCULARIZATION IN A CASE OF CHORIORETINAL COLOBOMA TREATED WITH INTRAVITREAL ANTI-VEGF INJECTONS: A CASE REPORT

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Abstract

Introduction: *Chorioretinal coloboma (CRC) results from abnormal closure of the embryonic fissure. Choroidal neovascularization (CNV) is a rare complication that associated with coloboma of the choroid. VEGF is an important factor in the development of CNV.*

Case Report: *A 52-year-old woman with gradual blurred vision of the left eye since 4 months ago. Right eye was already blurred since she was a child with uncorrected visual acuity (UCVA) was 0.5/60. Her right iris showed coloboma in inferior and chorioretinal coloboma. UCVA of the left eye was 6/20. Her left iris showed inferior coloboma, chorioretinal coloboma and macular edema with soft drusen. Macular optical coherence tomography (OCT) confirmed macular subretinal fluid, and indicated a CNV lesion of the left eye. She underwent a loading dose of three monthly intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections (bevacizumab) for the left eye. One month after completion of treatment, UCVA of the left eye improved to 6/12.*

Discussion: *CNV is a complication associated with CRC. Intravitreal Anti-VEGF treatment using loading dose regimen is shown to be effective in treating CNV. One month after completion of treatment, UCVA of the left eye improved.*

Conclusion: *Chorioretinal coloboma is a rare posterior segment congenital anomaly. Classical, bilateral coloboma of the choroid and iris indicates a deformation of the choroidal fissure closure. Coloboma of the choroid can have a complication such as choroidal neovascularization. Treatment with a loading dose of three monthly intravitreal anti-VEGF injections showed good anatomical and functional results.*

Keywords: *Chorioretinal coloboma, iris coloboma, choroidal neovascularization, intravitreal Anti-VEGF injections*

Cite This Article: SIMANJUNTAK, Dicky Budiman; VICTOR, Andi Arus; ANDAYANI, Gitalisa. CHOROIDAL NEOVASCULARIZATION IN A CASE OF CHORIORETINAL COLOBOMA TREATED WITH INTRAVITREAL ANTI-VEGF INJECTONS: A CASE REPORT. International Journal of Retina, [S.l.], v. 5, n. 2, sep. 2022. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/124>. Date accessed: 27 sep. 2022. doi: https://doi.org/10.35479/ijretina.2022.vol005.iss002.124.

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INTRODUCTION

Chorioretinal coloboma (CRC) is characterized by absence of part of the choroid and retinal pigment epithelium (RPE). Colobomas can present in various parts of ocular tissue, such as eyelid, iris, uvea, lens or optic nerve. [1-3] CRC results from abnormal closure of the embryonic fissure. This leads to the absence of choriocapillaris and formation of a defective Bruch membrane and postulated to be an entry site for the growth of abnormal blood vessels.[4-6] Ocular coloboma is a rare condition that occurr in only 0.5 until 2.4 infants per 10.000 live births. CRC can present out of the whole colobomas for 60 to 70%.[7-9,10-13]

Clinically, CRC presents as a prominent depigmented white zone most commonly located in the inferonasal quadrant. Because of incomplete closure of the embryonic fissure, so the inner layer grows faster than the outer layer. The defective development of RPE can cause absence of choroid in the area of coloboma since normal choroidal development is influenced by RPE. [2,8,9,14,15]

Choroidal neovascularization (CNV) is a complication that associated with choroid's coloboma. CNV development can be found at the edge of the coloboma. Signs of CNV include: hemorrhagic detachment of the retina, RPE with subsequent fibrous tissue, subretinal membrane, RPE proliferation and disciform scarring, subretinal or intraretinal or exudates in the absence of retinal vascular disease, serous detachment of the RPE and subretinal pigment epithelial ring lesions. [4,16-18]

Fluorescein angiography is important tools to detect and evaluate CNV in clinical practice. OCT also can be performed, CNV usually presented as thickening of the choriocapillaris or well-defined CNV and fusiform disruption, suggesting breaks in the RPE makes penetration of new vessels. The coloboma-related CNV can be seen with fundus fluorescein angiography, or with macular OCT; both located at the edge of coloboma, if it is located in macula/fovea area can cause the blindness.[19-20]

Progressive worsening to spontaneous resolution of visual acuity (VA) can be be achieved by the untreated of coloboma-associated CNV. The primary treatment of CNV are photodynamic therapy (PDT), focal laser photocoagulation and intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF).[21-24]

The development of CNV is influenced by VEGF. The hypoxic RPE cells produces VEGF and induces retinal vascular permeability and endothelial cell proliferation. VEGF is as a major mediator of retinal ischaemia-associated neovascularisation. The anti-VEGFs has improved treatment outcomes in CNV patients, beside conventional treatments such as PDT and laser photocoagulation. Anti-VEGFs can maintain or improve vision of patients when vision loss can occur even with conventional treatments.[25]

Clinical response of anti-VEGFs cannot be estimated by the duration of action and it needs to be individually assessed. Ranibizumab can inhibit all subtypes of VEGF-A, it is a humanised monoclonal antibody that has a rapid onset of action. After ranibizumab injection, optical coherence tomography (OCT) changes can be assessed from 12 hours to 24 hours. In 2006, ranibizumab has FDA approval for the treatment of neovascular AMD. Bevacizumab also binds all VEGF subtypes, it is also a humanised monoclonal antibody that has onset 3-4 days with visual improvements reported within a week, it has a longer onset of action than ranibizumab. Intravitreal bevacizumab has off-label in AMD and it is practiced worldwide. In 2004, intravenous bevacizumab was approved for use in metastatic colorectal cancer.[26,27]

The following case demonstrates a case of chorioretinal coloboma with the complication of macular edema and soft drusen in the good eye, successfully managed with intravitreal anti-VEGF (bevacizumab).

CASE REPORT

Female, 52 years old came to our clinic at Kirana Ciptomangunkusumo Hospital with chief complaint gradual blurred vision of the left eye since 4 months ago. There was no history of redness, floaters, recurrent red eye, headache, and trauma. Her family history was also noncontributory. She had history of hypertension controlled by amlodipine, and diabetes mellitus type 2 controlled by metformin.

Based on the eye examination (four months after the chief complaint), her UCVA of the right eye was 0.5/60 with an intraocular pressure was 20.5 mmHg. The right eyelids and bulbar conjunctiva were quiet. Cornea was clear. The anterior chamber was deep with no cells and flare. There was an iris inferior coloboma (figure 1). The lens showed grade 2 cataract. Fundus examination of the right eye showed chorioretinal coloboma, which extends past the macular area. The UCVA of the left eye was 6/20, with an intraocular pressure of 17.9 mmHg. The left eyelids and bulbar conjunctiva were quiet. Cornea was clear. The anterior chamber was deep with no cells and flare. There was iris inferior coloboma (figure 1). The lens showed grade 1 cataract. Fundus examination of the left eye showed chorioretinal coloboma and macular edema with soft drusen.

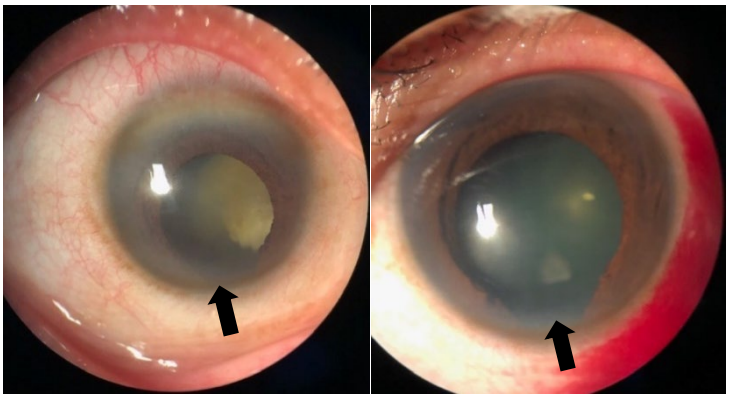

Figure 1**. Slitlamp examination of the right eye (left) and the left eye (right) showed iris coloboma**.

Macular OCT of the left eye was performed, which revealed subretinal fluid (SRF) and RPE disturbance (figure 2). There was also thickening of the neurosensory retina and a hyperreflective area at the edge of coloboma, indicating CNV lesion. Treatment with a loading dose of three monthly intravitreal anti-VEGF injections (bevacizumab) was administered to the left eye.

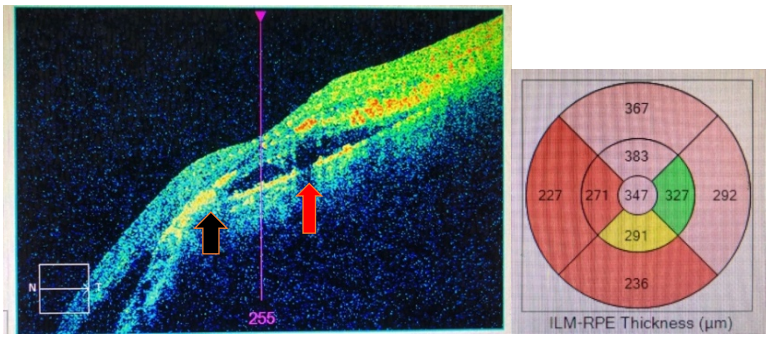

Figure 2. **Macular OCT of the left eye before loading dose of three monthly intravitreal anti-VEGF injections showed hyperreflective area at the edge of coloboma (black arrow), subretinal fluid (SRF) involving the fovea (red arrow) and RPE disturbance with central macular thickness (CMT) 347 µm.**

The patient underwent a loading dose of three monthly intravitreal anti-VEGF injections (bevacizumab). One month after completion of treatment, UCVA of the left eye improved to 6/12. Left eye macular OCT showed absorbed SRF and CMT decreased from 347 μm to 201 μm (figure 3). Fundus photography was also performed (figure 4&5).

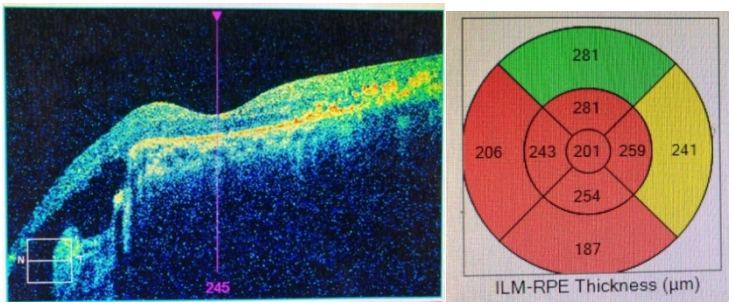

Figure 3**. Macular OCT of the left eye after loading dose of three monthly intravitreal anti-VEGF injections showed SRF absorbed with CMT 201 μm.**

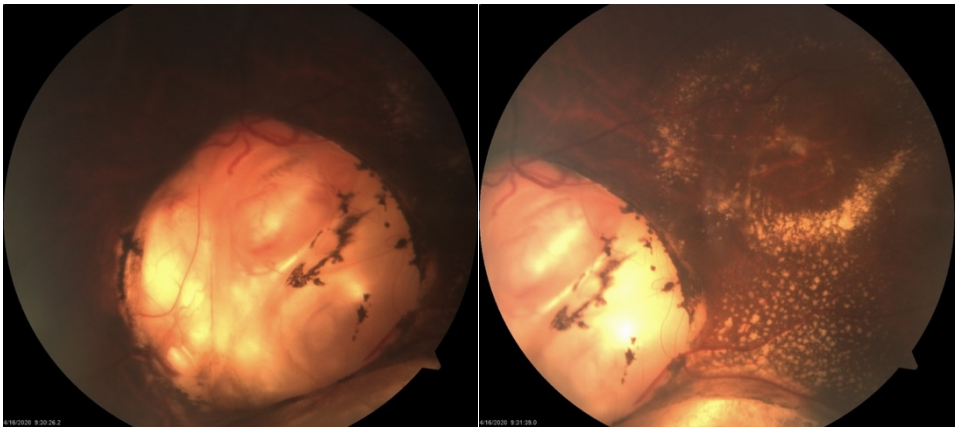

Figure 4**. Fundus photography of the left eye after loading dose of three monthly intravitreal anti-VEGF injections showed chorioretinal coloboma with macular edema and soft drusen.**

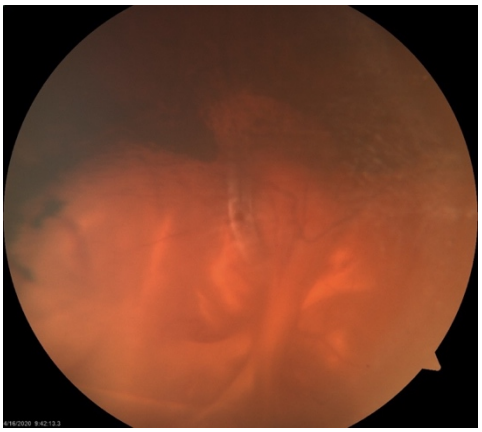

Figure 5. **Fundus photography of the right eye showed chorioretinal coloboma.**

DISCUSSION

Our patient was an adult female who came with gradual blurred vision of the left eye since 4 months ago with no history of previous systemic illness. Her right eye already blurred since she was child. At presentation, we found that initial UCVA of the right eye was 0.5/60 with grade 2 cataract and UCVA of the left eye was 6/20 with grade 1 cataract. In this case, the left eye is the functional eye. Variable dependent of the severity visual disability is dependent on size of coloboma, cataract, extend of optic nerve or macular involvement. Visual disability is also associated with anomalies of the eye such as nystagmus, microphthalmos, retrobulbar cysts and microcornea.[2,28,9]

Vincent et al.[29] reported that in the 87% eyes with colobomas had a VA <20/200. Uhumwangho and Jalali[2] observed that bilateral chorioretinal coloboma patient is 69.7% and patient with unilateral involvement is 29.8%. Asymmetrical involvement in bilateral colobomas because of its histopathological nature in both eyes, it presented with different VA level.

Iris defects in coloboma are related to D trisomy, but coloboma of the choroid are rare. Dysplasia of the retina in trisomies is opposed to inhibiton of morphogenesis of choroid and retina through deletions. Furthermore, coloboma of the choroid can be observed with various other anomalies of chromosomes sporadically and with the oculoanalsyndrome regularly.[30]

Ophthalmological examination in our patient revealed iris coloboma in inferior and cataract on both eye. Fundus examination of the right eye showed chorioretinal coloboma and left eye showed chorioretinal coloboma and choroidal neovascularization. The presence of iris coloboma and chorioretinal coloboma of both eye were strong indicator of ocular coloboma. Coloboma of iris and choroid on both sides indicates a deformation of the choroidal fissure closure but it is not specific for an aberration of chromosomes. There is no reliable comparison with other described cases since the chromosome of group D involved and the extent of the deletion was in individual cases.[31,32]

Macular OCT of the left eye indicated CNV the presence of SRF and RPE disturbance, with CMT 347 μm. CNV is best viewed with Fundus Fluorescein Angiography (Figure 6). However, due the unavailability, this diagnostic modality cannot be performed in this case. We believe it was a CNV because of its positive response with anti-VEGF treatment. Previous studies have reported various treatment modalities for CNV associated with CRC. Management options of coloboma-related CNV are photocoagulation therapy, PDT alone, and anti-VEGF intravitreal monotherapy and in combination.[19,33-35]

Figure 6. Example of patient with an active CNV showing the leak of the CNV surrounded by blocked fluorescence of the subretinal haemorrhage in the late-phase angiogram.[36]

Treatment of the left eye was warranted immediately, because it is the functional eye, and also there is a risk of blindness due to the potential complications of CNV to the macula. The patient underwent a loading dose of three monthly intravitreal anti-VEGF injections (bevacizumab). One month after completion of treatment, macular OCT was performed and showed SRF absorbed and CMT decreased from 347 μm to 201 μm. Fundus photography was also performed. UCVA of the left eye after a loading dose of three monthly intravitreal anti-VEGF injections was 6/12. All these findings showed that the left eye of the patient responded well with intravitreal anti-VEGF treatment.

In this case, our patient had positive response with anti-VEGF treatment. Anti-VEGF was preferred than PDT due to the unavailability, but in clinical practice, verteporfin PDT is usually performed in subfoveal CNV but it can cause severe damage to the RPE. Anti-VEGF was preferred than laser photocoagulation due to this patient had a CNV with SRF and

located in fovea, meanwhile laser photocoagulation can treat extrafoveal and juxtafoveal CNV at distance of >200 μm and 1–199 μm from the center of the foveal avascular zone.[37,38,39]

Bhende et al[16] reported three cases treatment of PDT for coloboma with CNV. In Cases 1 and 2, intravitreal bevacizumab combined with reduced fluence PDT had good results, and anti-VEGF monotherapy was also taken into consideration. Case 3 was treated with standard fluence PDT monotherapy and had regression with RPE atrophy. Cases 1 and 3 were closely monitored compared to case 2, however all cases were stable within five months post treatment.

Anti-VEGF type that was given to the patient in this case was bevacizumab. The reason of choosing bevacizumab, beside it is not an expensive anti-VEGF, it also was widely used, the structure is also very close to ranibizumab. The indication of anti-VEGF intravitreal injections agents was rapidly indicated to other diseases complicated by CNV.[40,41,42]

Bevacizumab is composed of structural region of human antibody (93%) and complementarity-determining region of murine monoclonal antibody (7%). it is also a full-length humanized anti-VEGF monoclonal antibody. It binds to all the VEGF isoforms, mainly VEGF-A. So, it can inhibit the biological activities of VEGF.[43,44,45]

The usage of intravitreal anti-VEGF injections with or without PDT in treating coloboma with CNV have been reported by several authors. There was a successful treatment of Intravitreal bevacizumab in 67-year-old patient coloboma associated CNV with subfoveal hemorrhage and CNV. After two months follow up, she had successful hemorrhage resolution and improvement of BCVA from finger counting to 20/200. After one month, the patient who did not get an intervention had CNV spontaneous regression and 12 months later, fluorescein angiography did not show evidence of leakage.[46-48]

A recent study determined that qualitative OCT and clinical examination combination can be used for guiding anti-VEGF treatment if monthly anti-VEGF injections are not administered, it worked by maintaining 'normal' retinal anatomy to maximize the benefit to risk ratio (VA gains to number of injections required ration). Patients should be assessed monthly to know whether the patient should get intravitreal anti-VEGF injections.[49,50]

Future plan management in this case if there is a recurrency of the CNV we can do anti-VEGF injections pro re nata and plan macular OCT to examine macula condition. The treatment depending on OCT findings and VA. If the CNV remained perfused, some authors suggested deciding additional treatments or performing one initial injection. A single initial intravitreal injection, if necessary followed by other injections may be a wise option in an unproven therapy and avoid unnecessary injections although it is not yet possible to define the best approach.[51]

CONCLUSION

Chorioretinal coloboma (CRC) is an rare congenital anomaly of the posterior segment. Classical, bilateral coloboma of chorioretina and iris, indicates a deformation of the choroidal fissure closure. CNV is a complication associated with CRC. Intravitreal Anti-VEGF treatment using loading dose regimen is shown to be effective effective in treating CNV associated with CRC.

REFERENCES

1. Gan NY, Lam WC. Retinal detachments in the pediatric population. *Taiwan J Ophthalmol*. 2018;8:222-36.

2. Uhumwangho OM, Jalali S. Chorioretinal coloboma in a pediatric population. *Eye*. 2014;28:728-33.

3. Chang L, Blain D, Bertuzzi S. Uveal coloboma: clinical and basic science update. *Curr Opin Ophthalmol*. 2006;17:447-70.

4. Gupta V, Gupta A, Dogra MR. Subretinal neovascularization associated with retinochoroidal coloboma. Indian J Ophthalmol. 1997;45:116–7.

5. Lee SH, Ahn JK, Yu HG. The development of recurrent choroidal neovascularization in a patient with choroidal coloboma. Korean J Ophthalmol. 2011;25:63–5.

6. Rouland JF, Constantinides G. Retinochoroidal coloboma and subretinal neovascularization. Ann Ophthalmol. 1991;23:61-2.

7. Bermejo E, Martinez-Frias ML. Congenital eye malformations: clinical-epidemiological analysis of 1,124,654 consecutive births in Spain. Am J Med Genet. 1998;75:497-504.

8. Daufenbach DR, Ruttum MS, Pulido JS. Chorioretinal colobomas in a pediatric population. Ophthalmology. 1998;105:1455-8.

9. Nakamura KM, Diehl NN, Mohney BG. Incidence ocular findings, and systemic associations of ocular coloboma: a population-based study. Arch Ophthalmol. 2011;129:69-74.

10. Gregory-Evans CY, Williams MJ, Halford S. Ocular coloboma: a reassessment in the age of molecular neuroscience. J Med Genet. 2004;41:881-91.

11. Chang L, Blain D, Bertuzzi S, Brooks BP. Uveal coloboma: clinical and basic science update. Curr Opin Ophthalmol. 2006;17:447-70.

12. Ozeki H, Shirai S, Nozaki M, Ikeda K, Ogura Y. Maldevelopment of neural crest cells in patients with typical uveal coloboma. J Pediat Ophthalmol Strabismus. 1999;36:337-41.

13. Blake KD, Issekutz KA, Smith IM, Prasad C, Graham JM. The incidence and prevalence of CHARGE syndrome. The CPSP annual report 2002 and 2003.

14. Hornby SJ, Adolph S, Gilbert CE. Visual acuity in children with coloboma: clinical features and a new phenotypic classi cation system. Ophthalmology. *2000*;107:511-20.

15. Hussain RM, Abbey AM, Shah AR, Drenser KA, Trese MT, Capone A. Chorioretinal coloboma complications: retinal detachment and choroidal neovascular membrane. JOVR. 2017:12:3-9.

16. Bhende M, Suganeswari G, Gopal L, Bhende PS, Gopal L, Rao Chetan. Choroidal neovascularization associated with coloboma of the choroid: a series of three cases. Indian J Ophthalmol. 2011;59:148-51.

17. Gass JDM. Serous retinal pigment epithelial detachment with a notch; a sign of occult choroidal neovascularization. 1984;4:205-20.

18. Gass JOM. Radial chorioretinal folds; asign of choroidal neovascularization. Arch Ophthalmol. l981;99:1016-8.

19. Stanga PE, Lim JI, Hamilton P. Indocyanine green angiography in chorioretinal diseases: indications and interpretation: an evidence-based update. Ophthalmology. 2003;110:15–21.

20. Hee MR, Baumal CR, Puliafito CA, Duker JS, Reichel E, Wilkins JR, et al. Optical Coherence Tomography of Age,related Macular Degeneration and Choroidal N eovascularization. 1996;1260-70.

21. Takenaka J, Yimane K, Minamoto A, Mishima HK, Hayashida H. Subretinal neovascularization associated with retinochoroidal coloboma. Eur J Ophthalmol. 2005;15:815-7.

22. Gupta V, Gupta A, Dogra MR. Subretinal neovascularization associated with retinochoroidal coloboma. Indian J Ophthalmol. 1997;45:116-7.

23. Maberley AL, Gottner MJ, Antworth MV. Subretinal neovascularization associated with retinochoroidal colobomas. Can J Ophthalmol. 1989;24:172-4.

24. Brodsky MC, Ford RE, Bradford JD. Subretinal neovascular membrane in an infant with a retinochoroidal coloboma. Arch Ophthalmol. 1991;109:1650-1.

25. Pe'er J, Shweiki D, Itin A. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. 1995;72:638-45.

26. Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci. 2005;46:726-33.

27. Iu LP, Kwok AK. An update of treatment options for neovascular age-related macular degeneration. Hong Kong Med J. 2007;13:460-70.

28. Berk AT, Yaman A, Saatci AO. Ocular and systemic findings associated with optic disc colobomas. J Pediatr Ophthalmol Strabismus. 2003;40:272-8.

29. Vincent D, Venincasa VD, Modi YS. Clinical and Echographic Features of Retinochoroidal and Optic Nerve Colobomas. Invest Ophthalmol Vis Sci. 2015;56:3615-20.

30. Cagianut B. Eye manifestations in chromosomal disorders. Ophtalmologica. 1968;155:148-66.

31. Bain AD, Gauld IK. Multiple congenital abnormalities associated with ring chromosome. Lancet 2. 1963:304-5.

32. Wallace C. Anderson IF. Group B/D translocation chromosome in a case with stigmata of the D Trisomy. S.Afr Med J. 1964:325-35.

33. Naithani P, Vashisht N, Mandal S. Intravitreal bevacizumab in choroidal neovascularization associated with congenital choroidal and optic nerve coloboma in children: long-term improvement in visual acuity. J AAPOS. 2010;14:288-90.Goodwin P, Shields CL, Ramasubramanian A. Ranibizumab for coloboma-related choroidal neovascular membrane in a child. J AAPOS. 2009;13:616-7.

35. Von EJ, Hoh H, Rehfeldt K. Photodynamic therapy for choroidal neovascularisation due to choroidal coloboma in a 5 1/2-year-old child. Klin Monbl Augenheilkd. 2007;224:140-5.

36. Rajendran A, Gupta S, Brahadeesh S. Intravitreal bevacizumab for choroidal neovascularization associated with a retinochoroidal coloboma. Eye. 2010;24:933-4.

37. Cohen SY, Bulik A, Dubois L, Quentel G. Photodynamic therapy for juxtafoveal choroidal neovascularization in myopic eyes. Am J Ophthalmol. 2003;136:371-4.

38. Parodi MB, Da Pozzo S, Ravalico G. Retinal pigment epithelium changes after photodynamic therapy for choroidal neovascularization in pathological myopia. Acta Ophthalmol Scand. 2007;85:50-4.

39. Soubrane G, Pison J, Bornert P, Perrenoud F, Coscas G. Re śultats de la photocoagulation des ne óvaisseaux sous re tiniens de la myopie forte. Bull Soc Ophtalmol Fr. 1986;86:269-72.

40. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. Retina. 2005;25:119-34.

41. Lipski A, Bornfeld N, Jurklies B. Photodynamic therapy with verteporfin in paediatric and young adult patients: long-term treatment results of choroidal neovascularisations. Br J Ophthalmol. 2008;92:655-60.

42. Chang LK, Spaide RF, Brue C, Freund KB, Klancnik JM Jr, Slakter JS. Bevacizumab treatment for subfoveal choroidal neovascularization from causes other than age-related macular degeneration. Arch Ophthalmol. 2008;126:941-5.

43. Simo R, Hernandez C. Intravitreous anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. Diabetologia. 2008;51(9):1574-80.

44. Kaiser PK. Antivascular endothelial growth factor agents and their development: therapeutic implications in ocular diseases. Am J Ophthalmol. 2006;142(4):660-8.

45. Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of Bevacizumab (Avastin) on survival in metastatic solid tumors, a meta-analysis and systematic review. PLoS One. 2013;8(1):51780.

46. Rajendran A, Gupta SR, Brahadeesh S, Ramasamy K. Intravitreal bevacizumab for choroidal neovascularization associated with a retinochoroidal coloboma. Eye. 2010;24:933-4.

47. Naithani P, Vashisht N, Mandal S, Sankaran P, Garg S. Intravitreal bevacizumab in choroidal neovascularization associated with congenital choroidal and optic nerve coloboma in children: Long-term improvement in visual acuity. J AAPOS. 2010;14:288-90.

48. Bhende M, Suganeswari G, Gopal L, Bhende PS, Gopal L, Rao C. Choroidal neovascularization associated with coloboma of the choroid: A series of three cases. Indian J Ophthalmol. 2011;59:148-51.

49. Brown DA, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: Applying clinical trial result to the treatment of everyday patients. Am J Opthalmol. 2007;144:627-37.

50. Lalwani GA, Rosenfeld PJ, Fung AE. A variable-dosing regimen with intravitreal ranibizumab for neovascular age- related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol. 2009;148:43-58.

51. Fung AE, Lalwani GA, Rosenfeld PJ. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol. 2007;143:566 -83.