Case Report

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Choroideremia With Choroidal Neovascularization

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1.Abstract

1.1. Purpose: To present a case with choroideremia accompanied by choroidal neovascularization (CNV) in bilateral eyes of a teenager boy, in which the disease was detected a hemizygous missense variant c.808C>T (p. Arg270Ter) and controlled with intravitreal anti-vascular endothelial growth factor (VEGF) drugs.

1.2. Observations: A 13-year-old boy complaining of visual impairment and nyctalopia was diagnosed as choroideremia accompanied by active and scarred CNV in both eyes based on clinical examinations. The genetic test of the boy and his mother and the similar symptoms of his grandfather were confirmed the diagnosis. The aqueous humor samples collected from this patient's left eye showed the increased level of basic fibroblast growth factor. While, CNV in both his eyes tended to be in a stable condition after four times intravitreal injection of anti-VEGF drugs.

1.3. Conclusions and Importance: This is a rare case of CNV formation in both eyes of a young patient with choroideremia. Though only the increased level of basic fibroblast growth factor was found in this young patient, prompt intravitreal injection of anti-VEGF drugs was still efficacious and could recommend to prevent the further irreversible vision loss and allow the young boy to continue his study in his teens.

2.Keywords: Cho roideremia; choroidal neovascularization; gene

3. Introduction

Choroideremia (CHM) is a kind of X-linked hereditary choroidal dystrophy, characterized by progressive degeneration of the choriocapillaris, retinal pigment epithelium (RPE), and outer retina. Its prevalence is about 1 in 50,000–100,000 people all over the world1. Clinically, male patients are more common than female. The impairment of night vision and peripheral visual field loss are common complaints of patients with CHM, which occur usually in the early stage of the disease, and progressively worsen throughout their whole life1-3. Choroidal neovascularization (CNV) is an uncommon complication of CHM. The CNV formation in CHM may share similar pathogenetic features with that in pathologic myopia3. Characteristic appearance of CNV can be found by optical coherence tomography (OCT), fundus fluorescein angiography (FFA). CHM is generally considered as incurable for the atrophy of the choriocapillaris, RPE, and outer retina. Some new attempts has been under investigation, such as gene therapy, stem cells, retinal prosthesis systems and so on4. Anti-VEGF therapy has been reported to be effective on preventing the subretinal fibrosis of CNV and irreversible vision loss in patients with CHM3. Here we presented a case of young boy with CHM accompanied with CNV to summarize the clinical features and the managements.

4. Case presentation

A 13-year-old boy presented for ophthalmic evaluation with the complaint of the progressive visual impairment and nyctalopia for 6 years and the worsened situation for one year in our eye center. And his grandfather had similar symptoms without any eye examination. At his first visit in other hospital in 2015, his best-corrected visual acuity (BCVA) was 20/25 in both eyes. While BCVA in his right and left eye had significantly reduced to 20/400 and 20/200, respectively in this visit. The anterior segment in both eyes was normal and intraocular pressure was 18 mmHg and 19 mmHg in the right and left eye, respectively. Fundus examinations (figure 1) showed the subretinal proliferative membrane in macular area and the irregular pigment disorder with widespread atrophy of the RPE, choriocapillaris, and the exposed choroidal big vessels in both eyes.

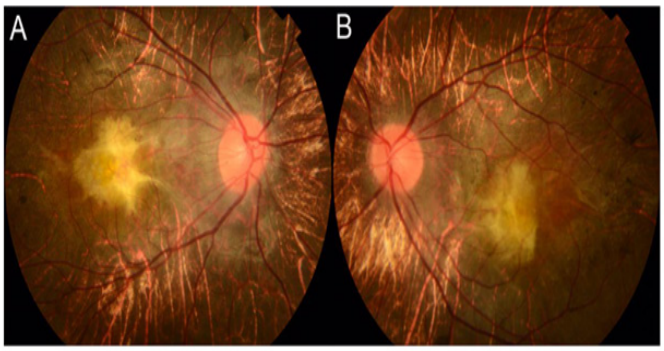

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Figure1: Fundus photographs of both eyes (A and B) show the pigment disorder of retina, yellowish white fibrotic scar and subretinal proliferative membrane on the macular regions and widespread atrophy of choroid with exposed choroidal big vessels. In his left eye, subretinal hemorrhage can be seen at the temporal of the proliferative membrane(B)

FFA (figure 2) showed the atrophy of choroid and the scarring and leakage of CNV in macular. Electroretinogram (ERG) revealed the poor responses of cone and rod in both eyes.

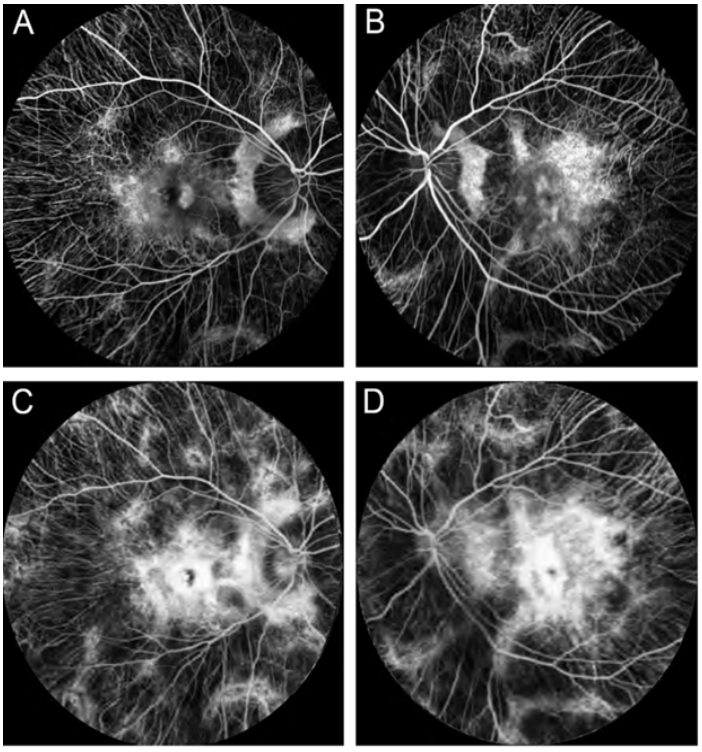

Figure 2: The FFA images in the early stage (A, B) and late stage (C, D) of the patient's eyes show the diffuse atrophy of the choriocapillaris, and the hyperfluorescence caused by the leakage of active CNV and the tissue staining of scarring CNV in the macular

OCT (figure 3A, 3B) revealed the atrophy of the ellipsoid zone (EZ), RPE and choroid in the macular regions, as well as hyperreflective areas in outer retina and the rupture of RPE layer and Bruch's membrane. The aqueous humor samples were collected from this patient's left eye and measured by cytometric bead array to detect of the concentration levels of intraocular cytokine, such as IL-6, IL-8, IL-10, VEGF, basic fibroblast growth factor (bFGF) and vascular adhesion molecule. The level of bFGF in the aqueous humor of this boy was found to be 6.0 pg/ml, which was the only cytokine significantly higher than the normal level. Peripheral blood samples of the boy and his parents were collected for the genomic test. The boy was found to a hemizygous missense variant c.808C>T (p. Arg270Ter), which could induce CHM. His mother was found to be the heterozygous variant carrier, while the same variant was not found in his father. After four times intravitreal injection of anti-VEGF drugs (three injections of Lucentis and one injection of Conbercept), no recurrence of active CNV was observed and BCVA was stabilized to 20/400 in both eyes of this boy with CHM. OCT of both eyes (figure 3C, 3D) showed that subretinal hyperreflective fibrosis at the macular areas were in a relatively stable situation and the retinal edema of both eyes reduced compared with pre-treatment (figure 3A, 3B), while the retinal and choroidal degeneration was still observed in both eyes.

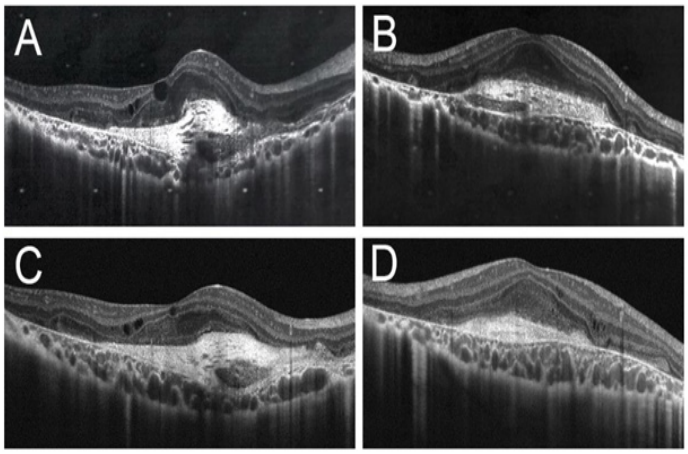

Figure 3: The OCT images of both eyes (A, B) show macular edema and the atrophy of the EZ, RPE and choriocapillaris in the macular regions, as well as CNV and the rupture of Bruch's membrane. After 4 doses of intravitreal anti-VEGF, OCT (C, D) showed subretinal hyperreflective fibrosis were in a relatively stable situation in both eyes and the cystic cavities of macular edema in the right eye were smaller than that before treatment.

5. Discussion

This uncommon case highlights the presentation of CHM with type 2 CNV. CHM is an X-linked recessive hereditary disorder that classically affects males due to the presence of only one X chromosome in males3. Females are usually carriers due to the presence of counterpart X chromosome, but manifestations of CHM are seen in heterozygous carrier females. In this case, DNA analysis in this patient and his parents had proved the diagnosis of CHM. The boy's hemizygous missense variant caused CHM was from hie mother, which was possibly inherited from his grandfather.It is acknowledged that visual loss secondary to CHM is associated with the atrophy of retina, RPE and choroidal, cystoid macular edema and rarely CNV5. CNV is a relatively rare complication of CHM6. The formation of CNV in CHM is thought to occur secondary to the degeneration of RPE, which is similar with that of pathologic myopia3,5,7. The degeneration of PRE and the rupture of Bruch's membrane make it possible for the pathological CNV to grow into subretinal space. The anti-VEGF drugs have been reported to be useful in the treatment of CHM with CNV5,8,9, although there is no evidence indicating that the VEGF level increases in the eye of CHM with CNV. In this case, we found the level of bFGF in aqueous humor of this young boy with CHM was strikingly higher than normal level, while the VEGF was normal. The effect of intravitreal injection of anti-VEGF drugs in our patient also had some effective but

was not ideal. The likely explanations were as follows: First is his long course of disease and pre-existing subretinal fibrosis of scarring CNV; Second is the normal VEGF level in the boy's aqueous humor. Why anti-VEGF drug could stable the high bFGF-induced active CNV? bFGF is a number of the human FGF family, consisting of 22 members10. FGF is a representative growth factor which has the potential ability to repair tissue and stimulate the fibrous proliferation, and the main pathway of the FGF signal is the RAS/MAP kinase pathway10. It is well known that both VEGF and bFGF are important proangiogenic factors and play a crucial role in prompting endothelial cell proliferation and migration and stimulating angiogenesis11,12. Previous studies have confirmed that there are a large number of cross-talks between VEGF and FGF during the angiogenesis of neovascularization13,14. Therefore, anti-VEGF treatment can inhibit the bFGF-induced CNV. And we recommended the prompt treatment of anti-VEGF to inhibit the CNV and prevent the irreversible visual impairment of patients with CHM accompanied by CNV.

6. Conclusion

We here reported a young boy with CHM accompanied by CNV and the high level of bFGF in aqueous humor, whose CNV was controlled by the intravitreal injection of anti-VEGF drugs. Although CHM with CNV is an uncommon occurrence, health education and follow-up are important for this kind of patients. The emergence of visual field and vision loss should be sufficient attention, and timely intravitreal anti-VEGF treatment for CNV in the early stage can preserve the limited visual acuity of CHM patients. It was a pity in this case that this boy didn't go to the hospital timely and missed the best treatment time, finally with a relatively poor BCVA at his young age. We hoped that this case report would assist and inspire other clinicians in the management of patients with CHM, even accompanied by CNV.

7. Patient consent

Oral consent to publish the case report was obtained from the patient and his parents, although this report does not contain any personal information that could lead to the identification of the patient.

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