Case Reports in Ophthalmology

Case Rep Ophthalmol 2022;13:825–831
DOI: 10.1159/000527319
Received: February 4, 2022
Accepted: September 25, 2022
Published online: November 10, 2022

Case Report

Successful Use of Conbercept to Treat Choroidal Neovascularization: A Case Report

Jin Yang[a, b] Zheng Liu[c] Tao Liu[b]

[a]Department of Ophthalmology, Shaanxi Provincial People's Hospital, Xi'an, China; [b]Guihang Guiyang Hospital Affiliated to Zunyi Medical University, Guiyang, China; [c]College of Medical Laboratory Science, Guilin Medical University, Guilin, China

Keywords
Choroidal neovascularization · Chronic urticaria · Conbercept

Abstract
Chronic urticaria is a dermatological condition characterized by the appearance of wheals or angioedema longer than 6 weeks. It could cause serious complications such as laryngeal edema, vasculitis, and diarrhea. However, the pathologic changes of the ocular fundus caused by chronic urticaria are rarely reported. In this study, we described the pathologic changes of ocular fundus in a patient with history of chronic urticaria and central serous chorioretinopathy. A 28-year-old female was presented with blurred vision and distorted images in her right eye for 6 days. The patient was diagnosed with choroidal neovascularization. She received an intravitreal injection of conbercept (0.5 mg/eye/time) monthly. Finally, no abnormality was found in her ocular examination after 4 months of first injection. In conclusion, chronic urticaria could cause central serous chorioretinopathy, leading to choroidal neovascularization. Intravitreal conbercept injection showed an excellent local therapeutic efficacy for this eye condition.

Background

Chronic urticaria is a skin disease characterized by activating skin mast cells with subsequent degranulation and the release of histamine and other proinflammatory mediators such as leukotriene, prostaglandin, and tumor necrosis factor-α [1]. It is clinically defined by

Jin Yang and Zheng Liu contributed equally to this work.

Correspondence to:
Zheng Liu, zliu1111@163.com
Tao Liu, taoliustone@163.com

Case Rep Ophthalmol 2022;13:825–831
DOI: 10.1159/000527319

the presence of wheals or angioedema on the skin, with daily or intermittent symptoms lasting more than 6 weeks [2]. The known factors that initiate clinical manifestations of urticaria include autoimmune disorders, diseases of the gastrointestinal tract, bacterial and viral infections [3]. Although the pathophysiology of chronic urticaria is not well understood, it is clear that the vascular dilatation and leakage of fluid into the surrounding tissues in response to molecules released from mast cells are central to the process [4]. As a result, the endothelium gets activated, resulting in vasodilation and extravasation, clinically visible as erythema and wheals [5].

Chronic urticaria may be accompanied by angioedema, which occurs at submucosal surfaces of the upper respiratory, gastrointestinal tracts, and musculoskeletal systems [6]. Central serous chorioretinopathy (CSC) caused by chronic urticarial was observed in previous reports [7]. In the present study, we report a patient with choroidal neovascularization (CNV). She has a history of chronic urticarial and CSC. In the treatment, intravitreal conbercept injection improved the eye condition of this patient. The therapeutic mechanism of conbercept is discussed in the discussion section.

Case Presentation

A 28-year-old female presented right eye distortion and blurred vision for 6 days. Medical records showed that the patient had a 16-year history of chronic urticarial and 5-year history of CSC. Unfortunately, the patient did not keep the imaging of eyes for the diagnosis of CSC. She received photocoagulation treatment in another hospital, but her condition recurred. The patient had a history of traditional Chinese medicine treatment for CSC, but she did not keep medical records. Skin examination found several white wheals on her back and limbs. Ophthalmic examination revealed that her visual acuity was 0.6 on the right and 1.0 on the left. The intraocular pressure was 17 mm Hg on the right eyes and 19 mm Hg on the left. Lens was transparent. In addition, the examination results from blood routine, erythrocyte sedimentation rate, liver and kidney function, tuberculosis antibody, rheumatoid factor were all in the normal range. However, an increased level of C-reactive protein to 1.38 mg/L was reported. The examination found the reflective layer corresponding to retinal pigment epithelium (RPE) and Bruch membrane in the right eye was broken (Fig. 1a). No obvious abnormality was found in left eye (Fig. 1d). The spindle-shaped hyper-reflective lesion was observed in the macular area (Fig. 2a), and no obvious abnormality was found in left eye (Fig. 2d). Fluorescein fundus angiography and indocyanine green choroidal angiography were examined with the HRA-2 Heidelberg Retina Angiography system (Heidelberg Engineering, Heidelberg, Germany). Spectralis HRA + OCT device (Heidelberg Engineering, Heidelberg, Germany) was used to scan the reflective layer corresponding to RPE and Bruch membrane.

The patient was diagnosed with CNV in the right eye based on the investigations. The previous study revealed that the vascular endothelial growth factor (VEGF) was a major stimulator in the model of CNV [8]. Anti-VEGF therapy was a promising treatment for CNV [9]. Therefore, the patient was given the treatment of intravitreal conbercept injection once a month, 0.5 mg each time. The reflective layer of the right eye becomes continuous (Fig. 1b), and the hyper-reflective lesion becomes weak (Fig. 2b) after 1 month of first injection. Figures 1e and 2e show the conditions of the left eye after 1 month of first injection. After 4 months of first injection, no abnormality was found in her ocular examination (Fig. 1c, 2c). Figures 1f and 2f show the conditions of the left eye after 4 months of first injection. In the process of writing and preparing the manuscript, we have read the CARE Checklist (2013). The manuscript was prepared and revised according to the CARE Checklist (2013), which is uploaded as an

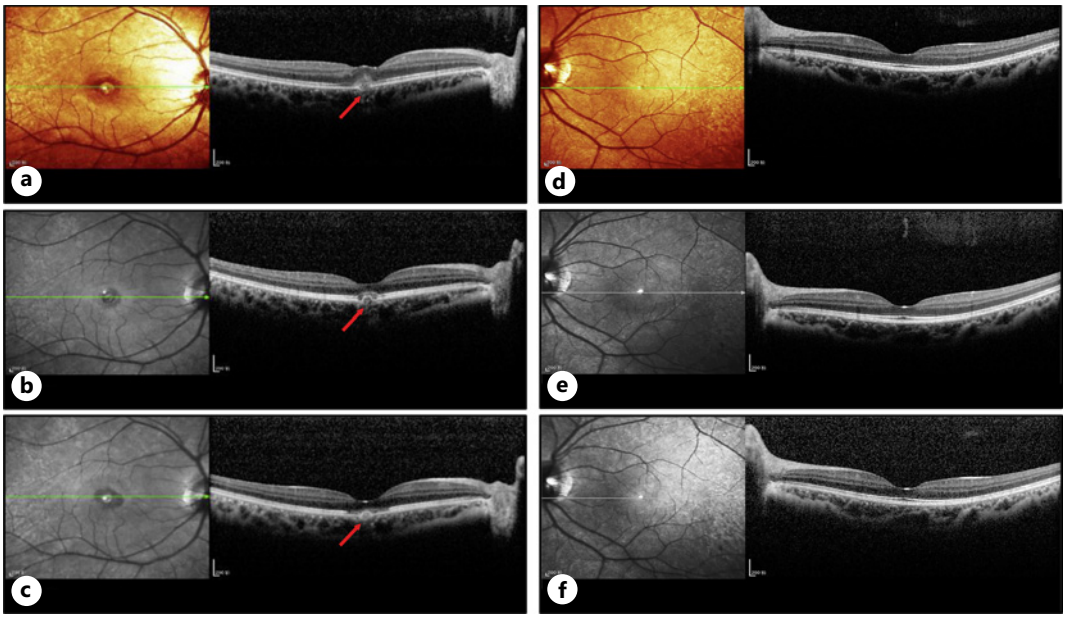

Fig. 1. The images showed disruption of reflective layer by OCT examination. **a** The reflective layer corresponding to RPE and Bruch membrane in the right eye is broken (baseline, OD). There is a spindle high reflective layer under the neuroepithelial layer. **b** The reflective layer of the right eye corresponding to RPE and Bruch membrane becomes continuous (1 month after 1st injection, OD). Intraretinal, subretinal fluid accumulation and pigment epithelial layer is detached. **c** The reflective layer corresponding to RPE and Bruch membrane in the right eye is thickened (4 months after 1st injection, OD). A small amount of RPE lower fluid can be seen. The conditions of the left eye at the same time (no obvious abnormality found) are shown at baseline, OS (**d**), 1 month after 1st injection, OS (**e**), and 4 months after 1st injection, OS (**f**).

online supplementary file (see www.karger.com/doi/10.1159/000527319 for all online suppl. material).

Discussion

In the present study, the patient is diagnosed with CNV. CNV is the pathological growth of new blood vessels in the sub-RPE space from the choroid through a break in the Bruch membrane [10]. In many cases, CNV can occur as a complication of long-standing CSC [11]. Previous reports have shown that CSC might occur associated with chronic urticarial [12]. CSC is a retina disease characterized by the accumulation of subretinal fluid at the posterior pole of the fundus, creating a circumscribed area of serous retinal detachment [11]. It is usually caused by fluid leakage from the choroid through the defect Bruch membrane [11]. This patient has a 16-year history of chronic urticarial and 5-year history of CSC. We reasonably speculate that her CNV was developed from CSC, which is caused by chronic urticarial.

Figure 3 illustrates the possible pathogenesis of CNV that may be caused by CSC, which may be caused by chronic urticarial. This pathogenesis relates to the damage of the Bruch membrane. Bruch membranes are two adjacent RPE cells that form a closed strand surrounded by each epithelial cell in a continuous reticular structure [13]. It regulates the

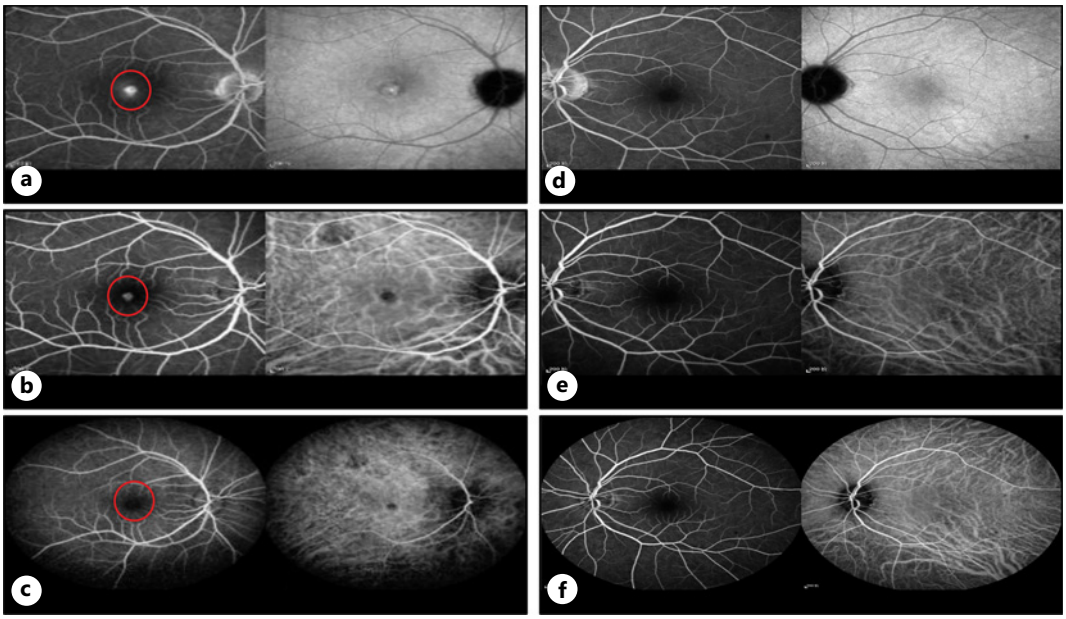

Fig. 2. The images showed high fluorescence in the macular area by FFA/ICGA examination. **a** Fluorescence angiography showed high fluorescence in the macular area (late frames, baseline, OD). No enhancement and expansion were observed in the late stage. Indocyanine green angiography showed neovascularization in the macular area. **b** Fluorescence angiography showed weak fluorescence in the macular area (late frames, 1 month after 1st injection, OD). No enhancement and expansion were observed in the late stage. Indocyanine green angiography showed fluorescence masking in the macular area. **c** Fluorescence angiography and indocyanine green angiography have no obvious abnormalities (late frames, 4 months after 1st injection, OD). The conditions of the left eye at the same time (no obvious abnormality found) are shown at late frames, baseline, OS (**d**), late frames, 1 month after 1st injection, OS (**e**), and late frames, 4 months after 1st injection, OS (**f**).

permeability of cells and participates in the regulation of cell polarity, morphology, and signal transduction [14]. Bruch membrane divides the surface of epithelial cells into top and bottom sides. It participates in forming of the polarity of RPE cells, thus restricting the lateral diffusion of membrane proteins and lipids, which is the "fence" of the tight junctions [15]. Under physiological condition, the Bruch membrane not only selectively absorbs substances from choroidal vessels of peripheral blood circulation, but also blockades circulating immune cells, inflammatory cells, and macromolecules through the tight junctions through blocking and regulating the permeability of intercellular space. In pathological state, RPE cells are defective, and Bruch membrane is destroyed. The intercellular permeability increases, and plasma components in blood vessels leak into peripheral tissues of blood vessels, resulting in CSC. In long-term or recurrent CSC, CNV in the detachment areas can occur [16]. The development of CSC to CNV is related to the degree of inflammation and the course of the disease [16].

As we expected, the patient received an intravitreal conbercept injection, and no abnormal result was found after 4 months of first injection. Conbercept is a recombinant fusion protein with a high affinity to all VEGF isoforms. It was developed and approved in China to treat age-related macular degeneration in December 2013 [17]. In 2014, Li et al. [17] proved that conbercept had safety and efficacy in neovascular age-related macular degeneration. After that, conbercept treatment has also shown good efficacy in other

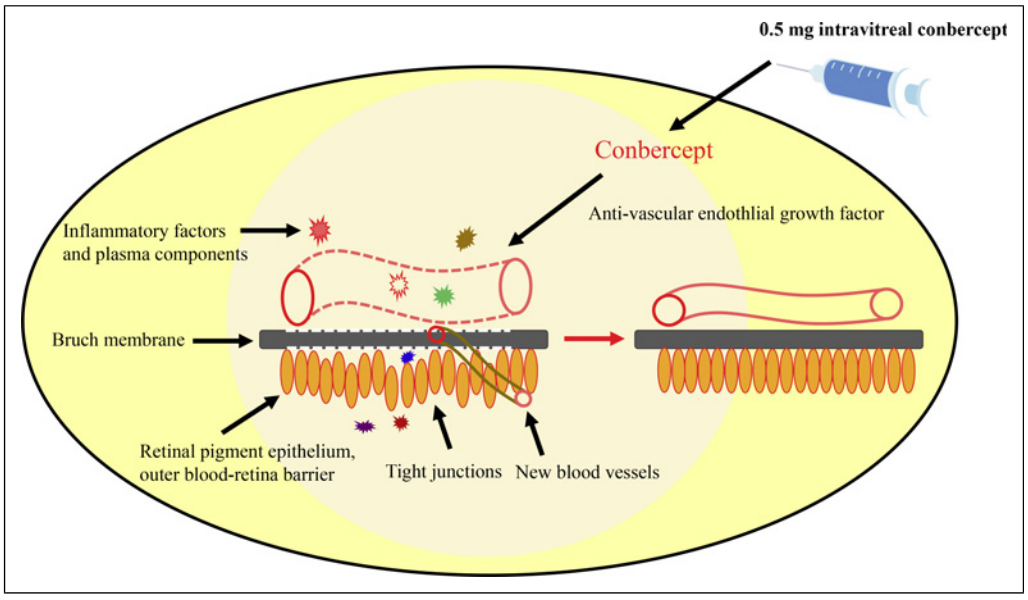

Fig. 3. Treatment mechanisms of conbercept. When retinal pigment epithelium is damaged (left panel), the inflammatory factors and plasma components leak into peripheral tissues of blood vessels. Intravitreal conbercept injection reduces the vascular growth, narrows the tight junctions, and relives the inflammation (right panel).

ophthalmic diseases such as diabetic macular edema, macular edema secondary to retinal vein occlusion, and retinopathy of prematurity [18, 19]. Based on the above literature analysis and drug function analysis, we therefore speculate that the mechanisms of conbercept treating CNV are through reducing the vascular growth, narrowing the tight junctions, and relieving the inflammation.

Conclusion

We here report the pathological changes of ocular fundus in a patient with chronic urticaria. Moreover, intravitreal conbercept injection shows an excellent local therapeutic efficacy for CNV that may be caused by CSC, which may be caused by chronic urticaria.

Acknowledgments

We thank the patients for their participation.

Statement of Ethics

This study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and approved by the Hospital Research Ethics Committee of Guihang Guiyang Hospital, approval number (No. GH2020005).

Conflict of Interest Statement

The authors report no conflicts of interest.

Funding Sources

This study was funded by the Key Research and Development Program of Shaanxi Province (2017ZDXM-SF-067). The funding had no role in the study design, data collection, data analysis, data interpretation, and writing the manuscript.

Author Contributions

Tao Liu and Zheng Liu: manuscript writing and editing. Jin Yang and Zheng Liu: patient management and data collection. All coauthors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Korczyñska-Krawczyk P, Kupryś-Lipiñska I, Kupczyk M, Wągrowska-Danilewicz M, Szemraj J, Bienias W, et al. The effect of levocetirizine and montelukast on clinical symptoms, serum level and skin expression of COX-1 and COX-2 enzymes in patients suffering from chronic autoimmune urticaria: a pilot study. Postepy Dermatol Alergol. 2020;37(1):73–80.
2 Moestrup K, Ghazanfar MN, Thomsen SF. Patient-reported outcomes (PROs) in chronic urticaria. Int J Dermatol. 2017;56(12):1342–8.
3 Darlenski R, Kazandjieva J, Zuberbier T, Tsankov N. Chronic urticaria as a systemic disease. Clin Dermatol. 2014;32(3):420–3.
4 Puxeddu I, Petrelli F, Angelotti F, Croia C, Migliorini P. Biomarkers in chronic spontaneous urticaria: current targets and clinical implications. J Asthma Allergy. 2019;12:285–95.
5 Kocatürk E, Grattan C. Is chronic urticaria more than skin deep? Clin Transl Allergy. 2019;9(1):48.
6 Mostmans Y, De Smedt K, Richert B, Elieh Ali Komi D, Maurer M, Michel O. Markers for the involvement of endothelial cells and the coagulation system in chronic urticaria: a systematic review. Allergy. 2021;76(10):2998–3016.
7 Gravina AG, Priadko K, Ciamarra P, Granata L, Facchiano A, Miranda A, et al. Extra-gastric manifestations of *Helicobacter pylori* infection. J Clin Med. 2020;9(12):3887.
8 Xin H, Biswas N, Li P, Zhong C, Chan TC, Nudleman E, et al. Heparin-binding VEGFR1 variants as long-acting VEGF inhibitors for treatment of intraocular neovascular disorders. Proc Natl Acad Sci U S A. 2021;118(21):e1921252118.
9 Miere A, Oubraham H, Amoroso F, Butori P, Astroz P, Semoun O, et al. Optical coherence tomography angiography to distinguish changes of choroidal neovascularization after anti-VEGF therapy: monthly loading dose versus Pro Re Nata Regimen. J Ophthalmol. 2018;2018:1–7.
10 Zhu S, Shi F, Xiang D, Zhu W, Chen H, Chen X. Choroid neovascularization growth prediction with treatment based on reaction-diffusion model in 3-D OCT images. IEEE J Biomed Health Inform. 2017;21(6):1667–74.
11 van Dijk EHC, Boon CJF. Serous business: delineating the broad spectrum of diseases with subretinal fluid in the macula. Prog Retin Eye Res. 2021;84:100955.
12 Yeo JH, Oh R, Kim YJ, Kim JG, Yoon YH, Lee JY. Choroidal neovascularization secondary to central serous chorioretinopathy: OCT angiography findings and risk factors. J Ophthalmol. 2020;2020:1–9.
13 Willermain F, Libert S, Motulsky E, Salik D, Caspers L, Perret J, et al. Origins and consequences of hyperosmolar stress in retinal pigmented epithelial cells. Front Physiol. 2014;5:199.

14 Xia T, Rizzolo LJ. Effects of diabetic retinopathy on the barrier functions of the retinal pigment epithelium. Vis Res. 2017;139:72–81.
15 Rizzolo LJ, Peng S, Luo Y, Xiao W. Integration of tight junctions and claudins with the barrier functions of the retinal pigment epithelium. Prog Retin Eye Res. 2011;30(5):296–323.
16 Hage R, Mrejen S, Krivosic V, Quentel G, Tadayoni R, Gaudric A. Flat irregular retinal pigment epithelium detachments in chronic central serous chorioretinopathy and choroidal neovascularization. Am J Ophthalmol. 2015;159(5):890–903.e3.
17 Li X, Xu G, Wang Y, Xu X, Liu X, Tang S, et al. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: AURORA study. Ophthalmology. 2014;121(9):1740–7.
18 Zhou J, Liu Z, Chen M, Luo ZH, Li YQ, Qi GY, et al. Concentrations of VEGF and PlGF decrease in eyes after intravitreal conbercept injection. Diabetes Ther. 2018;9(6):2393–8.
19 Bai Y, Nie H, Wei S, Lu X, Ke X, Ouyang X, et al. Efficacy of intravitreal conbercept injection in the treatment of retinopathy of prematurity. Br J Ophthalmol. 2019;103(4):494–8.