

Optical coherence tomography angiography of myopic choroidal neovascularization treated by anti-VEGF therapy

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Research article

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Abstract

Background: To analyze the efficiency of anti-vascular endothelial growth factor (anti-VEGF) therapy for myopic choroidal neovascularization (CNV) by optical coherence tomography angiography (OCTA) and to determine the reduction ratio of CNV lesions after anti-VEGF therapy. **Methods:** A total of 41 patients (41 eyes) with myopic CNV who were treated with anti-VEGF were included in the study. The best corrected visual acuity (BCVA), superficial vessel density, deep vessel density, the area of foveal avascular zone (FAZ), central macular thickness (CMT) and the area and the flow area of CNV lesion at baseline and at the follow-up after 1, 2, 3 and 6 months were measured. **Results:** After treatment, BCVA improved ($F=6.848$, $P<0.05$), while the CMT ($F=2.489$, $P<0.05$), the area ($F=3.125$, $P<0.05$) and the flow area ($F=3.558$, $P<0.05$) of CNV lesion reduced. On the other hand, superficial vessel density, deep vessel density and the area of FAZ had no change. The mean reduction ratio of lesions was 50.32% (7.07% to 100%). Only in two cases, 100% lesion regression was observed (4.88%). There was a negative correlation between the CNV lesion area and reduction ratio ($r=-0.380$, $P=0.042$) and the flow lesion area and reduction ratio ($r=-0.402$, $P=0.030$). **Conclusions:** Anti-VEGF therapy is efficient for myopic CNV without affecting superficial vessel density and deep vessel density of retina, but it is unable to completely eliminate CNV lesions in most cases. The mean reduction ratio is 50.32%, and the bigger myopic CNV lesions have a lower reduction ratio.

Background

Myopic choroidal neovascularization (CNV) is defined as CNV secondary to pathologic myopia (refractive error $\geq -6D$ or axial length ≥ 26 mm, associated with complications of the posterior segment secondary to excessive elongation of axial length), which has great impairment in vision and may cause legal blindness. Individuals (5.2%–11.3%) with pathologic myopia may develop myopic CNV, and approximately 15% of patients have bilateral CNV lesions.

Fundus fluorescein angiography is the standard examination and is most commonly used to evaluate myopic CNV; however, it's an invasive and time-consuming examination that has some risks for patients, such as anaphylactic shock. Optical coherence tomography angiography (OCTA) performs scans of areas of retinal tissue and constructs microvascular flow maps to evaluate the flow in various layers of the retina free of an injected dye. Various studies compared OCTA and fluorescein fundus angiography (FFA) and reported the potential of OCTA to diagnose and evaluate CNV."

Anti-vascular endothelial growth factor (Anti-VEGF) therapy is an efficient therapy for myopic CNV. As a noninvasive and fast technique, OCTA is more commonly applied during the follow-up after anti-VEGF therapy. Several studies assessed the anti-VEGF therapy for myopic CNV by OCTA. Cheng, Y. et al. demonstrated that the size of the CNV area and flow area decreased after the intravitreal administration of Ranibizumab for 1 week and 1 month in 13 eyes. Gilda, C. et al. followed up 20 eyes and found that the neovascular area but not the vessel density by OCTA was decreased after Ranibizumab therapy for 6 months. Cai, M. et al. compared the changes at 1, 3 and 6 months after treatment and revealed a

progressively smaller vascular lesion and reduction in capillary density of lesion. All these studies proved the reduction in the area of CNV lesion after treatment. However, there are only a few studies on the reduction ratio of CNV lesions and whether they will completely disappear after anti-VEGF therapy. Our study is designed to follow-up before and until 1, 2, 3 and 6 months after anti-VEGF treatment to know the variation tendency of CNV lesions better.

We aim to measure the vessel density and the area of myopic CNV lesion by OCTA, analyze the reduction ratio of CNV lesions and the relationship between visual acuity and determine the reduction ratio of CNV lesions to investigate the efficiency of anti-VEGF treatment for myopic CNV after treatment.

Methods

This study reviewed 41 patients (41 eyes) diagnosed with myopic choroidal

neovascularization who received intravitreal anti-VEGF therapy from January 2016 to October 2018 at the Hangzhou Branch of Eye Hospital of Wenzhou Medical University. Criteria for inclusion were: (1) refraction of myopia ≤ -6 D or axial length ≥ 26 mm; (2) hyperfluorescence in early phases and fluorescent leakage in the late phases on FFA (Spectralis, Heidelberg, Germany) and a hyperintense vascular anastomotic network on OCTA; (3) accept intravitreal Ranibizumab or Conbercept, a single injection followed by treatment given pro re nata (1+ PRN); (4) follow-up until 6 months after first injection. Criteria for exclusion were: (1) idiopathic choroidal neovascularization or secondary CNV to other diseases; (2) accompanied with other eye diseases, such as age-related macular degeneration (AMD), central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy, glaucoma or ocular trauma; (3) previous treatments, including Laser photocoagulation, photodynamic therapy or vitreoretinal surgery.

Anti-VEGF treatment regimen: intravitreal Ranibizumab or Conbercept 0.5 mg, a single injection followed by the treatment given pro re nata (1+ PRN). Retreatment criteria included any of the following findings during follow-up, (1) macular edema or subretinal fluid or serous retinal detachment in the optical coherence tomography (OCT) images; (2) CNV leakage on FFA; (3) new subretinal hemorrhage from the myopic CNV; (4) Significant loss of visual acuity (VA).

All patients underwent complete ophthalmological work-up, including slit-lamp examinations, dilated fundus examinations, intraocular pressure measurements, best corrected visual acuity (BCVA) testing, IOL-master, B-Ultrasound, OCTA, FFA and another testing as needed. The BCVA was evaluated by standard logarithmic visual acuity chart and was converted into LogMAR for statistical analysis. The central macular thickness (CMT) was assessed by an ophthalmologist using the manual measurement of the distance between the inner limiting membrane and retinal pigment epithelium (RPE) at the fovea on OCT. The superficial vessel density and deep vessel density of retina and the area of the foveal avascular zone (FAZ) were assessed by OCTA. The area and the flow area of CNV were automatically measured when the range of CNV was manually selected by an ophthalmologist in the outer retina on 3×3 OCTA images. The CNV flow area was the flow area of the selected area. The data were measured

three times using the manual measurement, and the mean value was recorded. All the data were measured by the software based on Optovue. The scan quality was $\geq 6/10$.

Observed indicators included LogMAR BCVA, superficial vessel density, deep vessel density, the area of FAZ, CMT and the area and the flow area of CNV lesion before and 1, 2, 3 and 6 months after initial anti-VEGF intravitreal injection. During the follow-up, patients received additional injection if necessary.

Statistical analyses were performed using SPSS version 19.0 (SPSS 19.0, Inc., Chicago, IL). All data were expressed as mean \pm standard deviation. Serial changes in LogMAR BCVA, superficial vessel density, deep vessel density, CMT, the area of FAZ, the area and the flow area of CNV lesion and CMT were compared using one-way ANOVA. The relationship between different parameters was evaluated using Pearson's correlation. Comparison of two groups (CNV area before treatment $>0.5\text{mm}^2$ and $\leq 0.5\text{mm}^2$) was used independent t-test. A P-value of less than 0.05 was considered statistically significant.

Results

A total of 41 patients (41 eyes, 11 males and 30 females) with myopia CNV were included in this study. The mean age of these patients was 52.93 ± 14.22 (22 to 77 years), and the mean time of intravitreal injection was 1.88 ± 0.87 . 22 eyes were injected with Ranibizumab, and 19 eyes were injected with Conbercept. (Table 1)

LogMAR BCVA

The mean LogMAR BCVA was 0.56 ± 0.30 at baseline and 0.41 ± 0.27 , 0.33 ± 0.27 , 0.31 ± 0.26 and 0.30 ± 0.27 at 1, 2, 3 and 6 months follow-up, respectively (Fig. 1). The difference between LogMAR BCVA at baseline and at 1, 2, 3 and 6 months follow-up was statistically significant ($F=6.848$, $P<0.05$). The intravitreal anti-VEGF therapy improved the logMAR BCVA at 1-month ($P=0.017$), 2-month ($P=0.001$), 3-month ($P=0.000$) and 6-month follow-ups ($P=0.000$).

Superficial vessel density of retina

The mean superficial vessel density of retina was $42.24 \pm 5.90\%$ at baseline and $43.43 \pm 6.11\%$, $42.08 \pm 5.85\%$, $41.12 \pm 6.28\%$ and $41.08 \pm 5.72\%$ at 1, 2, 3 and 6 months follow-up, respectively. There was no significant difference before and after the treatment ($F=1.071$, $P>0.05$).

Deep vessel density of retina

The mean deep vessel density of retina was $46.63 \pm 5.53\%$ at baseline and $46.24 \pm 5.88\%$, $46.31 \pm 4.77\%$, $46.55 \pm 5.47\%$ and $46.16 \pm 5.85\%$ at 1, 2, 3 and 6 months follow-up, respectively. There was no significant difference between them ($F=0.055$, $P>0.05$).

FAZ

The mean FAZ was 0.253 ± 0.090 mm² at baseline and 0.258 ± 0.091 mm², 0.261 ± 0.079 mm², 0.271 ± 0.093 mm² and 0.266 ± 0.097 mm² at 1, 2, 3 and 6 months follow-up, respectively. There was no significant difference between them ($F=0.119$, $P>0.05$).

CMT

The mean CMT was 289.15 ± 74.76 μ m at baseline and 256.44 ± 61.77 μ m, 258.32 ± 55.70 μ m, 254.05 ± 53.29 μ m and 252.59 ± 62.21 μ m at 1, 2, 3 and 6 months follow-up, respectively (Fig. 2). The difference between the CMT at baseline and at each follow-up was statistically significant ($F=2.489$, $P<0.05$). However, there was no difference in the values of CMT between 1, 2, 3 and 6 months follow-up.

The area and flow area of CNV lesion

The mean area of CNV lesion was 0.645 ± 0.773 mm² at baseline and 0.356 ± 0.426 mm², 0.318 ± 0.377 mm², 0.355 ± 0.433 mm² and 0.320 ± 0.399 mm² at 1, 2, 3 and 6 months follow-up, respectively (Fig. 3). The mean flow area of CNV lesion was 0.494 ± 0.556 mm² at baseline and 0.264 ± 0.306 mm², 0.255 ± 0.293 mm², 0.261 ± 0.313 mm² and 0.234 ± 0.295 mm² at 1, 2, 3 and 6 months follow-up, respectively (Fig. 4). The difference between the area ($F=3.125$, $P<0.05$) and flow area ($F=3.558$, $P<0.05$) of the CNV lesion at baseline and at each follow-up was statistically significant. However, there was no difference between 1, 2, 3 and 6 months follow-up. Although the area of the CNV lesion reduced after injection, in most patients (95.12%), it didn't disappear even when its activity had been controlled. The mean reduction ratio of lesions was 50.32% (7.07% to 100%). In only two cases, 100% lesion regression was observed (4.88%).

T-test

We divided the patients into two groups according to the CNV area before treatment (>0.5 mm² and ≤ 0.5 mm²). The reduction ratio in the two groups was compared using independent t-test ($t=2.136$, $P=0.042$). The reduction ratio in the group with preoperative CNV area >0.5 mm² was smaller than the other group.

Correlation analysis

The Pearson correlation analysis showed the negative correlation between the area of the CNV lesion and the reduction ratio ($r=-0.380$, $P=0.042$) and between the flow lesion area and the reduction ratio ($r=-0.402$, $P=0.030$). It means the bigger the CNV lesion is, the lower is the reduction ratio. There is no significant difference between the reduction ratio and other factors, such as age, LogMAR BCVA and CMT before treatment and the improvement of BCVA.

Case 1. In a 33-year-old female with myopia CNV in the right eye, the refraction of myopia was -7.0 D and the LogMAR BCVA was 0.1. The lesion disappeared completely after one intravitreal Ranibizumab injection, and the LogMAR BCVA was improved to 0 (Fig. 5).

Case 2. In a 58-year-old female with myopia CNV in the right eye, the refraction of myopia was -9.5 D and the LogMAR BCVA was 0.7. The lesion just became smaller but still existed after three times intravitreal Conbercept injection, and the LogMAR BCVA was improved to 0.15 (Fig. 6).

Discussion

Our study found that anti-VEGF therapy could not eliminate the myopic CNV lesions completely in most cases (95.12%) at 6 months after treatment. The mean reduction ratio of lesions of 41 patients was 50.32% (varying from 7.07% to 100%). CNV is affected by various factors, such as interleukin 8 (IL8); monocyte colonization protein (MCP), etc. Simple anti-VEGF probably can't block all the factors that induce CNV. New treatments, such as anti-VEGF associated with other factors antagonists, are needed to be studied in the future.

There were two cases (4.88%) who reached complete regression of CNV lesions at 6-month follow-up. In both cases, the CNV lesions at baseline were relatively small (0.076 and 0.222 mm²) and the patients were young (26 and 33 years old). We speculate that the size of lesions and the age of patients may be the factors related to the complete regression of the lesions. According to the Pearson correlation analysis, we found that the smaller lesions would regress more ($r = -0.380$, $P = 0.042$). According to independent t-test, the reduction ratio in the group with preoperative CNV area ≤ 0.5 mm² was smaller than the other group.

Previous research studies on the treatment for CNV secondary to AMD by OCTA found that anti-VEGF therapy only prunes subtle small newly growing vessels and does not achieve vascular normalization." Cheng, Y. et al. researched myopic CNV and found attenuation in capillaries and small caliber feeder vessels but not in large caliber feeder vessels treated by intravitreal Ranibizumab.⁸ We guess the reasons for larger lesions leading to a lower reduction ratio are as follows: (1) larger lesions more likely have bigger feeder vessels that are more difficult to clear up; (2) larger lesions are more likely to be old lesion whose feeder vessels have been formed that are difficult to regress. There is no correlation between the lesion area and age. Maybe those two young persons had a better consciousness of visiting clinic leading to earlier treatment and better prognosis. Besides, we didn't find other factors that are related to the regression rate; thus further studies are needed.

In this study, the VA of patients improved after treatment, which proved the positive effect of anti-VEGF on myopic CNV. The change of VA had no relationship with the reduction ratio. We suspected that the VA was affected by various factors, such as age, axial, former fundus condition, duration of myopic CNV, etc. We didn't perfectly control these variables of the patients enrolled in our study. It is not enough to prove that visual acuity and reduction ratio are irrelevant. We also analyzed the other parameters measured by

OCTA to investigate the efficiency of anti-VEGF. The CNV lesion area, the flow area of CNV lesion and CMT reduced mostly at the first month after injection and was stable in the following 5 months, which indicates that the anti-VEGF therapy is mainly effective during the first month. The FAZ, superficial vessel density and deep vessel density didn't change before and after treatment.

There are some limitations to this study. The number of patients enrolled was relatively small. The type of anti-VEGF therapy used was not identical for all the patients, the efficiency of Ranibizumab and Conbercept might be different. Thus, further studies may expand the number of samples and carry out control studies of Ranibizumab group and Conbercept group.

Conclusion

Anti-VEGF therapy is efficient for myopic CNV without affecting superficial vessel density and deep vessel density of retina but unable to eliminate CNV lesions completely in most cases, the the mean reduction ratio is 50.32%, the bigger myopic CNV lesions have lower reduction ratio. Further studies are needed to find new treatments to cure myopic CNV.

Abbreviations

OCTA: optical coherence tomography angiography; CNV: myopic choroidal neovascularization; VEGF: vascular endothelial growth factor; BCVA: best-corrected visual acuity; FAZ: foveal avascular zone; CMT: central macular thickness; RPE: retinal pigment epithelium; LogMAR: logarithm of the minimum angle of resolution; AMD: age-related macular degeneration; OCT: optical coherence tomography; FFA: fluorescein angiography; PRN: pro re nata;

Declarations

Ethics approval and consent to participate

This study followed the tenets of the Declaration of Helsinki and was approved by the ethical committee of Eye Hospital of Wenzhou Medical University. Informed consent was obtained from each patient before the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

JM and YS contributed to the conception and design of the study, data collection, analysis and interpretation of data, writing the article, final approval of the article. LC, ZC, CY, YZ, ZX contributed to data collection, analysis and interpretation of data, final approval of the article. LS contributed to the conception and design of the study and final approval of the article.

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Not applicable

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Table

Table 1 Data of the patients

	Baseline	1-month follow-up	2-month follow-up	3-month follow-up	6-month follow-up
Age	52.93±14.22 (22-77)				
Sex(F/M)	30/11				
Times of intravitreal injection	1.88±0.87				
Anti-VEGF(Ranibizumab/Conbercept)	22/19				
Superficial vessel density of retina (%)	42.24±5.90	43.43±6.11	42.08±5.85	41.12±6.28	41.08±5.72
Deep vessel density of retina (%)	46.63±5.53	46.24±5.88	46.31±4.77	46.55±5.47	46.16±5.85
FAZ (mm ²)	0.253±0.090	0.258±0.091	0.261±0.079	0.271±0.093	0.266±0.097

Figures

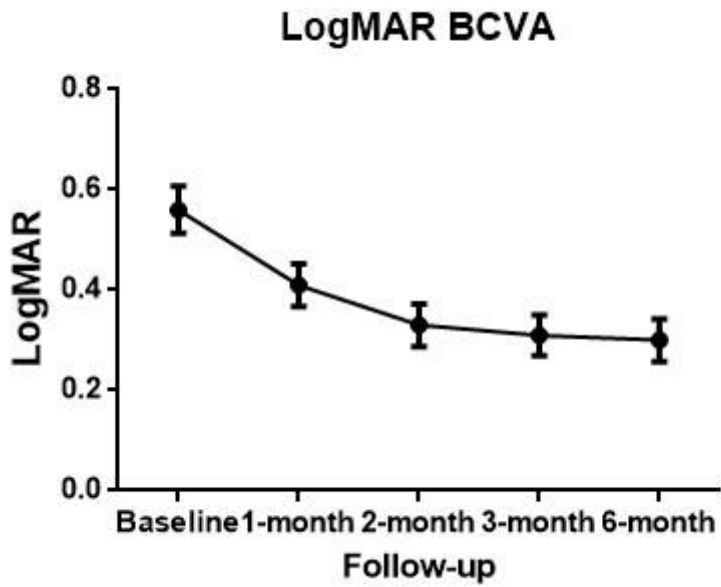


Figure 1

The tendency of LogMAR BCVA. The error bars represent the standard error of the mean value.

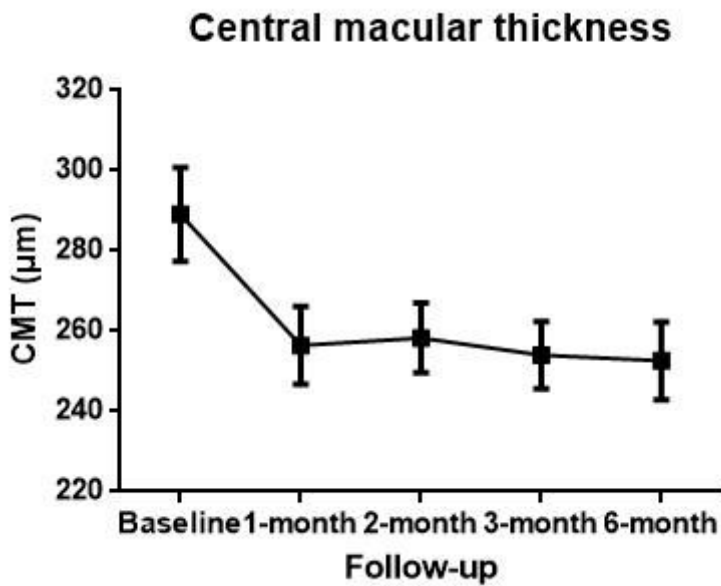


Figure 2

The tendency of CMT. The error bars represent the standard error of the mean value.

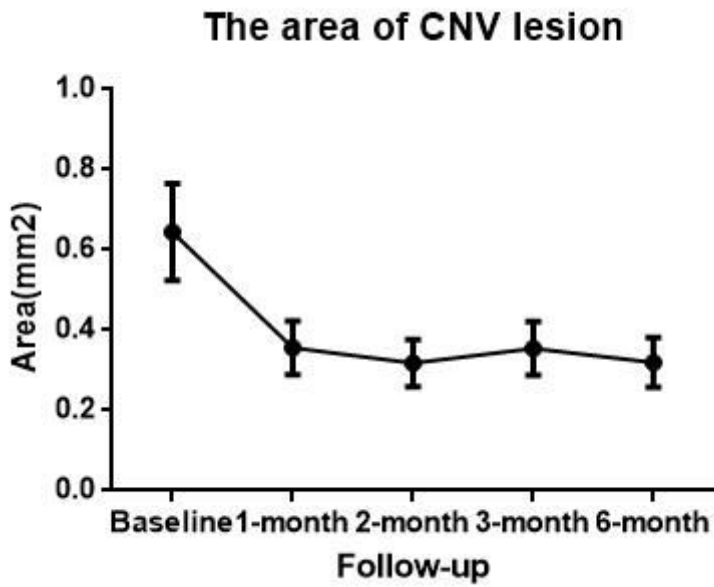


Figure 3

The tendency of the area of CNV lesion. The error bars represent the standard error of the mean value.

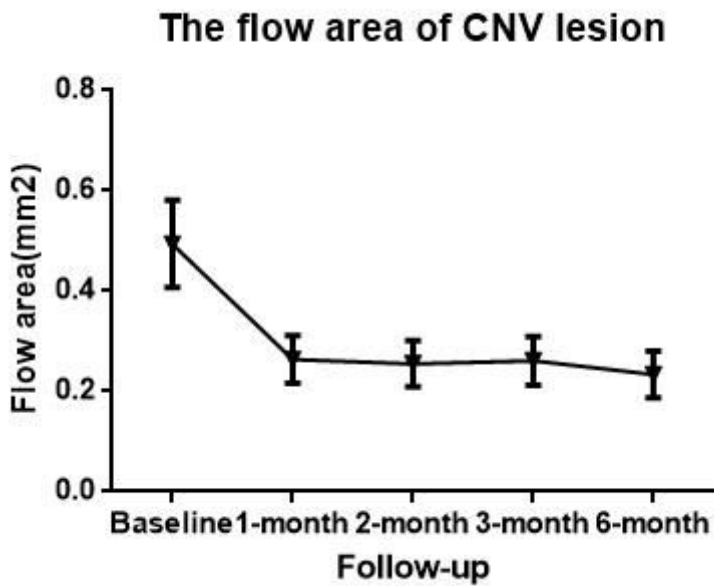
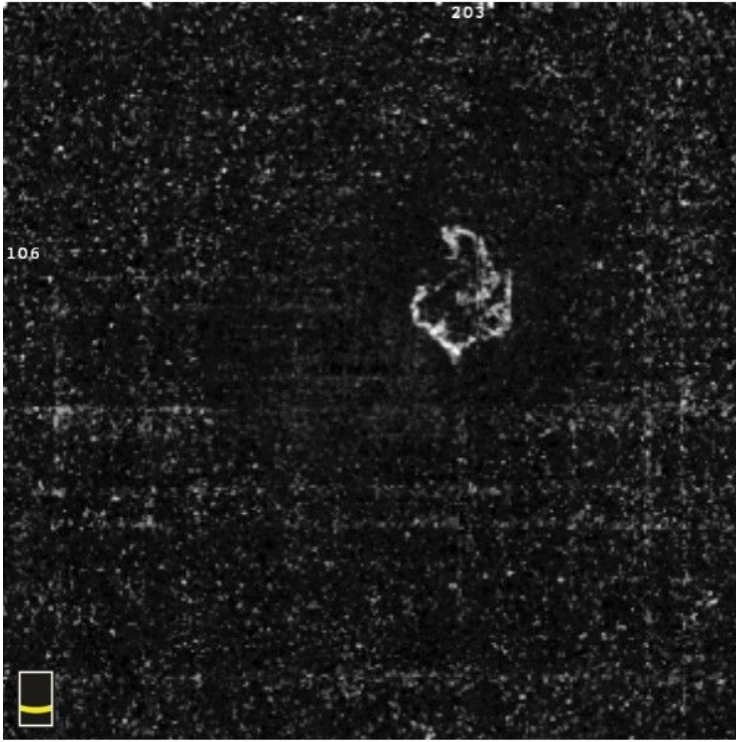


Figure 4

The tendency of the flow area of CNV lesion. The error bars represent the standard error of the mean value.

A



B

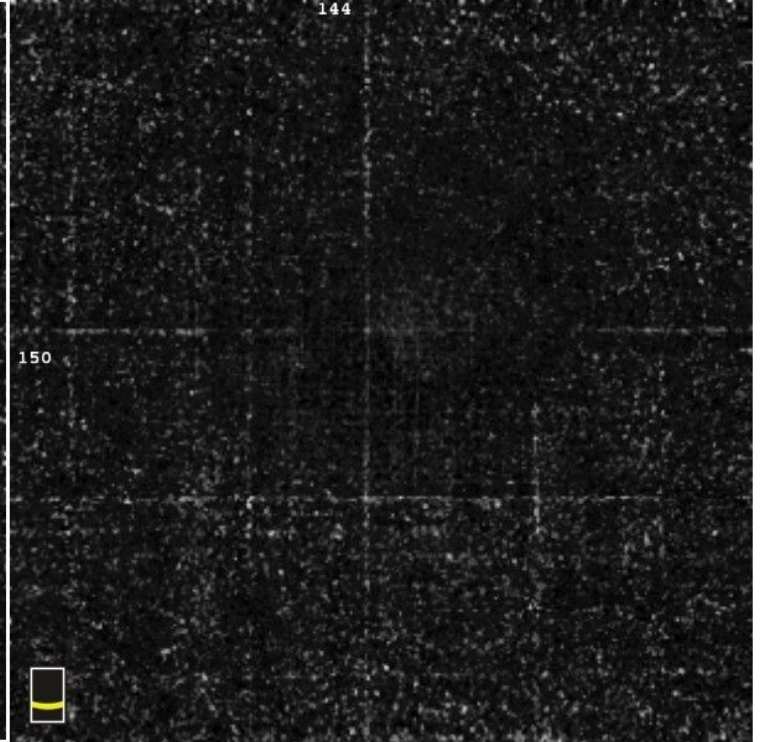


Figure 5

The CNV lesion at baseline (a) and at 1-month (b) follow-up of case 1.

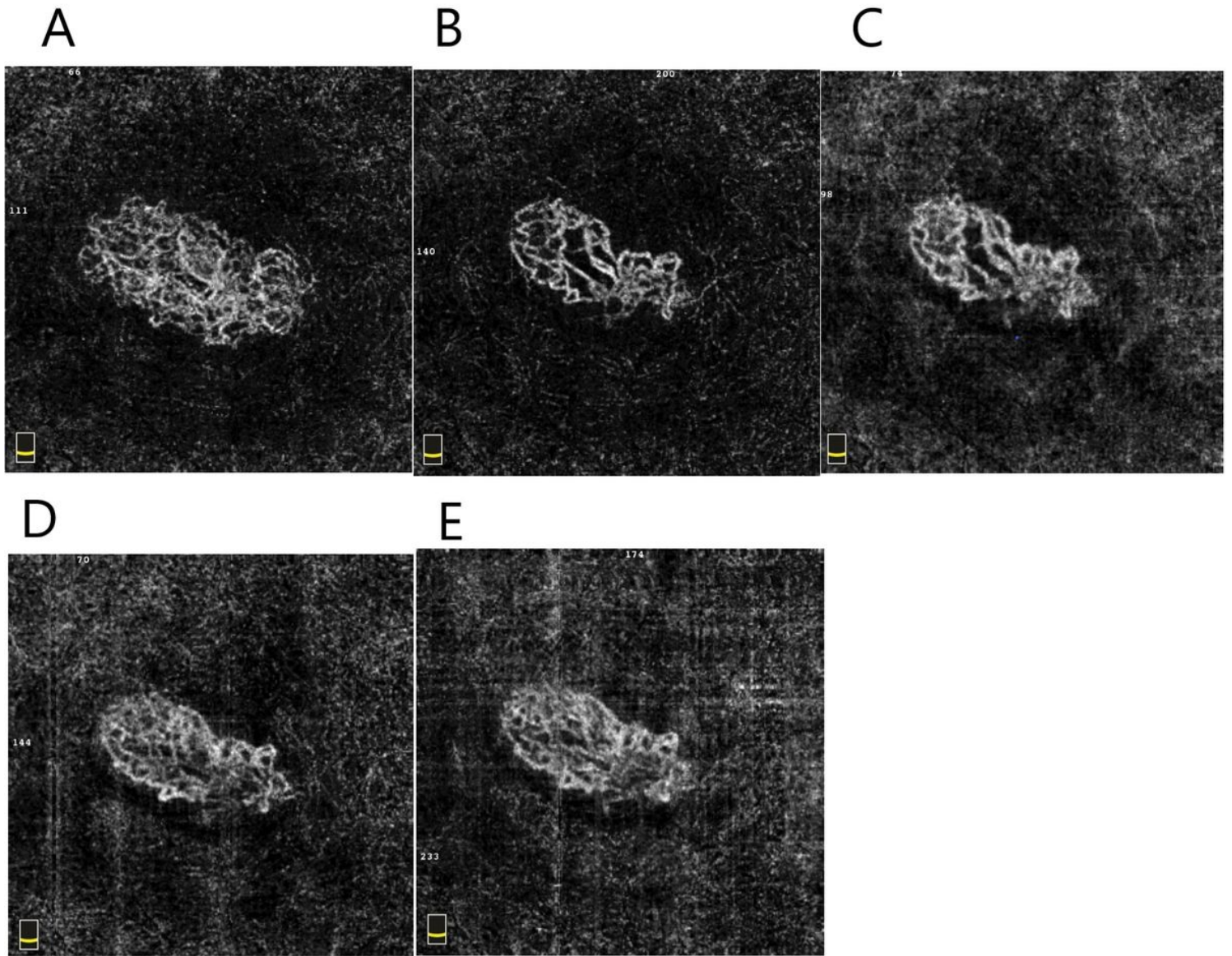


Figure 6

The CNV lesion at baseline (a) and at 1 (b), 2 (c), 3 (d) and 6 months (e) follow-up of case 2.