

CORRELATION BETWEEN FOCAL CHOROIDAL EXCAVATION AND UNDERLYING RETINOCHOROIDAL DISEASE

A Pathological Hypothesis From Clinical Observation

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Purpose: To evaluate focal choroidal excavation (FCE) in eyes with various diseases using multimodal imaging modalities and to investigate the correlation of FCE and underlying chorioretinal diseases.

Methods: This retrospective observational study included 62 eyes from 56 patients who were identified by optical coherence tomography as having FCE. All included patients underwent comprehensive clinical examinations and multimodal imaging to identify and detect the characteristics of FCE and its correlation with underlying chorioretinal diseases.

Results: All included patients were of Chinese descent, and the median age at diagnosis was 43 years (range: 15–66). Seventy-three FCEs appeared in these included eyes. Most FCEs were formed at sites with anatomical changes caused by various chorioretinal diseases. Choroidal osteoma, punctate inner choroidopathy, and central serous chorioretinopathy were the most common etiologies of FCE. During follow-up, 14 eyes (22.58%) exhibited a pattern change and three eyes (4.84%) developed new-onset choroid neovascularization.

Conclusion: Focal choroidal excavation is a common sign found in a variety of chorioretinal diseases. Processes that involve impairment or tissue loss of the outer retina and inner choroid and disrupt the balance of intraocular pressure and choroidal pressure because of mechanical disturbance may play a role in FCE formation.

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Focal choroidal excavation (FCE) was first described by Jampol et al based on optical coherence tomography (OCT) findings of choroidal excavation without evidence of posterior staphyloma. Margolis et al then divided FCE into conforming and nonconforming types according to whether a subretinal space between the photoreceptor tips and the retinal pigment epithelium (RPE) could be observed on OCT.^{1,4} However, this classification is mainly based on morphology, and the etiology and pathogenesis of FCE remain enigmatic. Some researchers consider FCE to be a congenital posterior segment malformation because, in some cases, FCEs are asymptomatic and unaccompanied by any pathology.^{1,2} Some patients are bilaterally

affected, which has also been regarded as evidence of the congenital origin of FCE. However, with the extensive application of OCT and OCT angiography, researchers have found that acquired forms of FCE may exist, as they have appeared with many clinical conditions ranging from pachychoroid spectrum diseases, white dot syndrome, and macular dystrophy. Park et al³ also reported that among 1,697 eyes from 858 children and young adults, only three eyes were identified with FCE. The low incidence of FCE in young patients suggests that FCE is most likely acquired during adulthood. Investigating the spectrum of diseases associated with FCE may deepen the understanding of FCE and provide improved guidance

for clinical interventions. To clarify the etiopathogenesis and prognosis of FCE, more cases with long-term follow-up are required.

In this study, to further investigate the pathophysiology of FCE, we reviewed patients who presented with FCE in a consecutive cohort. By analyzing the clinical features of FCE with underlying retinochoroidal disease and the sequential evolution of FCE, we aimed to investigate the correlation between FCE and underlying retinochoroidal disease. Furthermore, we explored the possible mechanism of FCE formation.

Methods

This retrospective observational study was conducted at Zhongshan Ophthalmic Center with the approval of the Institutional Review Board of the Zhongshan Ophthalmic Center at Sun Yat-sen University and followed the tenets of the Declaration of Helsinki. Patients with at least one areas of FCE were included and followed up between January 2015 and January 2020. Focal choroidal excavation is defined as excavation of the choroid into Bruch's membrane (BrM) focally as determined by spectral domain OCT (SD-OCT) without any evidence of posterior staphyloma.¹ Focal choroidal excavation usually appears as a concavity with an intact sensory retina and no sensory retinal thickening or loss of foveal architecture, which is different from the macular caldera or coloboma seen in some cases of retinal dystrophy with developmental tissue defects and atrophy at the macular area.

All included patients underwent comprehensive clinical examinations along with multimodal imaging, including best-corrected visual acuity (BCVA) analysis, slit-lamp examination, fundus color photography (Zeiss FF450 plus fundus camera; Carl Zeiss,

Inc, Jena, Germany or a Topcon 50 VT fundus camera; Topcon Corp, Tokyo, Japan), fundus fluorescein angiography, indocyanine green angiography (ICGA) (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), OCT angiography (AngioVue, RTVue XR Avanti; Optovue, Fremont, CA, V.2015.1.0.90), and spectral domain OCT (SPECTRALIS SD-OCT; Heidelberg Engineering). The diagnosis of concurrent retinal pathologies was made by a retinal specialist (F.W.) on the basis of clinical examinations and multimodal imaging. Enhanced-depth imaging optical coherence tomography was performed by a well-trained technician (N.L.); the protocol consisted of a line scan across every lesion center with 100 averaged B scans per image and a dense volume scan encompassing an area with 40 averaged B scans per image. The measurements of subfoveal choroidal thickness (from the outer border of the RPE-BrM complex to the inner sclera) were analyzed using the horizontal line scan that passed through the fovea. Two investigators (Y.G. and Y.S.) manually measured the choroidal thickness and greatest linear dimension (GLD) of the FCE with a built-in tool in Spectralis. The average value of the two investigators' measurements was recorded.

Statistical analyses were performed using SPSS (version 16.0; SPSS, Inc, Chicago, IL). Descriptive statistics are reported as the mean \pm SD. Patient-related observations were compared using the independent *t*-test, Kruskal–Wallis test, the chi-square test, or Fisher's exact test as appropriate. A *P* value < 0.05 was considered statistically significant.

Results

Characteristics of the Included Patients

Seventy-three FCEs were detected by OCT in 62 eyes from 56 patients. Table 1 shows the demographic and clinical characteristics of the included patients. All patients were of Chinese descent, and the median age at diagnosis was 43 years (range, 15–66 years). The youngest patient with FCE was diagnosed with best vitelliform macular dystrophy. There were 26 men and 30 women, and there was no sex predilection. Six eyes from six patients with FCE had no symptoms, whereas the rest presented with complaints of metamorphopsia, blurred vision, or scotoma. Twenty-eight eyes (45.16%) from 28 subjects were myopic, and the mean spherical equivalent was -2.13 diopter (range, -11.5 to 2.5) diopters. Multiple excavations were identified in eight eyes (12.9%), whereas most eyes (87.1%) presented with a single FCE.

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Table 1. Demographic and Clinical Characteristics of Patients With FCE

Characteristic	
Age, years, median (range)	43 (15 to 66)
Gender, male, number of patients (%)	26 (46.43)
FCE appeared in bilateral eyes, number of patients (%)	6 (10.71)
Asymptomatic, number of eyes (%)	6 (9.68)
Baseline BCVA of the FCE-involved eyes, median (range)	20/40 (20/200-20/20)
BCVA of the FCE-involved eyes on the last follow-up, median (range)	20/25 (20/200-20/20)
Presence with CNV at baseline, number of eyes (%)	37 (59.68)
Refractive error of eyes with FCE, diopter, mean (range)	-2.13 (-11.5 to 2.5)
Myopia eyes, number of eyes (%)	28 (45.16)
Eyes with multiple FCEs, n (%)	8 (12.9)
FCE morphology at baseline	
Conforming, number of FCEs (%)	38 (52.05)
Nonconforming, number of FCEs (%)	35 (47.95)
SFCT of FCE-involved eyes, μm , mean \pm SD	285.45 \pm 131.23

BCVA, best-corrected visual acuity; CNV, choroidal neovascular membrane; SFCT, subfoveal choroidal thickness.

Correlation Between Focal Choroidal Excavation and Underlying Retinochoroidal Disease

A total of 73 FCEs were identified in the included patients. Of all the included eyes with FCE, 57 eyes (91.9%) had other retinochoroidal diseases, whereas 5 eyes (8.1%) had FCE without evidence of any other chorioretinal disease. Among the eyes with FCE, 14 (22.58%) had choroidal osteoma (CO), 12 (19.35%) had punctate inner choroidopathy (PIC), 10 (16.13%) had central serous chorioretinopathy (CSC), 8 (12.90%) had age-related macular degeneration (AMD) (among which 5 eyes were diagnosed with polypoidal choroidal vasculopathy), 7 (11.29%) had idiopathic choroidal neovascularization, 3 (4.84%) had multiple evanescent white dot syndrome (MEWDS), 2 (3.23%) had bestrophinopathy (one eye from one subject was diagnosed with adult-onset foveomacular vitelliform dystrophy, and one eye from one subject was diagnosed with best vitelliform macular dystrophy), and one had angioid streaks. Five eyes with FCEs from four patients had no history of ocular disease and no apparent etiology for the FCEs according to the findings of the ophthalmological examinations. Most FCEs showed close etiological and topographic relationships with concurrent retinal lesions. Forty FCEs (54.79%) appeared within the lesions of the underlying disease, 21 FCEs (28.77%) were located at the edges of the lesions, and 12 FCEs (16.44%) were separate. As shown in Table 2, the clinical and morphological features of FCEs with underlying retinochoroidal disease were analyzed.

Choroidal osteoma is the most common disease in eyes with FCEs. All FCEs in CO were located at the edge of the osteoma (Figure 1M). These FCEs were quite wide, with a mean dimension GLD of 2,409.28 \pm 1,432.80 μm (significantly larger than FCEs in

PIC and CSC, with $P < 0.05$). Punctate inner choroidopathy is the second common etiology of FCEs. All FCEs due to PIC were classified as conforming. Because PIC has a predilection for young, myopic women, the PIC patients with FCEs were, on average, significantly younger than the CSC patients with FCEs ($P = 0.031$). Punctate inner choroidopathy patients also had a higher degree of myopia than FCE patients with other retinochoroidal diseases ($P < 0.05$). Ten eyes with FCEs from seven subjects were diagnosed with CSC (2 patients with acute CSC and five patients with chronic CSC). Patients with CSC were more likely to exhibit FCEs in both eyes than patients with other retinochoroidal diseases. The subfoveal choroidal thickness of eyes with CSC was found to be thicker than that of eyes with PIC ($P = 0.02$) or idiopathic choroidal neovascularization ($P = 0.023$). Age-related macular degeneration (including polypoidal choroidal vasculopathy) was identified in eight patients with FCEs; among these patients, seven FCEs coincided with the CNV sites, and four FCEs were located at the edges of the CNV sites or branching vascular networks. Five eyes with FCEs from four patients had no other signs of fundus disease after a comprehensive ophthalmic fundus examinations including slit-lamp examination, fundus photograph, SD-OCT, OCT angiography, autofluorescence, fluorescein fundus angiography, and ICGA (Figure 1, J-L). These cases of FCE were asymptomatic and had been accidentally identified during regular medical examinations. To investigate the relationship of FCEs and pachychoroid spectrum diseases, we found 21 eyes (33.88%) had choroidal hyperpermeability (CVH) in the mid phase of ICGA, as shown in Figure 1H. The CVH in ICGA mainly appeared in the eyes with CSC and AMD.

Table 2. Clinical and Morphological Features of FCE With Diverse Etiologies

Etiology	CO	PIC	CSC	AMD	ICNV	Unknown	MEWDS	VMD	AS
Eyes, n (%)	14 (22.58)	12 (19.35)	10 (16.13)	8 (12.90)	7 (11.29)	5 (8.10)	3 (4.84)	2 (3.23)	1 (1.61)
Age, years, mean ± SD	36.3 ± 13.0	31 ± 4.88	45 ± 12.77	57.8 ± 5.0	31.6 ± 5.59	36.8 ± 14.97	37 ± 12.51	34 ± 26.87	53
Refractive error of eyes with FCE, diopter, median (range)	0 (−4 to +2.5)	−6.375 (−11.5 to 0)	0 (−3.75 to 0)	(−10 to 2.5)	−5.25 (−6 to 0)	−1.5 (−6 to 0)	0 (−6 to 0)	−0.75 (−1.5 to 0)	−4
Baseline BCVA of the FCE-involved eyes, median (range)	20/50 (20/200-20/25)	20/40 (20/200-20/25)	20/32.5 (20/200-20/20)	20/62.5 (20/200-20/20)	20/40 (20/200-20/32)	20/20 (20/20-20/20)	20/25 (20/40-20/20)	20/40 (20/40)	20/32
Presence with CNV at baseline, n (%)	9 (64.29)	9 (75)	2 (20)	8 (100)	7 (100)	0 (0)	0 (0)	1 (50)	1 (100)
Eyes with multiple FCEs, n	2	0	1	2	2	1	0	0	0
Location of FCEs, n									
In the area of the lesions	0	10	10	7	7	0	3	2	1
At the edge of the lesions	17	0	0	4	0	0	0	0	0
Isolated	0	2	1	0	3	6	0	0	0
FCE morphology at baseline, conforming/nonconforming	1/16	12/0	9/2	5/6	1/9	6/0	3/0	0/2	1/0
GLD of FCE, μm, mean ± SD	2,409.28 ± 1,432.80	866.72 ± 808.27	1,141.75 ± 995.83	510.5 ± 910.58	1,578.83 ± 1869.72	419.6 ± 187.95	909 ± 670.36	1,208 ± 1,410.0	1,303
Choroidal thickness of FCE-involved eyes, μm, mean ± SD	295.57 ± 171.32	197.90 ± 68.24	399.50 ± 133.98	298.38 ± 138.27	231.67 ± 90.18	288.90 ± 140.42	324 ± 53.0	331.5 ± 113.84	290
Eyes with CVH on mild phase of ICGA (Y/N)	2/12	3/9	10/0	4/4	0/7	2/3	0/3	0/2	0/1

AMD, age-related macular degeneration; AS, angioid streaks; BCVA, best-corrected visual acuity; CNV, choroidal neovascular membrane; CO, choroidal osteoma; CSC, central serous chorioretinopathy; CVH, choroidal vascular hyperpermeability; GLD, greatest linear dimension; ICNV, idiopathic choroidal neovascularization; n, number; PIC, punctate inner choroidopathy; VMD, vitelliform macular dystrophy.

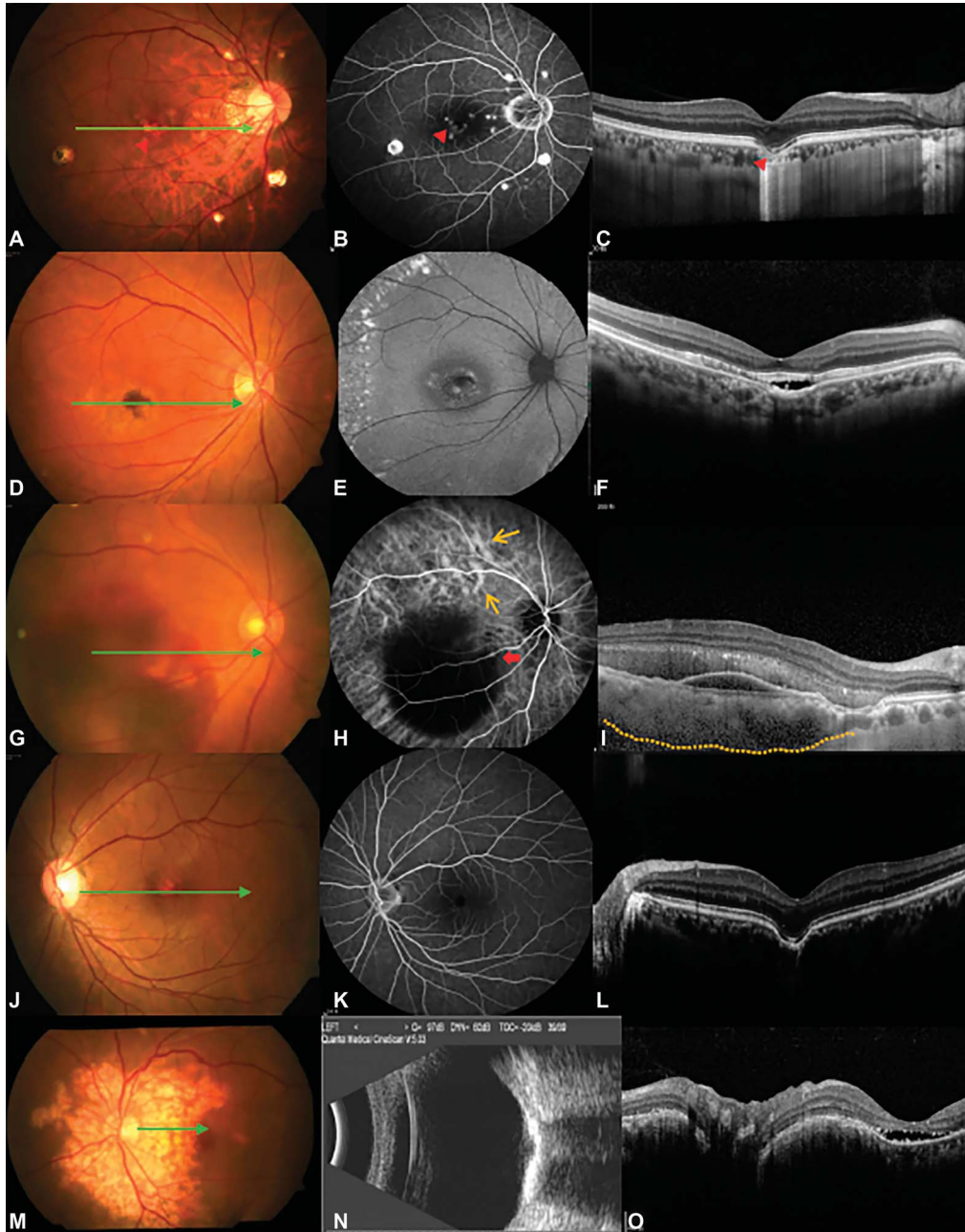


Fig. 1. Focal choroidal excavation with diverse retinochoroidal diseases. **A–C.** Focal choroidal excavation (red arrowhead) in the eye affected with PIC. **A.** Multifocal whitish-yellow lesions present in the posterior pole. **B.** In the late phase of fluorescein fundus angiography, multifocal lesions show hyperfluorescence, and FCE appears as transmitted fluorescence. **D–F.** Focal choroidal excavation in the eye affected by autosomal recessive bistrophinopathy. **D.** Fundus photography shows multifocal vitelliform material (VM) in the posterior pole and pigment proliferation in the macular area. **E.** Fundus autofluorescence shows markedly increased AF corresponding to the VM. **F.** Spectral domain optical coherence tomography shows subretinal fluid and elongation of the photoreceptor outer segments and FCE at the macula. **G–I.** Focal choroidal excavation in an eye affected with polypoidal choroidal vasculopathy. **G.** Fundus photography shows subretinal hemorrhage and detachment of the retinal pigment epithelium, with a reddish-orange subretinal nodule. **H.** ICGA shows hyperfluorescent polyps (red arrow) and dilation of pachyvessels with hyperpermeability (yellow arrow). **I.** Spectral domain optical coherence tomography shows an FCE adjacent to a large pigment epithelial detachment. Note the thickening of the choroid and the dilation of pachyvessels under the lesion. **J–L.** Focal choroidal excavation in the eye without any systemic or ocular conditions. **J.** Fundus photography shows an area of pigmentary mottling corresponding to the site of FCE. **K.** No apparent abnormality is noticed in fluorescein fundus angiography. **M–O.** Focal choroidal excavation in the eye with CO. **M.** Fundus photograph shows a focal orange–yellow tumor with depigmentation. **N.** Ultrasonography confirms CO with high acoustic reflectivity and corresponding after-shadow. **O.** Spectral domain optical coherence tomography shows a FCE adjacent to CO.

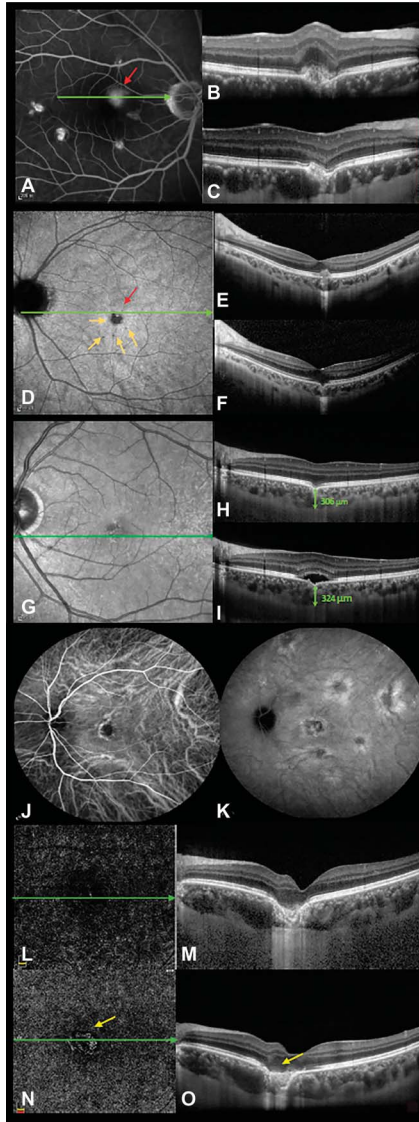


Fig. 2. The cases of FCEs with serial and tracked spectral domain optical coherence tomography. **A–C.** Focal choroidal excavation developed at the site of CNV. **A.** Late phase of fluorescein fundus angiography shows classic CNV leakage. **B.** Corresponding OCT shows active intraretinal fluid and hyperreflectivity suggestive of active CNV. **C.** Follow-up OCT at the same site shows the regression of CNV after anti-VEGF and the development of FCE. **D–F.** Focal choroidal excavation developed at the site of inflammatory lesion of an eye affected with PIC. **D.** Late phase of ICGA shows multiple hypofluorescence lesions (red arrow and yellow arrows) in the macular area. **E.** Corresponding OCT shows hyperreflectivity material over RPE (red arrow) suggestive of the active inflammatory lesion. **F.** Follow-up OCT in 2 months at the same site shows spontaneous regression of the PIC lesion and the development of FCE. **G–I.** Morphologic change of FCE in the eye affected with CSC and underwent several episodes of recurrence. A conforming FCE (**H**) spontaneously transfer into an unconforming FCE (**I**) with the slightly increase of subfoveal choroidal thickness. **J–O.** CNV developed at the site of FCE in the eye with chronic CSC. **J** and **K.** Multifocal dilated choroidal vessels and areas of choroidal vascular hyperpermeability appeared at early to middle phase of ICGA. Notice that no network of neovascularization shown at the baseline ICGA. **L.** Corresponding enface optical coherence tomography angiography shown no signal of neovascularization at baseline. **M.** Corresponding OCT shows a FCE at the macular fovea. Three months later, a CNV developed at the site of FCE as it is shown in optical coherence tomography angiography (**N**—yellow arrow) and OCT (**O**—yellow arrow).

Sequential Evolution of Focal Choroidal Excavation

To evaluate the prognosis of FCE, all patients were followed up for at least 3 months, with a mean follow-up duration of 11.5 months (range: 3–47 months). At baseline, 37 (59.68%) patients had CNV, and 33 eyes from those 37 patients received anti-vascular endothelial growth factor (VEGF) therapy (range: 1–5 injections). Among these patients with CNV, four eyes (12.12%) (2 eyes with PIC and two eyes with idiopathic CNV) experienced recurrence in the follow-up period. Among the eyes with FCE, three eyes (4.84%) developed CNV (one eye with CSC, one eye with MEWDS, and one eye with PIC). After anti-VEGF treatment, the visual acuity improved in most eyes with active CNV. The median BCVA of affected eyes at the last visit was 20/25 (range: 20/200–20/20), which was significantly better than the BCVA at baseline ($P = 0.007$).

To investigate the formation of FCEs, we reviewed the historical imaging data of all patients with FCEs. There were 54 eyes (87.1%) with FCEs at the first visit. Eight eyes (12.9%) developed FCEs during the follow-up period, and sequential formation of FCEs was recorded. Four eyes formed FCEs after the development of CNV and the administration of anti-VEGF therapy (Figure 2). Four eyes developed FCEs at the sites of PIC lesions (Figure 2). Among those eyes, three received immunosuppressive therapy, whereas one lesion spontaneously regressed and generated an FCE.

Most cases of FCE remained stable. At the initial baseline visit, the GLD of FCEs was $1,463.14 \pm 1,310.31 \mu\text{m}$. At the last visit, the GLD of FCEs was $1,452.18 \pm 1,336.68 \mu\text{m}$, and there was no significant difference between the values from the first and last visits ($P = 0.901$). As shown in Figure 2, morphological changes in FCEs caused by clinical intervention or progression of the underlying disease were common during the follow-up period. 14 eyes (22.58%) exhibited pattern changes. Ten nonconforming FCEs changed to the conforming type after treatment with anti-VEGF therapy. Two eyes (both affected by CSC) spontaneously transformed from nonconforming to conforming without any intervention. Two eyes (one eye with CSC and one eye with CO) with conforming FCE transformed to nonconforming FCE.

Discussion

As multimodal imaging techniques continue to advance, the essential qualities of fundus disease are being recognized, and knowledge is being further

refined. Because FCE was first described in 2006,⁴ clinicians have found, with the assistance of OCT, that FCE is not rare and is associated with many diseases. When initially reported, FCE was believed to be congenital, with no other concomitant pathology and little change during follow-up.^{1,4} However, FCE should be differentiated from macular caldera or coloboma, which is found in several macular dystrophies. Macular caldera or coloboma can occur in patients with North Carolina macular dystrophy, Stargardt disease, cone dystrophy, congenital ocular toxoplasmosis, etc., which are considered congenital posterior segment malformations. Eyes with FCE usually have normal foveal contours with a continuous BrM. In contrast to FCE, macular calderas or colobomas manifest as cavities within the outer choroid with an overlying retinal pigment epithelium, and retinal layers are absent or discontinuous. Therefore, based on the current research, with a restricted definition of FCE, we are inclined to believe that most FCEs are acquired because they usually form at sites with anatomical changes caused by other chorioretinal diseases. According to our study, 54.79% FCEs appeared within the lesions of the underlying disease and 28.77% were located at the edges of the lesions. The low prevalence of FCE among young patients also supports this view.³ Moreover, most FCEs usually appear in the eyes with underlying chorioretinal diseases, and only small part of FCEs appear in the eyes without any diseases. In our study, we identified 62 eyes with FCE, among which 14 (22.58%) had CO, 12 (19.35%) had PIC, 10 (16.13%) had CSC, 8 (12.90%) had AMD, 7 (11.29%) had idiopathic choroidal neovascularization, 3 (4.84%) had MEWDS, 2 (3.23%) had bestrophinopathy, and 1 had angioid streaks. Only 5 eyes (8.1%) presented with FCE without associated evidence of any other chorioretinal disease. These eyes were diagnosed on the basis of comprehensive fundus examinations. These five eyes (8.01%) from four patients exhibited FCEs and were incidentally discovered during conventional check-ups. These patients were young (with a mean age of 36.8 ± 14.97 years) and had no history of ocular disease. They all had good visual acuity (with median BCVA: 20/20). In addition, three of these patients (75%) were myopic, which was consistent with previous studies.^{1,4} However, because of the retrospective nature and limited sample size of this study, it was difficult to determine whether FCE was congenital or acquired under certain conditions among those eyes.

In our study, the clinical features and morphology of FCEs in association with different diseases were investigated. Choroidal osteoma is the most common etiology of FCE, and several cases of CO associated with FCE have been reported by other studies. Olguin-Manríquez

et al⁵ reported that 12.5% of CO cases resulted in FCE, and 18.75% of eyes showed choroidal depression associated with decalcification. In our study, most FCEs (16/17) coincided with the decalcification of CO. Progressive enlargement and decalcification seem to play an important role in the formation of FCEs in CO. In the **Supplemental Digital Content 1** (see **Figure**, <http://links.lww.com/IAE/B531>), we show the eyes of our patients with bilateral CO. The left eye with decalcified CO developed FCE, whereas the right eye with smaller calcified CO did not develop FCE. However, in our study, all FCEs cooccurring with CO were already present at the beginning of the study, and we did not record the FCE formation process in CO. Case reports by Basavaraj⁶ and Olguin-Manríquez⁵ documented sequential imaging of CO cases in which FCE developed, and the researchers concluded that decalcification of CO might result a pathogenic process with FCE formation, which corresponds to our view. Compared with other choroid masses, CO imposes a strong retraction force on the retina during the process of decalcification. The decalcification of CO results in impairment of the RPE and loss of the overlying choriocapillaris (CC), whereas the retina overlying the ossified CO is generally preserved. Therefore, FCE is a common complication of CO that may indicate the decalcification of the mass. Inflammation involving the outer retina and inner choroid (such as white dot syndrome) is also a common cause of FCEs. As reported by Hyesun Kim et al,⁷ 20% of eyes had FCE among patients with PIC or multifocal choroiditis, a much higher rate than observed in other diseases. Some researchers demonstrated a similar process of FCE formation in PIC, multifocal choroiditis, Vogt-Koyanagi-Harada syndrome, and MEWDS.⁸ In our study, we documented four eyes in which FCE formed at the sites of inflammatory lesions. Previous studies have hypothesized that inflammatory infiltrate weakens the RPE-BrM-CC complex, and when inflammation resolves, the decrease in choroidal exudation and subretinal fibrin exert direct pressure on the choroidal layer. Changes in choroidal thickness and blood flow seem to be another potential pathology for the development of FCE. During the recovery phase of PIC and CNV secondary to PIC, the choroid displayed the “sponge sign”: The choroidal thickness beneath inflammatory lesions significantly increased at the acute phase and decreased after therapy.⁹ Similarly, in pachychoroid disease, the change in choroidal thickness may also favor the development of FCEs. Choroidal vascular hyperpermeability and dilation of choroidal vessels have been reported to be associated with FCEs. In our study, 21 eyes (33.88%) showed CVH at the middle stage of ICGA. Eyes with CSC and AMD showed higher rate of appearance of CVH, and two eyes without other fundus disease or a history of

pachychoroid disease also showed CVH at the middle stage of ICGA. The pathological changes within the choroid in pachychoroid disease that facilitate the development of FCE might be explained by the speculation that atrophy of capillaries and impairment of the RPE could lead to a weakening of architectural support, causing the development of FCE. Choroidal vascular hyperpermeability and increased venous capillary pressure produce increased extravasation of proinflammatory and prothrombotic proteins and mediators into the choroidal stroma, including fibrinogen (fibrin) and metalloproteinase-2, which leads to focal tissue degeneration or atrophy in the choroidal stroma.¹⁰

The visual prognosis of FCEs was primarily determined by the underlying retinochoroidal disease and whether CNV developed. According to our study, FCE was associated with worse BCVA when it cooccurred with CO or AMD ($P < 0.05$). Although CNV may occur in eyes with FCEs, only some instances developed at FCE sites in our study. We found that at baseline, 16 FCEs (21.92%) appeared at CNV sites, and during the follow-up period, 3 (4.84%) eyes developed CNV secondary to FCE (one eye with CSC, one eye with MEWDS and one eye with PIC). The relationship between FCE and choroidal neovascular membranes is also elusive. It remains controversial whether FCE is a cause or effect of CNV.^{11,12} On the one hand, FCEs seem prone to develop at CNV sites. The development and fibrosis of the CNV impair the RPE-BrM complex and retract the inner choroidal structure, favoring FCE formation (as it shown in Figure 2, A–C). On the other hand, some researchers have suggested that the anatomical changes that occur in FCE may lead to the development of CNV. Lee et al¹² reported 16 eyes with CNV and FCE, among which all CNV either lay within the boundary or extended over the margin of FCE. Rajabia et al¹³ analyzed the retinal and choroidal vascular changes and choroidal stroma variations occurring in FCE; they found that deep capillary plexus and CC plexus rarefaction along with a decrease in perfusion in the region surrounding the FCE may potentially trigger CNV development.

Based on the results of our study and previous assumptions, we hypothesize that a common process might play a role in the development of FCE in diverse retinochoroidal diseases. As shown in Figure 3, two conditions that facilitate the development of FCE have been mentioned in other studies: 1) impairment or tissue loss of the outer retina and inner choroid resulting from inflammation, retinal degeneration, or pachychoroid disease (the weakening of the RPE-BrM complex would make them easily conform under the stress exerted); and 2) disruption of the balance of intraocular pressure and choroidal pressure because of a mechanical disturbance, which draws the overlying retinal tissues backward dur-

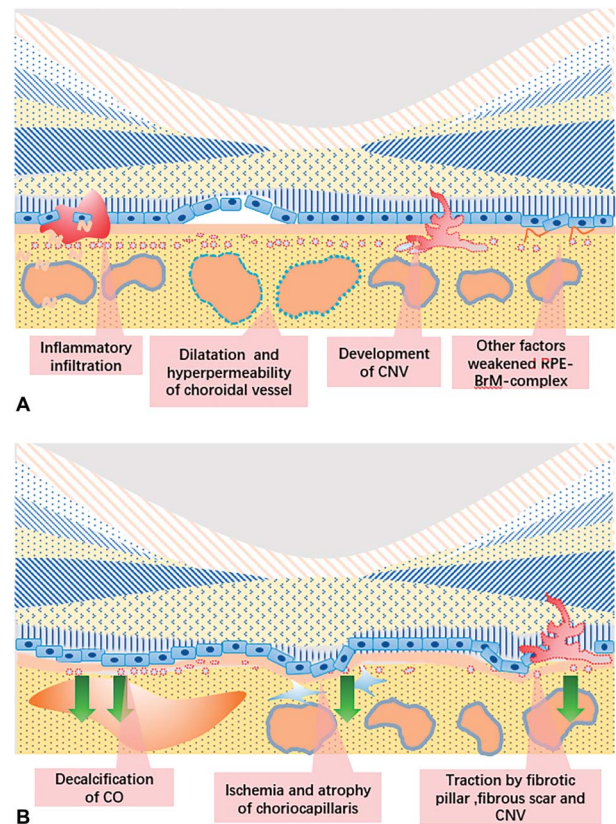


Fig. 3. Proposed mechanism for the formation of FCE. **A.** The weakening of the RPE-BrM complex by various factors (e.g., inflammatory infiltration, development of CNV, congestive pachyvessels, and atrophy of the CC) causes them to conform easily when subjected to stress. **B.** The balance of intraocular pressure and choroidal pressure is broken because of a mechanical disturbance, which draws the overlying retinal tissues backward during fibrosis accompanying CNV, inflammation, decalcification of CO, or atrophy of the CC.

ing the fibrosis that develops from CNV, or due to inflammation, CO decalcification, etc. Under the circumstances, Focal choroidal excavation should be regarded as a sign rather than a disease entity. In patients with FCE, further careful examinations are needed for FCEs correlated with various retinochoroidal diseases, as these lesions may require targeted therapy.

Our study has several limitations. First, we included only Chinese patients. Although FCE occurs mostly in Asia (approximately 90%), there might be selection bias based on race. Second, although our work represents the largest study examining subjects with FCE to date, a larger sample size is needed to cover various etiologies and clarify the etiopathology of FCE. Third, because of the retrospective nature of the study, only a small portion of our cases recorded the process of FCE formation. Therefore, longitudinal follow-up is still needed. The hypothesis regarding the development of FCE was based mainly on clinical findings for lack of experimental data. Animal models and clinicopathological studies are required in further studies.

In conclusion, we intensively investigated FCE and its correlation with underlying diseases. By reviewing eyes with FCE, we found that FCEs can cooccur with diverse chorioretinal diseases and that there might be common mechanisms underlying FCE formation. We have observed a considerable prevalence of FCE in our clinical work on the development of OCT; this phenomenon could be a sign of underlying retinochoroidal disease, and proper therapy is needed after comprehensive examinations.

Key words: focal choroidal excavation, multimodal imaging, optical coherence tomography, pathological hypothesis.

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