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Case report

Using optical coherence tomography angiography to guide the treatment of pathological myopic patients with submacular hemorrhage

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ABSTRACT

The present study aimed to investigate whether optical coherence tomography angiography (OCTA) could be used to guide the treatment of pathological myopic patients with submacular hemorrhage. Two pathological myopia patients with submacular hemorrhage were examined. Initially, choroidal neovascularization (CNV) was not observed during fundus angiography in both patients. However, based on OCTA, the first patient was diagnosed with myopic lacquer crack-related macular hemorrhage, and the second with CNV secondary to punctate inner choroidopathy. The first patient was treated with traditional Chinese medicine administered orally, and the second with intravitreal injections of anti-vascular endothelial growth factor (VEGF). Lesions in both patients were resolved. Submacular hemorrhage in pathological myopia patients could be caused by numerous mechanisms. OCTA is useful in differentiating inflammatory CNV from inflammatory lesions, particularly if CNV is not detected using other multimodal imaging techniques.

Myopic maculopathy, including lacquer cracks, patchy and diffuse chorioretinal atrophy, posterior staphyloma, myopic subretinal hemorrhage, and myopic choroidal neovascularization (CNV), is regarded as a significant cause of visual impairment in Asian countries [1]. For example, myopic CNV is a common vision-threatening complication associated with high myopia, developing between the neurosensory retina and the retinal pigment epithelium (RPE) [2]. As CNV is most common in high myopia among patients younger than 50 years [3], it is difficult to diagnose based on fundus examination alone because of associated myopic maculopathies.

Subretinal hemorrhage is common in myopic CNV, but it is also observed frequently for new-onset lacquer cracks [4]. Punctate inner choroidopathy (PIC) is a common kind of posterior uveitis in young myopic patients, and CNV could be present in up to 75% of all PIC cases [5]. In China, it is estimated that 63% of the patients with PIC develop CNV [6]. PIC-related CNV could also lead to subretinal hemorrhage in myopic eyes.

PIC is an idiopathic inflammatory disorder of the inner choroid [7,8]. The key characteristic of PIC in its early stages include small, creamy, yellowy-white lesions, without concomitant intraocular inflammation, located at the fundus of the eye [9]. Isolated inflammatory lesions usually occur in the outer retina, RPE, as well as choriocapillaris [10]. Therefore, it can be difficult to distinguish CNV from isolated punctate inflammatory lesions.

Both indocyanine green angiography (ICGA) and fluorescein angiography (FA) are considered as gold diagnostic standards for CNV. For myopic CNV, FA is an important diagnostic approach [11]. A recent report demonstrated that myopic CNV usually shows well-defined hyper-fluorescence and dye leakage in the early and late FA phases, respectively [12]. However, recent lacquer cracks could also result in fluorescein leakage [1]. Klein and Curtin proposed that fluorescein could leak from the choriocapillaris, as lacquer cracks are present in the RPE-Bruch's membrane-choriocapillaris (RPE-BM−CC) complex [13].

Optical coherence tomography angiography (OCTA) is a new non-invasive technique that acquires volumetric angiographic information without any dye injection [14]. The ability to recognize CNV without the need of fluorescein is a major advantage of OCTA over FA. Fluorescein is commonly associated with nausea, and it could cause severe complications including anaphylaxis and death in rare situations [15]. It was reported that OCTA could accurately display myopic CNV as a high-flow neovascular network with a 90% sensitivity [16]. In addition, CNV secondary to PIC could be classified as having "lacy wheel", "pruned large-trunk" or "dead tree aspect" vessel shapes, with or without areas of non-perfusion using OCTA [17]. Although FA could reveal the presence of dyes and identify potential leakage, it could not provide distinct evidence of PIC-related CNV. OCTA could detect

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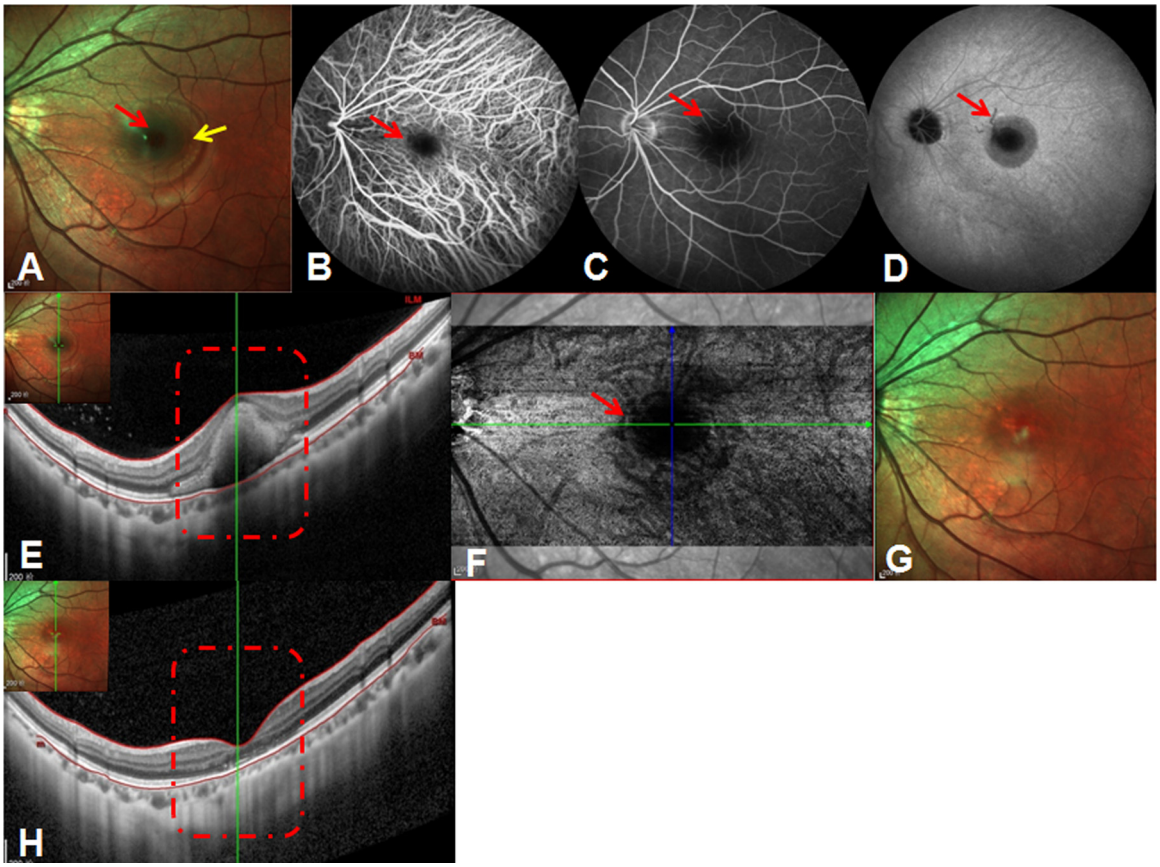

Fig. 1. Multimodal imaging of case 1. A. Multi-color image showing submacular hemorrhage (red arrow) surrounded by a slight serous macular detachment (yellow arrow) in the left eye. B. ICGA showing central macular blockage fluorescence (red arrow) in the middle phase. C. FA demonstrating central macular blockage fluorescence (red arrow) in the late phase. D. ICGA showing complete central fluorescence blockage, surrounded by a hypo-fluorescence wreath, and slit-like hypo-fluorescence band (red arrow), representing a myopic lacquer crack lesion. E. EDI − OCT showing subfoveal hyper- and hypo-reflection (red dotted box), with inset demonstrating the orientation of the EDI − OCT profile. F. OCTA did not detect a CNV signal in the foveal region. G. Multi-color image showing the disappearance of the submacular hemorrhage after treatment. H. EDI − OCT demonstrating that the submacular materials were absorbed and the elevated fovea was relieved. Inset indicating the orientation of EDI − OCT scanning.

abnormal flow in the outer retina, and reduced flow following intravitreal anti-vascular endothelial growth factor (VEGF) therapy. Furthermore, remodeling of the choroidal capillaries could be found in OCTA after the treatment [18]. While it may be helpful in detecting CNV lesions, OCTA alone is unable to differentiate active from inactive lesions, without being used in conjunction with multimodal imaging [19].

Previously, Peng et al. have reported that visual and anatomical outcomes in CNV secondary to PIC were significantly improved by intravitreal injection of conbercept [20]. In this study, we present two pathological myopia cases with submacular hemorrhage where OCTA was used to guide the anti-VEGF therapy.

The OCTA images were acquired using a OCT2 device (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany) with an A-scan rate of 70000/s. All follow-ups of the two enrolled cases were performed in the morning, and with the patients in the sitting position during OCTA. Written informed consent was obtained from both patients.

The first case was a 22-year-old female patient presenting with biocular high myopia, and blurred vision with black spots in her left eye for one week. The patient's best corrected vision acuity (BCVA) was 60/60 and 12/60 in the right and left eye, respectively. The bilateral intraocular pressure (IOP) was normal, and the same as the anterior segment examinations. Multi-color images showed bilateral leopard fundus, tilted optic disc, macular edema, and subretinal hemorrhage in the patient's left eye. Central macular blockage fluorescence without leakage was found using both FA and ICGA. However, a slit-like hypo-fluorescence band, which indicates the myopic lacquer crack, was observed in the inverted phase of ICGA. Enhanced depth imaging (EDI) OCT showed subfoveal hemorrhage, but signs of CNV were not detected in the angiography examinations. The myopic lacquer crack-related macular hemorrhage was diagnosed according to the multimodal image evidence described. Instead of intravitreal anti-VEGF injections, the patient was treated with a course of traditional oral Chinese medicine ("Hexue Mingmu Pian", which contains cattail root, *Salvia miltiorrhiza*, Rehmannia root, Mullein root, Chrysanthemum root, Scutellaria root (charcoal), Cassia seed, Plantain seed, Motherwort seed, *Ligustrum lucidum*, Prunella, Gentian, turmeric, Horsetail root, Red peony root, Peony skin, Angelica root, and Chuanxiong; auxiliary materials were dextrin and magnesium stearate; the medicine has no known anti-angiogenic effects) to absorb the hemorrhage. The subfoveal hemorrhage was absorbed completely at 1 month post therapy (Fig. 1).

The second case was a 28-year-old female patient with biocular high myopia and reported metamorphopsia and blurred vision in her left eye for 5 days. Her BCVA was 48/60 and 6/60 in the right and left eyes, respectively. The bilateral IOP and anterior segment examination were normal. Multi-color images showed bilateral leopard fundus, and one patched irregular subretinal hemorrhage with macular edema in the posterior pole of her left eye. Unlike case 1, there were no signs of myopic lacquer crack in the patient's left eye. The patient was allergic to fluorescein and only received ICGA, which showed central macular blockage fluorescence and a round dark spot nearby in the late phase. In the patient's left eye, signs of CNV were detected using OCTA.

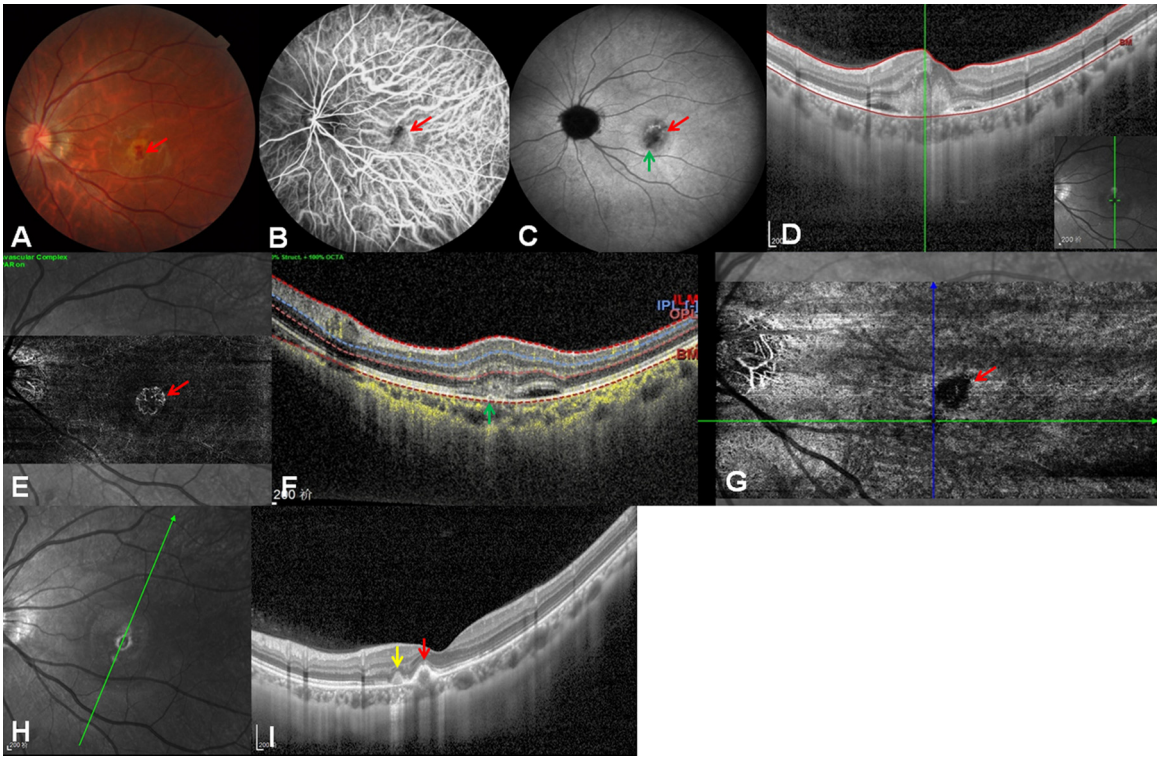

Fig. 2. Multimodal imaging of case 2. A. Multi-color image showing submacular hemorrhage (red arrow), surrounded by a slight serous macular detachment in the left eye. B. ICGA showing central macular patched blockage fluorescence (red arrow) in the middle phase. C. ICGA showing central patched macular blockage fluorescence (red arrow) with a round spot nearby (green arrow) in the late phase. D. EDI − OCT indicating central foveal elevation and sub-macular fibrovascular exudation, with inset showing the orientation of EDI − OCT scanning. E. OCTA showing corresponding central CNV signal (red arrow). F. Horizontal B scan OCTA demonstrated a small RPE turbulence (green arrow) under the serous macular detachment. The location of B scan OCTA was through the round hypo-fluorescent spot in Image C. G. OCTA showing that after three courses of anti-VEGF injections, the CNV was atrophied (red arrow). Round dark region, indicated by the intersection of the green and blue line, which was aligned with the lesion in Image F, marked by a green arrow. H. The direction of EDI − OCT in image I (green arrow) was through both the subfoveal CNV and the nearby focal lesion. I. EDI − OCT showing the subfoveal RPE elevation (red arrow), and its surrounding focal medium reflected signal with hyper-transmission (yellow arrow).

EDI − OCT of the left eye confirmed subretinal fluid and focal turbulence of the RPE nearby. Based on the imaging evidence, pathological CNV with high myopia was initially diagnosed for the left eye. The patient received three intravitreal anti-VEGF injections (conbercept) at 1-month intervals for her left eye. After the treatment, OCTA showed that the CNV still displayed atrophy with a round dark region nearby. EDI − OCT showed subfoveal RPE elevation, and its surrounding focal medium reflected signal with hyper transmission. Following treatment, the BCVA of the patient's left eye increased from 6/60 to 48/60. Therefore, we revised the diagnosis as CNV secondary to PIC in high myopic eye (Fig. 2).

OCTA using structural OCT assumes that the only moving entity in the retina is blood flow, and visualises the vasculature based on motion contrast; moving tissue continuously produces OCTA signals, while stationary tissue produces nearly constant reflection or scattering [21]. Using OCTA to investigate the etiology of myopic subretinal hemorrhage, and to guide the differentiation between inflammatory CNVs and inflammatory lesions, we successfully treated the patients in this report with either traditional Chinese medicine or anti-VEGF therapy.

Lacquer cracks are mechanical breaks in the RPE-BM − CC complex secondary to excessive axial elongation [13]. Therefore, subretinal hemorrhage with no pathologic myopic CNV could indicate the formation of a new lacquer crack in case 1.

In case 2, using OCT to examine active CNV via intra-retinal and subretinal fluids was proven to be unreliable in an inflammatory CNV setting. Leveziel et al. reported that exudation from myopic CNV is more obvious on FA than on OCT, suggesting that if myopic CNV is suspected, FA should be performed [22]. However, the patient in case 2 was allergic to fluorescein and only received ICGA, which did not detect CNV. Central macular blockage fluorescence due to hemorrhage, and a surrounding round dark spot in the late phase was displayed. However, it is important to note that it is difficult to distinguish leakage from inflammatory lesions and leakage from CNV using FA, as both would present signs of leakage [23]. Furthermore, the signs of CNV in conventional OCT and FA are similar to those of inflammation, making it difficult to make a differential diagnosis between CNV and isolated inflammatory lesions [24]. Similarly, EDI − OCT showed subfoveal RPE elevation, and its surrounding focal medium reflected signal with hyper transmission in case 2.

Considering the difficulty in differentiating inflammatory lesions from early CNV by OCT and FA, OCTA could be a valuable diagnostic tool for posterior uveitis related to CNV [15,25]. Histopathologically, the neovascular membranes in high myopia could be divided into three stages: immature, mature, and fibrotic [16]. An immature neovascular network would appear as small, disorganized vascular loops, whereas mature lesions would form larger, structured, interlacing networks on OCTA [16]. Indeed, OCTA from case 2 showed small, disorganized vascular loops, indicating an immature neovascular network at baseline. The appearance of the underlying CNV was obscured by the subretinal/outer retinal hyper-reflective changes and blurred RPE demarcation.

The natural course of PIC had been demonstrated using OCT [26]. In case 2, the horizontal scan OCTA revealed a small RPE turbulence under the serous macular detachment at baseline, identifying it as a stage II PIC lesion. On the other hand, the EDI − OCT showed a focal medium reflected signal above the RPE with hyper transmission, which

could be considered as a stage III PIC lesion. In a previous study by Pohlmann, eyes with punctuate lesions showed capillaries with crippled whitening on OCTA images, which could indicate erythrocyte accumulation in this area [16]. Moreover, areas of non-perfusion/hypoperfusion in the choriocapillaris were detected, which normally would not have been seen using standard imaging modalities [26]. In case 2, OCTA detected CNV atrophy and areas of non-perfusion/hypoperfusion in the choriocapillaris following anti-VEGF treatment.

Although no treatment was required for most PIC patients, PIC complicated by CNV has the potential to cause visual loss. VEGF, amongst other factors produced by the RPE such as interleukin-1 (IL-1), IL-2, IL-6, IL-10, as well as tumor necrosis factor α (TNF- α), could recruit macrophages to mediate an inflammatory response and promote the development of CNV in PIC [23].

Conbercept was approved to treat AMD by the State Food and Drug Administration of China in 2013 [20]. Compared with aflibercept, conbercept has a higher affinity to VEGF due to the addition of a fourth Ig-like domain of receptor VEGFR-2 in the Fab region [20]. Conbercept could reduce vessel leakage and leukocyte infiltration to inhibit inflammation [27]. Placental growth factor (PlGF) binds to VEGFR-1 to promote chemoattraction and aggregation of monocytes and macrophages [28]. The simultaneous inhibition of both VEGF and PlGF suppresses the expression of TNF- α, IL-1, and other inflammatory cytokines, which could alleviate CNV to some extent [27]. Due to the mechanisms above, OCTA detected CNV atrophy after three sectional intravitreal anti-VEGF injections, and the BCVA increased from 6/60 to 48/60. Treating CNV with anti-VEGF agents does not lead to normalization of the vasculature, but instead, results in the pruning of the vasculature [14].

The main components of the traditional Chinese medicine“Hexue Mingmu Pian”used in this study have been reported to have regulating functions on human vegetative nerves and vasoactive substances, with the promotion of platelet aggregation, blood clot absorption, blood stasis, retinal microcirculation, hematocerebral absorption, and microvascular elasticity. Additionally, the tolerance of the retina to hypoxia is enhanced, and retinal edema is reduced, thus leading to a gradual improvement of vision.

This study has a number of limitations. Only two cases were analyzed and FA was not performed in case 2, which could cause misdiagnosis of PIC at baseline. All these will be considered in future investigations.

From the two cases described above, it should be recognized that different mechanisms operate to cause submacular hemorrhage in pathological myopia, some of which do not require anti-VEGF therapy. Although anti-VEGF therapy could address issues associated with angiogenesis and permeability, it does not resolve all underlying problems. This study provides evidence that OCTA is an invaluable tool in the diagnosis of myopic submacular hemorrhage and the differentiation of inflammatory CNV from inflammatory lesions, and may provide guidance on treatment options.

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Declaration of Competing Interest

The authors declare that they do not have any competing interests.

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None.

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