

Case Report

Spontaneous Retinal Reperfusion of Capillary Nonperfusion Areas in Diabetic Retinopathy: A Comparative Angiographic Illustration by Fluorescence Fundus Angiography and Optic Coherence Tomography Angiography

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Keywords

Diabetic retinopathy · Macular ischemia · Reperfusion · Optic coherence tomography · Intraretinal microvascular abnormality

Abstract

Purpose: The aim of the study was to describe a case of diabetic macular ischemia developing reperfusion without any treatment involved. **Observations:** A 35-year-old diabetic lady with well-controlled blood glucose who complained about visual impairment in the left eye. When first seen, she had paramacular retinal nonperfusion on angiographic imaging, together with retinal thinning and intraretinal microvascular abnormalities. Marked reversal of the retinal perfusion occurred within 7 months. Some original nonperfusion areas were reperused with nearly normal capillary, while some showed revascularized with intraretinal microvascular abnormalities. **Conclusion and Importance:** There were rare reports that diabetic macular nonperfusion areas could be reperused spontaneously by revascularization. Our case presents an uncommon result of nonperfusion areas with the process being well captured by fundus fluorescein angiography and optic coherence tomography angiography.

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Introduction

Diabetic retinopathy (DR) is the leading cause of blindness in the global working-age population [1]. Progression of retinal capillary nonperfusion plays an important role in its pathophysiology process, which may lead to macular ischemia and then irreversible visual impairment, and retinal neovascularization and fibrovascular proliferation by overexpression of angiogenic factors [2, 3]. It is generally accepted that occlusion of retinal capillaries is progressive and irreversible, and that it needs retinal laser photocoagulation to prevent its progression. Although there previously have been reports of spontaneous reperfusion of nonperfusion areas (NPAs) in DR patients [4], of which the process and morphological characteristics remain unclear due to the limitation of fundus fluorescein angiography (FFA). We report a case of proliferative DR with retinal capillary NPAs in the macular. The patient had received pan-retinal photocoagulation (PRP) before visiting our clinic. At her first visit to our clinic, she received local supplementary laser photocoagulation for retinal neovascularization but received no intervention to the macular area. Seven months later, FFA and optic coherence tomography angiography (OCTA) showed almost complete reperfusion of capillary beds in the NPAs.

Case Report

A 35-year-old lady, known case of diabetes mellitus for half a year, visited our retinal clinic on November 16th, 2019, complaining about visual impairment in her left eye (OS) for half a year. She has been well treated with oral hypoglycemic medication, and her hemoglobin A1c was tested as 6.1% and received PRP in both eyes 2 months ago. At presentation, her lens-corrected visual acuity (LCVA) was 20/50 in the left eye. Clinical examinations showed the normal anterior segment. Dilated fundus examination revealed proliferative DR changes after PRP without macular edema (shown in Fig. 1a, i). FFA (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) confirmed the clinical diagnosis with new vessels noted superotemporal to the disc (shown in Fig. 1b, c). Angiography also revealed capillary NPAs close to the superotemporal foveal avascular zone (shown in Fig. 1d, g), where OCTA (Optovue, USA) correspondingly detected obliteration of both the superficial and deep capillary bed with thinner inner retinal thickness. And beyond this, OCTA demonstrated a better ability to elaborate the NPAs and the scattered plots of NPAs can be seen throughout the macula (shown in Fig. 1e, f, h, i). Laser photocoagulation was administered due to retinal neovascularization, but no other intervention therapy, except for oral compound xueshuantong capsule (a Chinese patent medicine) and calcium dobesilate, was given. Two months following the laser treatment, her LCVA in the left eye increased to 20/20, and OCTA showed a remarkable improvement in retinal perfusion in the areas of previously documented NPAs (shown in Fig. 2). Due to COV-19 in early 2020, the patient had been absent from our clinic until 9th June 2020. When she showed up, although her LCVA was stable to 0.7, FFA and OCTA both confirmed that almost all the NPAs were reperfused to nearly normal status, even in the NPA with thinner inner retina (shown in Fig. 3). Meanwhile, her hemoglobin A1c was tested as 5.6%. During the period of her absence from our clinic, she did not receive any intervention treatment other than oral hypoglycemic medication and calcium dobesilate. Her final visit was on 4th April 2021, when En-Face OCTA showed that all the macular perfused well, and the NPA with thinner inner retina got much better vascularized (shown in Fig. 4).

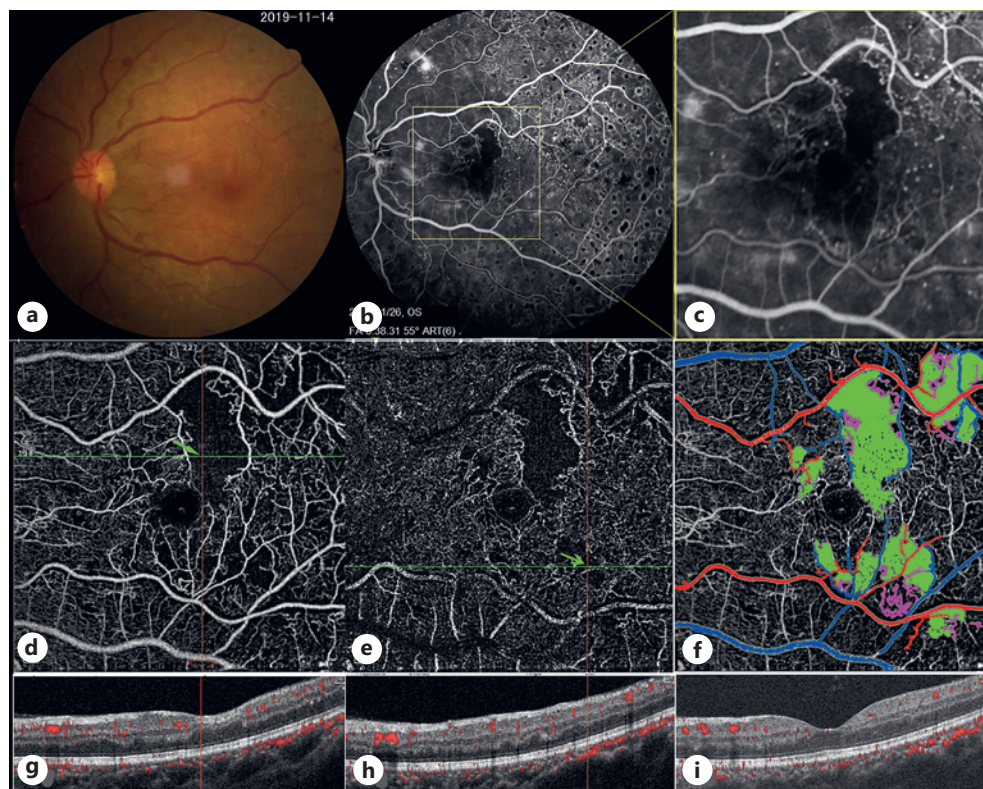


Fig. 1. Results of the patient's initial fundus examination, including color fundus photography (a), fluorescein angiogram (b, c), En-Face OCTA (d, f), and B-scan OCTA (g, i). d Showing the superficial plexus. e Showing the deep plexus. f Showing the whole plexus of retina, and highlighting artery (red), vein (blue), IRMA (magenta), and NPAs (green), whose extent surpasses that shown in c. g Showing the B-scan through the NPA with thinner inner retina that is corresponding to the line in d (green arrow). h Showing the B-scan through the NPA without retinal thinning that is corresponding to the line in e (green arrow). i Showing the B-scan through the macular foveola.

Discussion

The reperfusion of the occluded capillaries bed in the retina of patients with DR has been previously reported [4–7]. Generally, their reperfusions were confirmed by FFA. Although FFA has long been taken as the gold standard for evaluating the retinal microvasculature in DR, its characters of two-dimensional imaging and pathological dye leakage hinder it from further understanding the retinal microcirculation. OCTA is characterized by non-invasive, depth-resolved imaging, which can show more details of retinal microvasculature and can be helpful in DR to examine the micro-vasculopathy [8]. This case demonstrates the reperfusion of NPAs by FFA and OCTA with different ability of showing the extent of NPAs. The NPA confirmed by FFA showed thinner inner retina on B-scan of OCT, and its reperfusion was done in about 7 months, while the NPAs detected by OCTA outside the extent shown by FFA have normal retinal structure and thickness on B-scan of OCT, and the reperfusions were done in less than 2 months. In view of the understanding that the vasculature detected by FFA is the result of fluorescein filling, while the essence of OCTA is to visualize vasculature by detecting motion contrast of high-speed erythrocyte flow [8], we noticed that there are two types of NPA: NPA without retinal thinning, which can be detected only by OCTA, and NPA with thinner inner retina, which can be detected by FFA. NPA without retinal thinning may be the early stage of

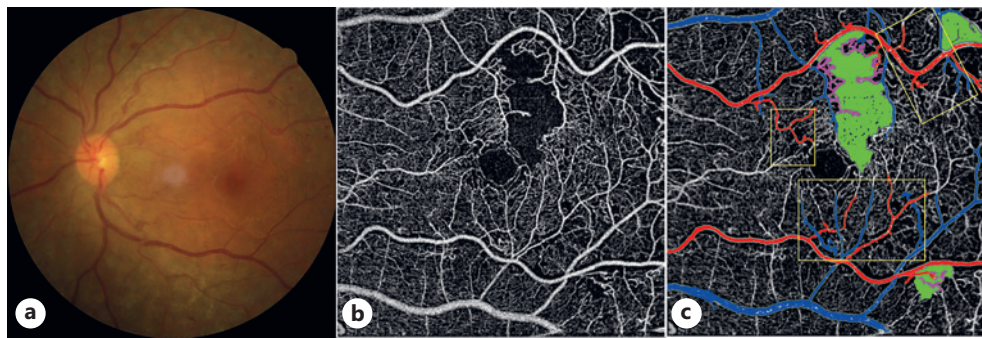


Fig. 2. The patient's color fundus photograph (a) and En-Face OCTA (b) at her first follow-up. b Showing the whole plexus of retina, where most of the NPAs have been reperused. c Showing the whole plexus of retina, and highlighting artery (red), vein (blue), IRMA growing into the NPA (magenta), NPAs (green), and reperused NPAs (yellow rectangular frame).

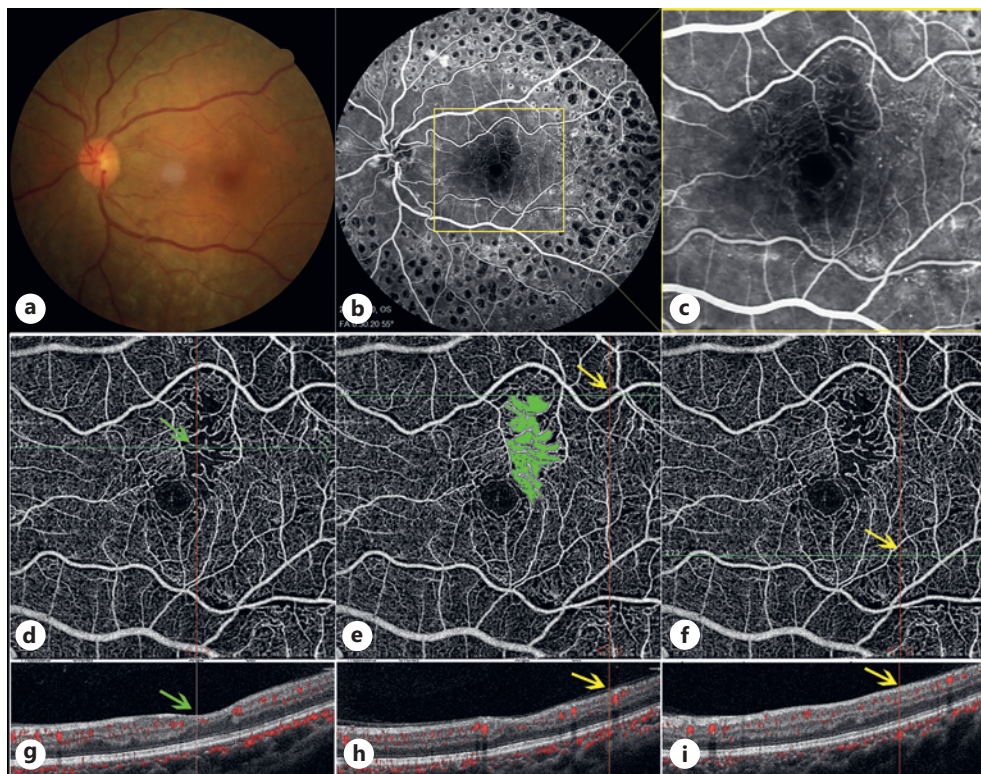


Fig. 3. Results of the patient's FFA and OCTA at her visit on June 9, 2020, which demonstrate almost all the NPAs were reperused. a–c FFA, showing the NPA reperused. d, g Showing the reperused NPA (whole plexus of retina/En-Face, green arrow) with thinner inner retina (B-scan, green arrow). e, f, h, i Showing the reperused NPA (whole plexus/En-Face, yellow arrow) with normal retina (B-scan, yellow arrow) and highlighting the reduced NPA (green).

NPA that is possible to reverse and restore perfusion. At this stage, the capillary bed may be not completely closed, and the capillaries, still with very slow blood flow, did not completely lose their function, while the retina corresponding to the NPA retain nearly normal on structural OCT. NPA with thinner inner retina may be the late stage of NPA, of which the

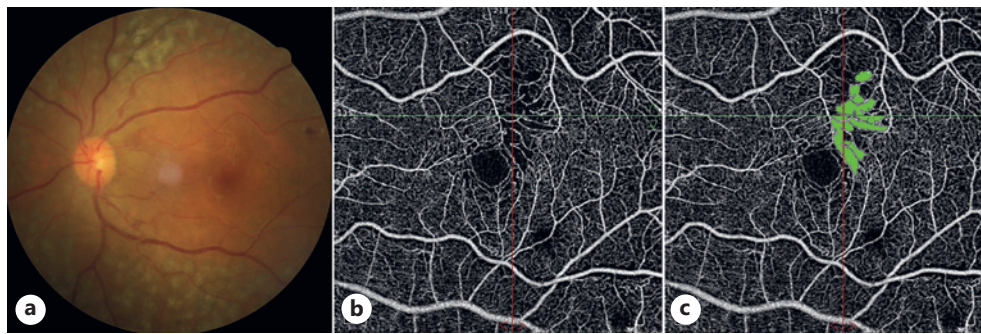


Fig. 4. The patient's color fundus photograph (a) and En-Face OCTA (b, c) at her final follow-up. **b** Showing the whole plexus of retina, where all the macular perfused well, and the NPA with thinner inner retina got much better vascularized. **c** Showing the whole plexus of retina, and highlighting the further reduced NPA (green).

capillaries become acellular and non-functional, and the retina corresponding to it become thinner or atrophic.

The mechanism of NPA reperfusion is still unclear. It has been reported that the reperfusion can occur in relatively small areas coincidental to the cotton-wool spots, can also occur following retinal photocoagulation or anti-vascular endothelial growth factor therapy, and can occur spontaneously [4, 6, 7, 9]. In this case, the patient received local laser treatment for NV, which covered only a small area outside the areas of NPA reperfusion during her first visit. The patient also took oral calcium dobesilate in the period, which was believed beneficial to suppress oxidative stress, stabilize the blood retinal barrier, and decrease capillary permeability [10]; however, no previous study showed that calcium dobesilate had ability to reverse NPA in DR. We speculated that NPA reperfusion may be the result of self-repairing mainly caused by well-controlled diabetes mellitus.

It is well accepted that there are two patterns of reperfusion, namely recanalization and intraretinal neovascularization [11]. According to FFA, Takahashi defined recanalization as that reperfused vessels simulate the normal vascular pattern, and intra-retinal neovascularization as that reperfused vessels show an abnormal vascular pattern [4]. In the case we reported here, all the reperfused NPAs showed a nearly normal vascular pattern; however, the reperfusion was obviously not a reflow of the obstructed capillaries or the recanalization since the intraretinal microvascular abnormalities (IRMA) were found in both the NPAs without retinal thinning and the NPA with thinner retina before reperfusion (shown in Fig. 1f).

IRMA is characterized as dilated, tortuous intra-retinal vascular loops that are not consistent with the natural distribution of normal capillaries, in which blood flow does not breach the inner limiting membrane on the OCTA B-scan [11]. This case demonstrated that the IRMAs can be initiated from both the venules and arterioles (shown in Fig. 1f), then slowly grew into the NPAs (shown in Fig. 2c), and later formed new capillary networks (shown in Fig. 3f and Fig. 4b) by remodeling branches, vascular calibers, and decreasing in convolution of vessels. Therefore, the IRMAs played an important role in the NPA reperfusion of this case.

Conclusion

The case demonstrates that there are two types of capillary NPAs, namely NPA without retinal thinning and NPA with thinner retina, and the case further strengthens the fact that

capillary bed occlusion in DR is not irreversible, and IRMA plays an important role in the NPA reperfusion.

Statement of Ethics

Written informed consent was obtained from the patient for publication, including the details of the medical case and imaging photographs, which has been submitted to the supplementary file. Our study is a retrospective, accidental finding. According to the criterion of the Beijing Tongren Hospital Ethics Committee, a retrospective study has no need to get the approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors attest that they meet the current ICMJE criteria for authorship and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, while each of them has main work as the followings. Yibin Li: conception or design of the work, manuscript revising, and final approval of the version. Simeng Hou: data analysis and interpretation of data and drafting manuscript. Yuanyuan Xiao: analysis and interpretation of data.

Data Availability Statement

The original data has been linked to the website: <https://zenodo.org/record/6330884#>. YiOMIPmTaNg. DOI: 10.5281/zenodo.6330884.

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