Macular Vascular Abnormalities Identified by Optical Coherence Tomographic Angiography in Patients With Sickle Cell Disease

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Sickle cell retinopathy (SCR) is characterized by retinal vascular ischemia due to abnormal sickle-shaped red blood cells in patients with sickle cell disease. The staging of SCR is based on the presence of arteriolar occlusions, arteriovenous anastomoses, neovascularization, vitreous hemorrhage, or retinal detachment. While peripheral findings typically predominate, macular abnormalities have been described, including hairpin venular loops, microaneurysmal dots, and irregularities of the foveal avascular zone.

Spectral-domain optical coherence tomography (SD-OCT) has enabled the capture of detailed in vivo images of macular function and morphologic features, revealing temporal and central macular thinning (macular splaying) in some patients with SCR. Because many patients are asymptomatic, the clinical relevance of these findings remains unclear. However, retinal sensitivity is decreased in areas of thinning, and macular thinning has been correlated with the presence of proliferative SCR.

Optical coherence tomographic angiography (OCT-A) is a nascent technology with several advantages over fluorescein angiography (FA), including noninvasive image acquisition without the need for contrast dye, and enhanced visualization of all retinal vascular layers, particularly the peripapillary and deep capillary networks.

This study describes macular vascular abnormalities visualized using OCT-A in patients with sickle cell disease and correlates the findings with prior articles describing macular abnormalities identified by findings using histopathologic evaluation, FA, and SD-OCT.

Methods

This study is a single-center, prospective, observational series evaluating clinical and multimodal imaging findings from patients with sickle cell disease. Approval was obtained from the Johns Hopkins Hospital Institutional Review Board and patients provided written informed consent to participate. The study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with the regulations set forth by the Health Insurance Portability and Accountability Act. Consecutive patients who met inclusion criteria were enrolled from February 2015 to April 2015. Patients with diabetes mellitus, hypertension, or known retinal vascular disease, including retinal artery or vein occlusion, were excluded. All patients underwent Early Treatment Diabetic Retinopathy Study visual acuity testing and dilated fundus examination. Multimodal imaging was performed, including SD-OCT and OCT-A (Avanti RTVUE XR; Optovue Inc) split-spectrum amplitude decorrelation angiography for all patients and standard-field or ultra-wide-field FA (P200Tx; Optos) at the investigators’ discretion.

Results

Ten eyes from 5 consecutive patients (3 men and 2 women) with sickle cell disease (4 patients with hemoglobin SS disease and 1 patient with hemoglobin SC disease) were included. The mean age was 37.6 years. Five of 10 eyes (50%) had retinal thinning that was identified using spectral-domain optical coherence tomography. Each of these eyes had corresponding loss of vascular density in the superficial or deep retinal plexus (or both).
ease (hemoglobin SC) were included. The mean age was 37.6 years. Five eyes (50%) had retinal thinning that was identified using SD-OCT, as defined by the loss of inner retinal structures (eTable in the Supplement). Each of these eyes had corresponding loss of vascular density in the superficial and deep retinal plexuses, with abnormalities being more apparent in the deep plexus. Three representative cases are described.

**Report of Cases**

**Case 1**
An African American man in his late 20s with hemoglobin SS disease and a history of avascular necrosis of the hip and acute chest syndrome presented for evaluation. The patient was visually asymptomatic and his visual acuity was 20/20 OU. Findings from the anterior segment examination were unremarkable. Dilated fundus examination findings revealed tortuous vessels, normal-appearing maculae, and several peripheral sunburst lesions in both eyes. Findings from ultra-wide-field FA showed peripheral arteriolar occlusions with arteriovenous anastomoses but no neovascularization. Findings from SD-OCT revealed temporal macular thinning in the right eye. Findings from OCT-A showed decreased vascular density in the area of thinning, predominantly in the deep capillary plexus. These vascular abnormalities were not apparent when using FA (Figure 1).

**Case 2**
An African American woman in her late 20s with hemoglobin SS disease and a history of avascular necrosis of the hip and acute chest syndrome presented for routine examination. She was visually asymptomatic and her visual acuity was 20/20 OU. Findings from the anterior segment and dilated fundus examination were normal in both eyes, without visible SCR, and the patient refused FA. Findings from SD-OCT demonstrated macular splaying and temporal thinning in both eyes. Findings from OCT-A showed enlargement of the foveal avascular zone with loss of blood flow in the superficial and deep capillary plexus vessels in areas of thinning (Figure 2).

**Case 3**
An African American man in his mid-20s with hemoglobin SS disease and a history of acute chest syndrome was seen for follow-up of proliferative SCR that was previously treated with scatter laser anterior to the equator in the temporal retinal periphery in both eyes. His visual acuity was 20/20 OU and he was visually asymptomatic. Findings from the anterior segment examination were normal and those of the dilated examination revealed fibrous proliferans without
new areas of retinal neovascularization in both eyes. Findings from SD-OCT showed temporal thinning in the right eye only with corresponding loss of blood flow in the superficial and deep plexus vessels on OCT-A in the area of thinning (eFigure in the Supplement).

Discussion

To our knowledge, this study is the first report of retinal vascular abnormalities in patients with sickle cell disease identified using OCT-A. Macular nonperfusion with predilection for occlusion of the terminal branches along the temporal horizontal meridian has long been observed in patients with sickle cell anemia. Early histopathologic studies demonstrated loss of the inner retinal layers in patients with retinal ischemia, and isolated studies using OCT have shown similar findings in areas of clinically apparent macular infarction. However, larger case series have demonstrated that macular thinning on SD-OCT is seen even in the absence of clinically apparent nonperfusion and with relative frequency (43% of eyes in the largest series to date). The exact etiology of macular thinning in the absence of clinically apparent nonperfusion remains unclear. Several recent case reports have described parafoveal acute middle maculopathy, which is characterized by a hyperreflective band on SD-OCT findings at the level of the inner nuclear layer in patients with sickle cell disease, suggesting that ischemia of the deep capillary networks may play a role.

Our case series supports the idea that nonperfusion of the deep capillary plexus may be responsible for the areas of macular thinning seen on SD-OCT, because each patient with macular thinning had corresponding findings of loss of vascular flow on OCT-A that was more apparent in the deep plexus than in the superficial plexus. Because the deep plexus is not well visualized by FA, OCT-A may be more sensitive than FA in identifying macular nonperfusion in patients with sickle cell disease, and may provide further insights into the pathophysiologic differences between the different sickle cell genotypes. For example, Mathew et al demonstrated that the incidence of macular thinning by SD-OCT in patients with hemoglobin SS is high (48% vs 35% in hemoglobin SC) despite peripheral SCR findings being more common in patients with hemoglobin SC. In our case series, 4 of 5 patients had hemoglobin SS, with 3 of these patients (4 of 8 eyes) demonstrating findings of macular thinning on SD-OCT and vascular nonperfusion on OCT-A. While no definitive conclusions can be drawn from this small number of patients, the findings raise the question of whether those with hemoglobin SS disease, even in the absence of visual symptoms, have subclinical vascular abnormalities that are now identifiable with OCT-A.

Certain limitations exist for this study, including its small sample size, qualitative nature, and the lack of normative data for OCT-A as a nascent technology. No eyes were included as controls, although asymmetry between eyes in the same patient (eg, case 3) and correlation with the prior clinical, histopathologic, and SD-OCT studies lend support to our findings.

Conclusions

Patients with sickle cell disease may have macular vascular abnormalities, including loss of flow in the deep retinal plexus, that are identifiable with OCT-A. The clinical relevance of these findings is unclear, and further studies are needed to elucidate their relevance regarding visual prognosis, relationship to sickle cell genotype, systemic disease morbidity, or severity of SCR, as well as their predictive value for determining disease stability or worsening.
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REFERENCES


