• Letter to the Editor •

Choroidal vascular occlusion in a young male patient with sickle cell trait

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Dear Editor,

Choroidal vascular occlusion is a rare finding[1]. Choroidal perfusion disorders may range from focal infarction of the choriocapillaris to fibrinoid arteriolar necrosis[2]. Vascular occlusion due to microembolism is more common in choroidal than in retinal vasculature. Due to its unique hemodynamic characteristics, which involve one of the highest rates of blood flow in the body and the fact that it is functionally an end artery system, the choroidal circulation is prone to platelet emboli associated with cardiovascular disease and other pathologies with increased risk of microembolism[3]. To the best of our knowledge, this is the first report of optical coherence tomography angiography (OCT-A) in choroidal vascular occlusion. This study was performed according to the Declaration of Helsinki. After detailed explanation of the nature and possible consequences of the study, the subject gave his written informed consent for participation.

Case Presentation A 31-year-old man presented with a two-day history of acute visual loss on his right eye (RE). The patient's medical history was remarkable for sickle cell trait (HbAS genotype) and moderate obesity (body mass index of 30.5). Best-corrected visual acuity (BCVA) was 6/19 RE and 6/6 left eye (LE), and intraocular pressure was normal. Funduscopy showed minimal retinal pigment epithelium (RPE) irregularity in the right fovea and bilateral retinal arteriolar tortuosity. Macular optical coherence tomography (OCT) scan revealed increased reflectivity in the deep retinal layers at the level of the inner segment/outer segment (IS/OS) junction (Figure 1).

Fluorescence angiography (FA) showed mild RPE irregularities. Due to the discrepancy between the subtle clinical findings and the visual acuity loss, an indocyanine green (ICG) angiography was performed, which demonstrated subfoveal choroidal ischemia (Figure 2). OCT-A was not available at presentation of the patient.

Further medical workup revealed mixed hyperlipidemia (total cholesterol 240 mg/dL, low-density lipoprotein LDL-cholesterol 170 mg/dL, triglycerides 330 mg/dL) and idiopathic arterial hypertension (blood pressure of 145/95 mm Hg). The patient was further investigated for autoimmune, thrombophilic, and hyperviscosity disorders. Auto-antibody levels were within normal limits. Laboratory evaluation including a complete blood count, peripheral blood smear, serum electrolytes and serum viscosity did not reveal abnormal findings. Additionally, a thrombophilia work-up including blood count, type and screen, total protein, albumin, antithrombin, prothrombin time, activated partial thromboplastin time, fibrinogen, international normalized ratio (INR), platelet count, urine and serum electrophoresis, protein C and S, Factor II, Factor V Leiden, Factor VIII level and *JAK2* gene mutations, was normal. Additional workup with chest radiography and brain magnetic resonance imaging did not show pathological results.

Due to his vascular profile and medical history, the patient was started on oral antiplatelet (clopidrogel 75 mg daily), anticoagulant (fondaparinux subcutaneously daily) and antihypertensive therapy. One month later on follow-up examination, his BCVA on the RE had improved to 6/7.5. At 6-month follow-up, funduscopic examination revealed residual RPE irregulaties (Figure 3) and there was auto-hypofluorescence corresponding to those areas of focal RPE atrophy in the macula (Figure 4). The swept source OCT showed a slight increase of choroidal reflectance due to retinal thinning and hypopigmentation (Figure 5), and OCT-A (Topcon, DRI OCT Triton, Swept source OCT) indicated loss of choriocapillaris at the fovea and mild enlargement of the foveal avascular zone area (Figure 6).

OCT Scans were taken from 6×6 mm^2 with each cube consisting of 320 clusters of four repeated B-scans centered on the fovea. En face images of the chorioretinal vasculature were generated from the superficial retinal layer (SRL), deep retinal layer (DRL) and choriocapillaris, based on the automated layer

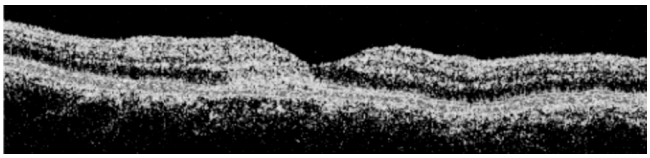

Figure 1 Macular OCT of the right eye Increased reflectivity was found in the deep retinal layers at the level of the IS/OS junction.

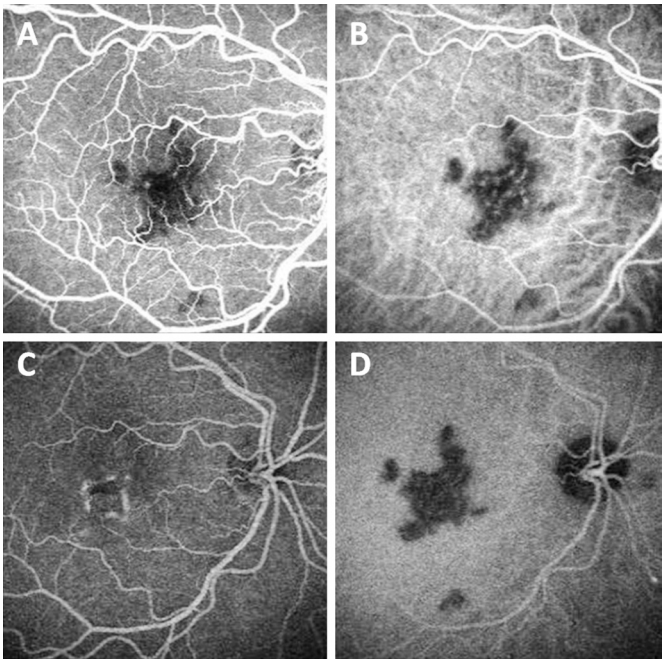

Figure 2 Simultaneous FA and ICG of the right eye A large subfoveal area of choroidal ischemia was evident in the early (A) and middle (C) FA stages, and also in the early (B) and middle (D) ICG stages.

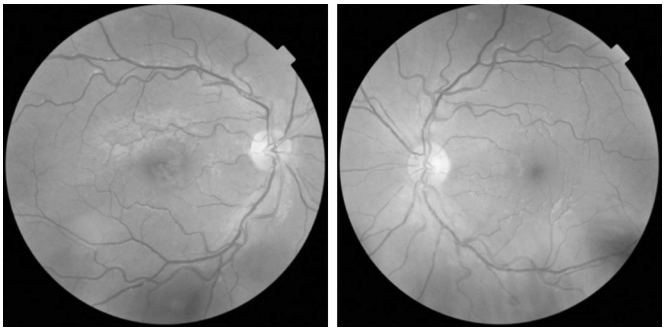

Figure 3 Infrared fundus imaging At 6-month follow-up, there was evidence of atrophic RPE changes of the right macula and there was also bilateral retinal arterioral tortuosity.

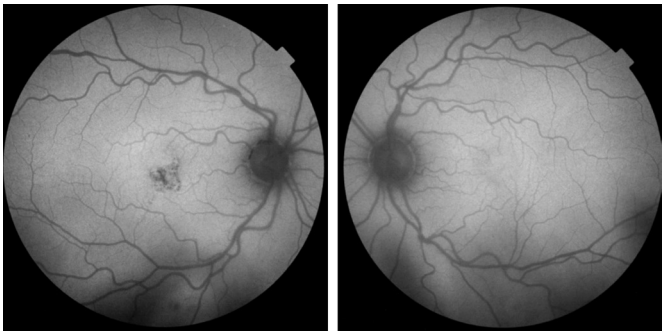

Figure 4 Autofluorescence fundus imaging There was auto-hypofluorescence corresponding to the areas of focal RPE atrophy in the right macula.

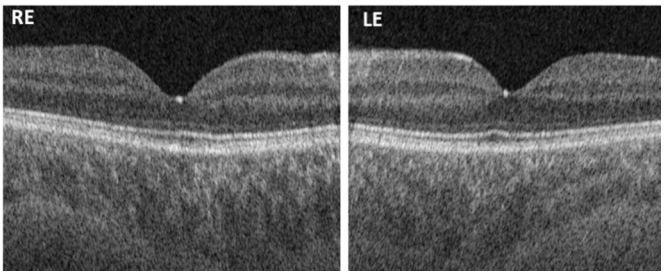

Figure 5 Swept source OCT Subfoveal disruption of the IS/OS junction and mild thinning of the RPE layer was found in the right eye. Additionally, there is increased choroidal reflectance due to retinal thinning and hypopigmentation in the right eye. The left eye OCT was normal.

segmentation performed by the OCT instrument software. Quantitative analysis of the vessel density and foveal avascular zone (FAZ) area were performed using the publically available GNU Image Manipulation Program GIMP 2.8.14 (http://gimp.org). The FAZ area was defined as the area inside the central border of the capillary network, which was outlined manually for the SRL and DRL with the lasso tool as described previously[4]. The software calculated the outlined area in pixels, and the measured area in pixels was converted to mm^2 based on the scan dimensions (6 mm×6 mm scan) and the 320-pixel width of the images. In order to perform quantitative analysis of the vessel density (VD), the enface images were "binarized" and vessels were defined as pixels having decorrelation values above the threshold level. VD was assessed as the ratio of the retinal area occupied by vessels for the SRL, DRL and choriocapillaris. At the level of the SRL, VD in the RE was 36% and in the LE 39.6%. At the level of the DRL, VD in the RE was 32.1% and in the LE 36.2%. Finally, at the choriocapillaris, VD in the RE was 45% and in the LE 54.6%. FAZ area at the level of the SRL was 0.25 mm^2 in the RE and 0.21 mm^2 in the LE. At the level of the DRL, FAZ area was 0.60 mm^2 in the RE and 0.36 mm^2 in the LE.

DISCUSSION

Choroidal perfusion abnormalities can pose diagnostic challenges, because they are not readily evident on funduscopy and even FA does not always straightforwardly confirms a choroidal vascular occlusion[1]. In our case there were subtle funduscopic changes; however, the decreased visual acuity and the tortuous retinal vessels prompted further diagnostic examination by means of ICG angiography. At presentation of the patient, OCT-A was not available in our institution; hence ICG angiography was chosen in order to facilitate diagnosis.

The differential diagnosis in this patient could include macular serpiginous choroiditis, which is a rare, progressive disease affecting young to middle-aged otherwise healthy individuals, and is characterized by grey-yellow discoid lesions with irregular borders deep to the retina involving the macular area. However, in cases of macular serpiginous choroiditis

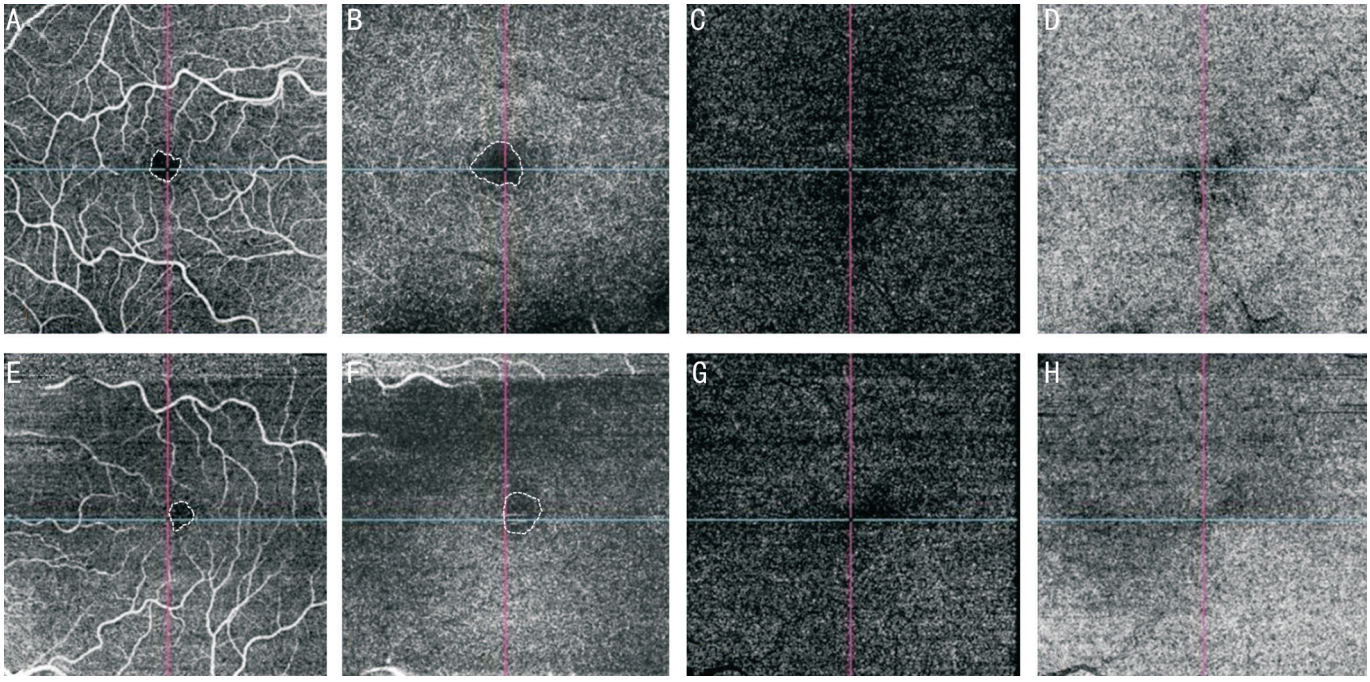

Figure 6 OCT-Angiography of the right (A-D) and left eye (E-H) OCT-A indicated loss of choriocapillaris at the fovea of the right eye (D). The foveal avascular zone area of the right eye (outlined by a white dashed line) also appears mildly enlarged (A, B). A, E: Superficial retinal layer; B, F: Deep retinal layer; C, G: Outer retina; D, H: Choroidal vessels.

FA reveals early hypofluorescence followed by leakage and staining of the borders without any evidence of choroidal ischaemia or retinal vascular abnormalities. Additionally, patients with macular serpiginous choroiditis later develop atrophic scars accompanied with pigment clumping and worse visual prognosis; hence, this entity could be excluded in the present case.

Choroidal circulation exhibits one of the highest rates of blood flow in the body. Several studies show that the choroid receives 65%-85%, while the retina 5% or less of the ocular blood flow[3]. However, the choroid is prone to vaso-occlusion by microemboli, because the blood flows in a functionally terminal fashion at the level of the choriocapillaris, and there is very little collateral flow after a focal occlusion[2]. A variety of diseases is associated with platelet microemboli, which appear to affect the choroidal circulation more than the retinal circulation. Associated diseases included toxemia of pregnancy, renal failure, systemic lupus erythematosus, disseminated intravascular coagulation, and thrombotic thrombocytopenic purpura. Platelet emboli may be more likely to become lodged in the choriocapillaris due to the rapid deceleration of the blood flow and the larger volumetric flow within the choroid.

OCT-A is a novel, non-invasive technique that is used to visualize the chorioretinal microcirculation without dye injection and provides high-quality images of the SRL, DRL, outer retina, and the choroidal vessels. In the present case of choroidal occlusion, quantitative analysis of VD and comparison of values between both RE and LE, showed that VD in the affected RE was reduced in all layers as compared to the LE, primarily in the choriocapillaris. Additionally, there was enlargement of the FAZ area in the RE which was more evident at the DRL level and is consistent with the reduced VD. In the SRL the FAZ area in both eyes (0.25 mm^2 in the RE and 0.21 mm^2 in the left eye) appeared to be similar with previous results, where the mean FAZ area in normal subjects varied from 0.25 to 0.34 mm[2,5-6]. However, in the DRL the FAZ area in the RE (0.60 mm^2) was considerably larger than the FAZ area in the LE (0.36 mm^2) and mean values reported previously (0.37±0.12 mm^2 and 0.358±0.105 mm^2)[5-6].

Our data suggest impairment of the chorioretinal microcirculation in the macular area, which was prominent in the deeper retinal layers and the choriocapillaris. Compromised circulation in the choroid may explain the disruption of the IS/OS junction, the thinning of the RPE layer and the enlargement of the FAZ area, as the outer retina and FAZ depend on diffusion from the choroidal circulation. Although structural changes were evident at the level of the IS/OS junction at 6mo follow-up, improvement in visual acuity suggests that some degree of reflow in obstructed choriocapillaris may have occurred. Alternatively, the deep retinal capillary circulation may supply the photoreceptor zones when the choroidal vasculature fails to autoregulate the blood supply.

Our findings are in accordance with a previous study reporting VD in control subjects and diabetic patients without diabetic retinopathy[7]. Apart from the differences between patients and controls, this study showed that VD in superficial retina was greater than in deep retina and that the choriocapillaris had the greatest VD of all layers[7]. Additionally, our results

are consistent with previous research suggesting that the FAZ area is larger in the DRL than in the SRL[5,8]. Other authors have also showed that in diabetic patients without diabetic retinopathy, the FAZ is enlarged in the superficial and deep retinal vascular plexi[9-10]. The present patient did not have diabetes mellitus, but he had several systemic cardiovascular risk factors, such as hyperlipidemia, obesity, idiopathic arterial hypertension and the sickle cell trait, which may have compromised the chorioretinal circulation. To the best of our knowledge the present case is the first to report on quantitative vessel density and FAZ area in a patient with choroidal occlusion.

Choroidal vascular compromise should alert the clinician to further diagnostic work-up for elevated blood pressure, lipid profile, carotid artery and cardiovascular disease, hyperviscosity syndromes and autoimmune disorders, such as Wegener granulomatosis. No evidence for autoimmune disease, hyperviscosity syndromes or coagulopathies has been found in our patient; however, he had underlying systemic cardiovascular risk factors, such as hyperlipidemia, obesity and idiopathic arterial hypertension.

The sickle cell trait in the present patient may also have played a role in the pathogenesis of the choroidal infarction[10]. Sickle cell trait (hemoglobin AS) is the most common genotype and is generally considered a benign disorder. Systemic and ocular complications are infrequent in patients with sickle cell trait. However, in the presence of concomitant systemic diseases or trauma leading to hypoxia, it can become a risk factor[11]. Ocular complications associated with sickle cell trait have primarily involved the retinal vasculature and include proliferative retinopathy, “black sunburst” lesions, “salmon patch” hemorrhages, angioid streaks, venous tortuosity, central and branch retinal artery occlusion, epiretinal membrane, ischemic optic neuropathy and optociliary shunt vessels[12-13]. However vaso-occlusive disease of the choroid and chorioretinal infarctions have been also reported[14]. The clinical manifestations of the disease are considered the result of the sickling of red blood cells, which are rigid and unable to alter their shape, so they become impacted in capillaries and arterioles leading to vascular occlusion[15-16]. The development of these changes seems to depend on the quantity of abnormal hemoglobin present[17]. Nagpal *et al*[12] proposed that the combination of systemic disease and sickle cell trait may be more pathogenic for the retina than each condition by itself. A similar pathogenesis has been also suggested in further cases of choroidal infarction occurring in patients with hematological disorders and primary vascular dysregulation[18-20].

In conclusion, this case illustrates that the presence of ocular vaso-occlusive disease in patients with sickle cell trait necessitates a comprehensive medical workup, including serologic testing to rule out concomitant systemic diseases. In the present patient, various factors could have contributed to the manifestation of the choroidal ischemia. In addition to the sickle cell trait, there was underlying arterial hypertension, hyperlipidemia and obesity, which could have potentially exacerbated the microvascular changes linked to the sickle cell trait. ICG specifically highlights choroidal perfusion and can be extremely useful in this context. However, the advent of OCT-A, which provides high resolution images of the chorioretinal capillaries and their lesions at all vascular networks, enables immediate non-invasive diagnosis and follow-up of choroidal occlusion. OCT-A identifies areas of nonperfusion at various retinal levels, quantifies FAZ and provides stratigraphic vascular details that have not been previously described by standard fluorescein and ICG angiography.

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Conflicts of Interest: Kotoula M, None; **Papageorgiou E,** None; **Xanthou F,** None; **Kalampalikis S,** None; **Androudi S,** None; **Tsironi EE,** None.

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