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Quantitative OCT angiography of the retina and choroid in non-ocular sarcoidosis

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Abstract. – OBJECTIVE: The aim of the study was to evaluate retinal and choroidal microvascular morphological changes in non-ocular sarcoidosis (NOS) patients using optical coherence tomography angiography (OCTA) and compare the results to age- and gender-matched healthy individuals.

PATIENTS AND METHODS: This study included 37 NOS patients (group 1, 37 right eyes) referred to the Ophthalmology Department between 2019 and 2021, as well as 31 healthy individuals (group 2, 31 right eyes). Non-ocular sarcoidosis was defined as sarcoidosis confirmed by a positive lung X-ray and biopsy without ocular manifestation. All participants underwent a comprehensive ophthalmic examination. The SPECTRALIS® OCT was used for both fundus photography and macular analysis. All OCTA procedures were performed in the Angio Retina mode (6.0x6.0 mm) to assess retinal and choroidal microvascular morphology.

RESULTS: Groups 1 and 2 had mean ages of 46.41±12.52 and 47.55±13.81 years, respectively (p=0.482). Group 1 had significantly increased superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel densities (VDs) in whole (p=0.059, 0.016), parafoveal (p=0.051, 0.015), and perifoveal (p=0.060, 0.010) regions relative to group 2. Group 1 was also associated with increased foveal avascular zone (FAZ) area (p=0.196), FAZ circumference (p=0.262), and foveal VD in 300 µm wide regions surrounding FAZ (p=0.003) relative to group 2. The outer retinal (p=0.712) and choriocapillaris (p=0.684) flows did not differ significantly between the two groups.

CONCLUSIONS: Quantitative OCTA analysis revealed a higher tendency for retinal and choroidal microvascular morphological changes in NOS patients, demonstrating the potential of this novel, non-invasive imaging technology, which may provide sensitive and reliable results without using contrast materials.

Key Words:
Choroid, Microvascular morphology, Non-ocular sarcoidosis, OCTA, Retina, Vessel density.

Introduction

Sarcoidosis is a multi-systemic inflammatory disease with an unknown etiology. This disease is characterized by the formation of non-caseating epithelioid granulomas in various organs, including eyes[1,2]. It affects both genders, as well as different age groups and races, with people in their thirties and forties being the most affected[3,4]. The prevalence of ocular involvement in systemic sarcoidosis ranges from 12 to 76%[5,6]. This condition may occur concurrently with asymptomatic systemic disease or years before systemic manifestation. Sarcoidosis-related granulomatous inflammation may affect any part of the eye and ocular adnexa[7], resulting in severe visual impairment and, in the worst cases, blindness. Posterior segment manifestations are typically bilateral, but they may also be asymmetric[5,7-9].

Optical coherence tomography angiography (OCTA) is a novel non-invasive technique for imaging retinal and choroidal microvascular system[10]. This technique employs laser light reflection from the surface of moving erythrocytes to accurately depict vessels from different ocular segments, obviating the need for intravascular dye[11]. Choroidal granuloma-induced choroidal

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microvascular displacement is typically visible on OCTA as dark spots or a vascular defect[12]. The non-invasiveness, repeatability, and time-saving properties of OCTA make it ideal not only for diagnosing but also for therapeutic monitoring of ocular sarcoidosis[13].

Some sarcoidosis patients do not always exhibit ocular involvement. Despite this, ophthalmological examinations of non-ocular sarcoidosis (NOS) cases may be valuable to clinicians. We hypothesized that early evaluation of retinal and choroidal microvascular morphology would help prevent blindness in these cases. Hence, timely therapeutic intervention against secondary posterior segment complications, in particular, may be possible. Therefore, this study aimed to evaluate retinal and choroidal microvascular morphological changes in NOS patients using OCTA and compare the results to age- and gender-matched healthy individuals.

Patients and Methods

Study Design and Participants

This study enrolled 37 NOS patients (group 1) who were followed up on at Afyonkarahisar Health Science University Medical Faculty Hospital's Chest Diseases Clinic between 2019 and 2021 and were consulted for ocular examination in the Ophthalmology Department. A control group (group 2) consisted of 31 age- and gender-matched healthy individuals who visited our clinic for routine exams. Non-ocular sarcoidosis was defined as sarcoidosis confirmed by a positive lung X-ray and biopsy in the absence of ocular manifestation during standard ophthalmological examination, including posterior segment spectral domain optical coherence tomography (SD-OCT) analysis.

The study protocol adhered to the principles of the Helsinki Declaration and was approved by the Ethics Committee of Afyonkarahisar Health Science University Faculty of Medicine. All participants provided written informed consent to have OCTA performed, measurements taken, and their medical records reviewed.

Inclusion and Exclusion Criteria

The study included sarcoidosis patients with the following features: (a) NOS condition, (b) absence of systemic disease other than sarcoidosis, (c) absence of ocular diseases like glaucoma, diabetic retinopathy, senile macular degeneration, choroidal neovascularization, and others that could affect anterior and posterior segments, (d) absence of prior ocular surgery or trauma, and (e) non-pregnancy and not breast-feeding.

Sarcoidosis patients who had the following features were excluded from the study: (a) a history of malignancy, interstitial lung disease, tuberculosis, or Behçet's disease, (b) a recent use of eye lubricants or contact lenses, (c) treatment for any other local and/or systemic diseases besides sarcoidosis, (d) high myopia and hypermetropia defined as refractive errors (spherical equivalent) of < -6.00 D and $> +6.00$ D, respectively, and (c) an axial length (AL) >26.5 mm.

Ophthalmological Assessment

All patients had a comprehensive ophthalmological examination. This included best-corrected visual acuity in logarithm of the minimum angle of resolution (logMAR) and intraocular pressure (IOP) (Goldmann; Haag-Streit AG, Köniz, Switzerland) measurements, as well as slit-lamp biomicroscopy before and after full pupil dilation. Pentacam (Pentacam HR, Oculus, Wetzlar, Germany) was used to evaluate the anterior segment. SPECTRALIS® OCT (Heidelberg Engineering, Heidelberg, Germany) was used for fundus photography as well as macular analysis. A contact A-scan ultrasonography (contact A-scan) was used to determine the AL. All tests were performed under standard conditions by the same clinician.

Optical Coherence Tomography Angiography Acquisition

Optical coherence tomography angiography device capable of detecting NOS in patients with systemic sarcoidosis was used to assess associated ocular findings, including those of the retinal and choroidal layers. An Angio Retina mode was used for all OCTA procedures (6.0x6.0 mm). To avoid any potential diurnal fluctuations, the procedures were performed between 9:00 a.m. and 11:00 a.m. after a minimum of 8 hours of fasting. Ocular movement-induced artifacts were reduced by using an eye-tracking mode and eliminated using a motion correction technology. All scans were scrutinized to ensure proper segmentation and image quality (Quality Index ≥ 7).

The AngioVue Analytics, RTVue-XR version 2017.1.0.155 software automatically quantified vessel densities (VDs) in whole, foveal, parafoveal, and perifoveal regions of superficial capillary plexus (SCP) and deep capillary plexus (DCP).

The software's foveal avascular zone (FAZ) mode yielded FAZ area, FAZ circumference, and foveal VD in 300 μm wide regions surrounding FAZ (FD-300). Microvascular flow parameters, including choriocapillaris and outer retinal flows were also measured (Figure 1).

Statistical Analysis

A statistical package (SPSS Corp., version 25.0, Armonk, NY, USA) was used for statistical analysis. Categorical data were described using observed frequencies and percentages, and continuous variables were summarized by their means and standard deviations. Individual probability charts in the comparison groups and time points were used to visually examine the normality assumption in quantitative variables, and statistical analysis was performed using the Shapiro Wilk test. The Pearson Chi-Square test was used to check gender distribution, and the Independent *t*-test was used to compare ages between groups. The Mann-Whitney U test was used to compare variables between groups. Statistical significance was defined as p-values <0.05.

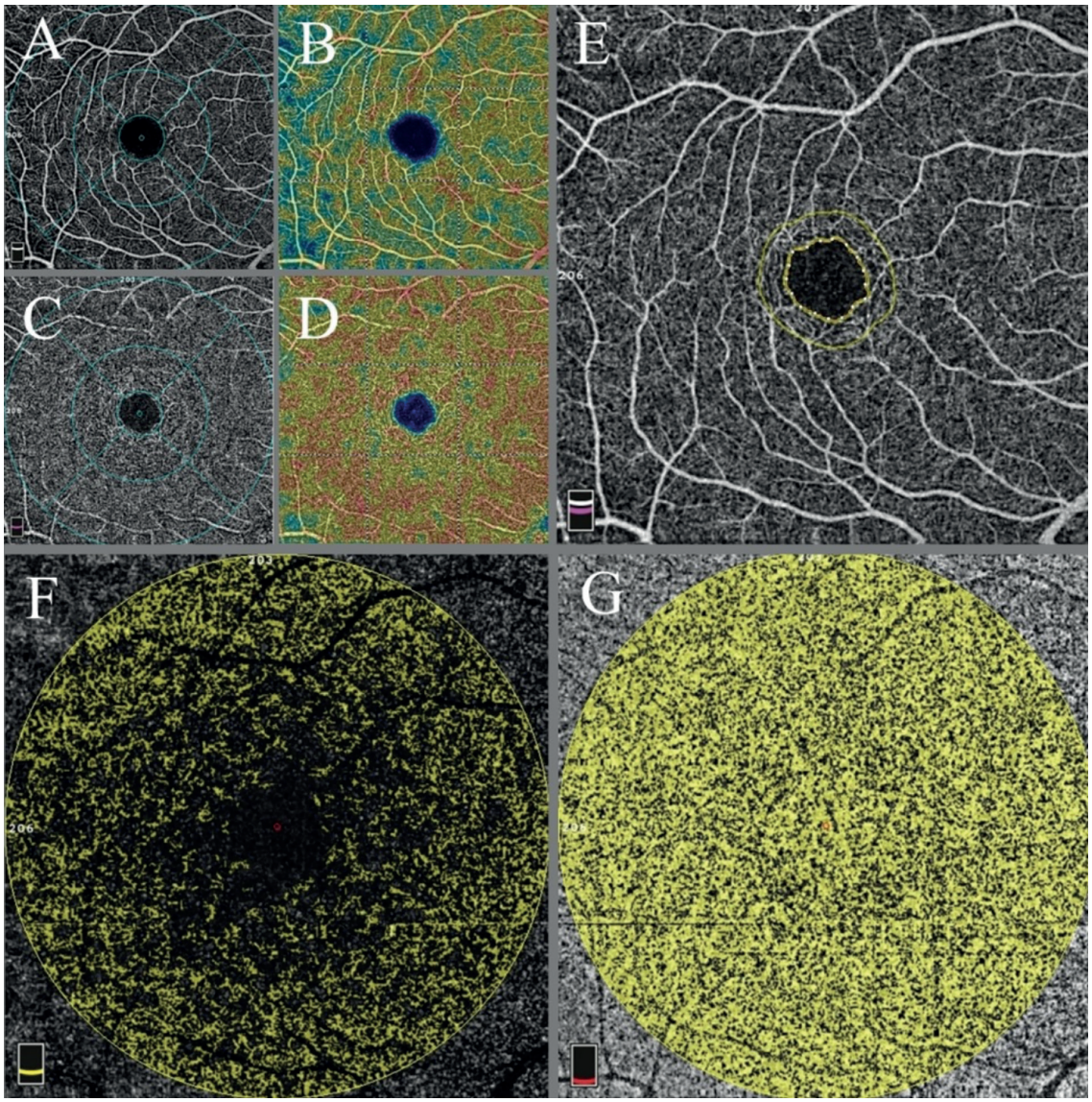

Figure 1. The optical coherence tomography angiograms of a non-sarcoidosis patient displaying superficial capillary plexus (**A**) with its vessel density map (**B**), deep capillary plexus (**C**) with its vessel density map (**D**), superficial retinal slab projection showing automated foveal avascular zone area measurements (**E**), outer retinal flow (**F**), and choriocapillaris flow (**G**) for quantitative assessment.

Table I. Demographic and clinical characteristics of the participants.

Parameters	Group 1† (N=37) (mean±SD)	Group 2‡ (N=31) (mean±SD)	*p*-value
Age (years)	46.41±12.52	47.55±13.81	0.722*
Female/Male	29/8	22/9	0.482**
BCVA (logMAR)	0.0±0.0	0.0±0.0	1.000
AL (mm)	23.08±0.36	23.04±0.39	0.760
CCT (µm)	548.82±29.84	555.20±30.42	0.810
IOP (mmHg)	14.98±3.56	15.12±3.82	0.880

†Non-ocular sarcoidosis patients, ‡Healthy individuals, SD=Standard deviation, N: Number of participants, BCVA: Best-corrected visual acuity, logMAR: logarithm of the Minimum Angle of Resolution, AL: Axial length, mm: Millimeter, CCT: Central corneal thickness, µm: Micrometer, IOP: Intraocular pressure, mmHg: Millimeter of mercury, *Independent *t*-test, **Pearson Chi-Square test.

Results

Group 1 included 37 right eyes of 37 NOS patients, while group 2 included 31 right eyes of 31 healthy individuals. Females made up the vast majority of participants in both groups (p=0.482). The mean ages were 46.41±12.52 (23-70) and 47.55±13.81 (21-70) years in groups 1 and 2, respectively. The AL (p=0.760), central corneal thickness (p=0.810), and IOP (p=0.880) were not significantly different between the two groups. Demographic and clinical characteristics of the participants are summarized in Table I.

Optical Coherence Tomography Angiography Analysis

Compared to group 2, group 1 was associated with increased SCP and DCP VDs in whole (p=0.059; 0.016), parafoveal (p=0.051; 0.015), and perifoveal (p=0.060; 0.010) regions. Group 1 was also associated with increased FAZ parameters, including FAZ area (p=0.196), FAZ circumference (p=0.262), and FD-300 (p=0.003) compared to group 2. The outer retinal (p=0.712) and choriocapillaris (p=0.684) flows did not differ significantly between groups 1 and 2 (Table II).

Table II. Comparison of OCTA microvascular morphological parameters.

Parameters	Group 1† (N=37) (mean±SD)	Group 2‡ (N=31) (mean±SD))	*p*-value*
Image Quality	8.35±0.72	8.30±1.01	0.775
Capillary Plexus VDs			
SCP (%)			
Whole	52.91±2.81	51.60±3.37	0.059
Foveal	21.02±6.81	21.94±4.53	0.526
Parafoveal	55.19±2.82	53.46±3.82	0.051
Perifoveal	53.27±3.14	51.63±3.93	0.060
DCP (%)			
Whole	56.87±6.62	52.80±6.69	0.016
Foveal	37.97±6.87	37.29±4.60	0.671
Parafoveal	59.21±3.56	56.34±4.87	0.015
Perifoveal	58.96±6.41	54.63±6.60	0.010
FAZ parameters			
FAZ area (mm2)	0.32±0.12	0.29±0.07	0.196
FAZ circumference (mm)	2.19±0.41	2.11±0.30	0.262
FD-300 (%)	56.22±2.76	54.21±2.52	0.003
Microvascular flow parameters			
Outer retinal flow	8.77±1.64	8.82±2.23	0.712
Choriocapillaris flow	19.25±1.24	19.45±1.16	0.684

†Non-ocular sarcoidosis patients, ‡Healthy individuals, OCTA: Optical coherence tomography angiography, SD: Standard deviation, N: Number of participants, *Mann-Whitney U test, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, VD: Vessel densities, FAZ: Foveal avascular zone, FD-300: Foveal vessel density in 300 µm-wide region around FAZ, Bold values are statistically significant values ($p < 0.05$).

Discussion

In this study, retinal and choroidal microvascular morphological changes were quantified and analyzed using OCTA in NOS patients, and the results were compared to age- and gender-matched healthy individuals. The use of OCTA for sarcoidosis diagnosis and therapeutic monitoring in patients with and/or without ocular involvement is particularly valuable. En-face OCTA images demonstrate a pathological change in the choroid, with areas of flow void indicating choriocapillaris loss or displacement secondary to granuloma. Analysis of en-face images and cross-sectional OCT scans aids in potentially confirming the presence of flow void areas by carefully ruling out artifacts and signal transmission loss[13]. Using OCTA in conjunction with other diagnostic imaging methods enabled more detailed evaluation of the structural and functional clinical findings of ocular sarcoidosis in a multimodal imaging study of a patient with definitive ocular sarcoidosis[14]. However, there are some drawbacks to this novel technology, including relatively small field of view, failure to detect vascular leakage, and predisposition for image artifacts caused by patient movement or blinking[15].

A number of non-invasive diagnostic imaging techniques have been investigated in ocular sarcoidosis patients. *In-vivo* confocal microscopy of the conjunctiva revealed an existence of multi-nucleated giant cells in patients with sarcoid conjunctival nodules, with 100% specificity and 50% sensitivity[16]. This method, however, needs technical skills. In some cases, the use of a high-resolution, deep-penetration instrument may also be required to improve sensitivity of the test. Anterior segment OCT can distinguish between an anterior chamber cell pattern that is predominantly mononuclear in active anterior uveitis caused by sarcoidosis or inflammatory bowel disease, and a pattern that is predominantly polymorphonuclear in HLA-B27-related uveitis[17]. The use of enhanced depth imaging OCT in patients with quiescent sarcoid posterior uveitis revealed decreased choroidal thickness compared to normal controls[18]. Further, a microarray analysis of gene expression in peripheral blood, lung, and lymph nodes revealed that sarcoidosis patients, with or without uveitis, had significantly higher levels of signal transducer and transcription 1 activator (STAT1) than healthy individuals[7,19].

The use of OCTA technology in our study revealed significantly increased whole, parafoveal, and perifoveal SCP and DCP VDs in NOS patients compared to healthy individuals. The same could be said for FAZ parameters, which increased in NOS patients than in healthy individuals, though only the FD-300 difference was statistically significant. While no ocular manifestations were detected during routine ocular exams in systemic sarcoidosis patients, it seems that there could be evolving ocular changes, particularly at the microvascular level. This highlights the importance of detailed ocular exams in patients with ocular sarcoidosis, as well as those with NOS. Finally, this would enable early detection of any potential sarcoidosis-related ocular complications that would otherwise go undetected by routine ocular exams. Patients with more pronounced microvascular morphological changes could thus be closely monitored.

Sarcoidosis-related granulomatous uveitis is commonly characterized by a number of clinical signs, including large mutton fat keratic precipitates[20], iris or trabecular meshwork nodules[21], and choroidal granuloma[22]. These signs, however, may not be present in all cases, especially those with an early onset, less severe inflammation, or who have been successfully treated. Further, these signs are not limited to sarcoid uveitis and may be seen in other types of uveitis as well, such as infections. A granulomatous appearance was observed in 81% of 112 eyes with sarcoid uveitis in one study[23]. Another study[20] reported that anterior chamber inflammation, which is possibly the most common symptom of sarcoid uveitis, was present in 91% of 46 patients with biopsy-confirmed sarcoid uveitis. Only the anterior chamber was involved in 38% of these patients, with no involvement from the posterior segment. Severe anterior uveitis, if left untreated, can cause anterior segment deformity and predispose to cataract formation. Mild sarcoid uveitis, on the other hand, is sneaky at first, and patients may be asymptomatic. Only screening or routine ocular exams can provide a diagnosis, and early detection is critical to potentially avoiding chronic inflammation sequelae.

We believe that routine screening of systemic sarcoidosis patients before ocular involvement, as performed in our study, is clinically necessary. This, in turn, could aid in comprehending significant findings concerning the degree of posterior segment microvascular involvement under normal ocular anterior segment conditions. Fur-

thermore, the absence of significant differences between NOS patients and healthy individuals, particularly in IOP, central corneal thickness, or AL, indicated that a normal anterior segment examination does not guarantee physiologically normal microvascular morphology of the retina and choroid, which has long-term implications.

Optical coherence tomography angiography is an excellent tool for detecting FAZ enlargement, especially in retinal-involved systemic diseases[24,25]. FAZ enlargement has been observed in OCTA prior to clinically observed retinopathy[15]. In our study, NOS patients had a non-significantly increased FAZ area, FAZ circumference, and a significantly increased FD-300 when compared to healthy individuals. These findings could point to ongoing early retinal and choroidal microvascular morphological changes even before they manifest in routine ocular exams.

Limitations

Our study has some limitations. The cross-sectional nature of this study limited our ability to discover processes related to the association between systemic sarcoidosis and the eye, specifically posterior segment microvascular morphology. There was no assessment of the disease duration or prior sarcoidosis-related medication. Further, unexplained analytical preferences may be caused by residual influencing factors. Since our study data came from a single center and only included participants of Turkish ethnicity, some of our findings may not be applicable to other ethnic groups. Our study population size was also relatively insufficient to improve the study's efficacy. To better understand the role of OCTA technique, more prospective and systematic large-scale studies are required. This is especially crucial in determining the pathophysiology and long-term effects of systemic sarcoidosis on microvascular changes, notably in the posterior segment before ocular manifestation.

We believe that our study provides the first quantitative description of retinal and choroidal microvascular morphological changes in NOS patients compared to age- and gender-matched healthy individuals using OCTA. The use of OCTA appears to be a promising method for detecting and characterizing retinal and choroidal microvascular changes in NOS patients. Its depth-resolved nature enables OCTA to evaluate each microvascular structure independently. Pre-treatment ophthalmological evaluation of systemic sarcoidosis patients may be recommended not just to identify patients with asymptomatic ocular sarcoidosis manifestations. This could also be helpful in determining the status of clinical features such as microvascular morphological changes in the retina and choroid.

Conclusions

Microvascular morphological changes were more common in NOS patients, particularly in whole, parafoveal, and perifoveal SCP and DCP VDs. This also applied to FAZ parameters, particularly FD-300. Using OCTA to quantify retinal and choroidal microvascular morphological changes in NOS patients has demonstrated the potential of this novel, non-invasive imaging technique, which may provide sensitive and reliable results without using contrast materials. As a result, clinicians will be able to take early visual acuity protective measures immediately after OCTA-assisted posterior segment evaluation. This is especially important in cases where ocular sarcoidosis is a possibility; thus, treatment may begin before full clinical manifestation. Nonetheless, supporting clinical evidence from large-scale long-term studies, even involving multi-racial participants, would be clinically valuable.

Conflict of Interest

The Authors declare that they have no conflicts of interest.

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None.

Financial Interest

All authors certify that they have no association or participation with any organization or individual with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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Authors' Contribution
Aydin BALCI: Conceptualization, Methodology, Formal analysis, Investigation, Writing-Original Draft, Writing-Review & Editing, Visualization, Project administrator; Ozgur EROGUL: Methodology, Investigation, Formal analysis, Project administrator; Mustafa DOGAN: Conceptualization, Methodology, Formal analysis, Investigation, Writing-Review & Editing, Visualization; Hamidu Hamisi GOBEKA: Conceptualization, Methodology, Formal analysis, Writing-Review & Editing, Project administrator; Muberra AKDOGAN: Methodology, Investigation, Formal analysis, Visualization; Ayse Yesim ORAL: Methodology, Investigation, Formal analysis, Visualization; Murat KASIKCI: Methodology, Investigation, Formal analysis, Visualization; Leyla ERYIGIT EROGUL: Methodology, Investigation, Formal analysis.

Availability of Data and Materials
The manuscript contains all data. The datasets used and/or analyzed during the current study, however, are available upon reasonable request from the corresponding author.

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