OCT-Angiographic Findings in Intermediate Uveitis-related Refractory Macular Edema

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Abstract

Objective :

To assess the microvascular structure of macula in uveitic refractory macular edema

Method:

In a cross-sectional observational study fifty-five patients in all were assessed for macular microvascular structure using Optuve OCT angiography: 30 patients with intermediate uveitis-related refractory macular edema (RME group), and 25 patients with intermediate uveitis without macular edema (control group).

Results:

Superficial layer density in RME and control group were significantly different in whole image and parafovea (P=0.027 , P= 0.001), however there was no significant differences between the two groups in fovea superficial density (P=0.711).There was no significant difference in deep layer density between the two groups (P>0.05).

Conclusion:

The density of superficial vessels is lower in refractory macular edema. Micro-cystic changes in inner retina and ischemia can be the cause of alteration in superficial layer density in refractory macular edema.

Introduction

Cystoid macular edema (CME) is the main cause of permanent visual impairment in almost 40 to 50% of patients with uveitis [1], and up to 80% in patients with intermediate uveitis.[2-4]

Strong associations have been shown between the occurrence of CME and various specific uveitis entities. Panuveitis showed the strongest association, with 66% of patients having CME, followed by intermediate uveitis at 60%, posterior uveitis at 34%, scleritis at 13%, and anterior uveitis at 11%.[1]

The pathophysiology of uveitic CME is still undetermined. In short, the blood-retinal barrier integrity is responsible for keeping the environment of ocular neurons and photoreceptors stable.[5] The blood-retinal barrier is kept at two levels: an outer barrier consisting of tight junctions between the retinal pigment epithelium, and an inner barrier consisting of tight junctions between the endothelium of retinal vessels.[6] Various inflammatory mediators (prostaglandins, interleukins, interferon gamma, and tumor necrosis factor alpha) break down the blood retinal barrier, leading to an outflow of fluid into and under the retinal tissue, resulting in extracellular edema.[7, 8] . Swelling of Müller glial cells should also be presumed in the development of CME, including intracellular fluid collection in the absence of vascular leakage, results in cysts formed by swollen and dying Müller cells.[9, 10]

Spectral domain optical coherence tomography angiography (SD-OCTA) is a unique imaging technology that employs the advances in OCT technology to make high-resolution angiographic displays of the retinal microvascular structure.[11-13] SD-OCTA permits both qualitative and quantitative evaluation of microvascular integrity in retinal vascular diseases, primarily in the parafovea, where visually significant pathology is often present (e.g., macular edema). In addition, SD-OCTA provides high-resolution macular capillary structural details along with a quantitative assessment of disease severity. Thus SD-OCTA provides near-histology-level resolution to assess capillary density and, in addition, is a non- invasive method that can be repeated frequently.[12]

Subject And Method

Patients

A cross-sectional observational study was conducted using recorded data of patients examined at the Nikoukari Eye Hospital (Tabriz, Iran). A total of 55 cases, including 30 patients with refractory uveitic macular edema and 25 patients with intermediate uveitis without macular edema were enrolled between March 2017 and February 2018. Refractory macular edema was defined as any macular edema that persisted after six months of treatment.

The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Tabriz University of Medical Sciences. Written informed consent was obtained and patient confidentiality was safeguarded through study.

Specific cases such as patients with other ocular diseases, history of eye surgery, pregnant women, inability to keeping the head and eye fixed for imaging such as nystagmus, and low image quality were excluded.

All patients underwent OCT-angiography (AngioVue Imaging System (Optovue, Inc., Freemont, CA), using split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. This instrument (Optovue) has an A-scan rate of 70,000 scans per second using a light source centered on 840 nm and a bandwidth of 50 nm. Each OCT-A volume consist of 304 × 304 A-scans with two consecutive B-scans took at each fixed position. Each OCT-A volume is acquired in 3 seconds, and two orthogonal OCT-A volumes are acquired for orthogonal registration using motion correction technology.(1, 2) This technique minimizes motion artifacts.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality was assessed using the Kolmogorov-Smirnov test. An independent-samples t-test was used to compare quantitative data and chi-square analysis was used for qualitative data. Descriptive statistics are expressed as frequency and percentage for categorical variables, mean ± standard error of mean for normally distributed variables. $P<0.05$ was considered statistically significant.

Results

This study enrolled fifty-five eyes with intermediate uveitis: 30 eyes from 20 patients with refractory macular edema due to intermediate uveitis (RME group), and 25 eyes from 17 patients with intermediate uveitis without macular edema (control group). Eight patients in RME group and 7 patients in control group were male (P=0.124). Averaged age of patients was 38.2 ± 7.9 (range 16-58years) in RME group versus 40.3 ± 9.4 (range 21-59 years) in control group. (P=0.753)

In refractory macular edema (RME) group underlying cause of intermediate uveitis (IU) was idiopathic in 27 eyes, Multiple Sclerosis related IU in 2 eyes and Tuberculosis related IU in one eye. In the control group, 22 eyes had idiopathic IU, 1 eye rheumatoid arthritis related IU, 1 eye sarcoidosis IU and 1 eye Tuberculosis related IU.

In the examination period, there was neither active inflammation in RME patients nor reported history of macular edema in the control group. All patients in both groups were phakic and negative for previous ocular surgery.

Vascular structure of whole image in the size of 6 × 6 mm, fovea (1.5 ×1.5 mm) and parafovea (0.5 mm circle around fovea) were analyzed in the two groups using superficial and deep layer vascular information.

Superficial layer density in RME and control group were 41.91± 5.36 vs 45.77 ± 5.55 in whole image, 17.09 ± 8.27 vs 17.93 ± 6.72 in fovea and 39.02 ± 9.75 vs 47.47 ± 6.75 in parafovea respectively. There were significant differences in superficial density of whole image and parafovea between the two groups (P=0.027, p= 0.001 respectively) however there was no significant difference between the two groups in fovea superficial density (P=0.711).

Deep layer density in the two groups were 44.78 ± 6.40 vs 45.03 ± 7.24, 32.93 ± 11.81 vs 33.04 ± 8.06, 49.95 ± 6.43 vs 51.82 ± 6.91 in whole image, fovea and parafovea respectively.

There was no significant difference in deep layer density between the two groups (P>0.05).

Cystoid space was seen in the superficial capillary plexus in all 30 eyes in the RME group and in the deep capillary plexus in 20 eyes (66%). (Figures 1 and 2)

Compared to the control group, whole image thicknesses of macula, central foveal thicknesses and parafoveal thicknesses were significantly higher in the RME group. (Table 1)

There were no significant differences between the two groups in FAZ, FAZ perimeter, acircularity index, or the foveal vessel density in 300μm-wide region around the FAZ (P>0 . 05) (Table **1** ,Figure 3).

There was no significant qualitative differences in overview images of OCT angiography print-out and vascular changes in the two groups such as capillary tuft, telangiectatic vessels or micro-aneurism.

Discussion

Leakage and trilaminar or triplanar patterns of the capillary plexus, particularly the deep capillary plexus limit evaluation of the foveal microvascular structure using fluorescein angiography (FA).[14-16] Other factors also limit FA visualization, including cataracts and blockage from macular edema. On the other hand, OCT angiography makes depth-resolved high-resolution images of both superficial and deep retinal capillary networks, making it possible to recognize microvascular abnormalities may not be identified using FA.

Our study found that vessel density in superficial capillary plexus was low in eyes with intermediate uveitis-related refractory macular edema compared to intermediate uveitis without macular edema.

In our study there was no significant difference in deep vessels density in fovea and parafovea and whole image between the two groups.

No significant differences were observed in FAZ, FAZ perimeter, Acircularity index and foveal vessel density in a 300-μm-wide region around FAZ between the two groups.

Study of Alice Y.Kim et al [17], revealed that Uveitic Macular edema was related with deep retinal layer vascular alteration. This study indicates that it is very unlikely to attribute causality of these vascular changes to either macular edema or uveitis alone. This study did not exclude patients with other ocular disease such as diabetic retinopathy. In their analysis, significant alterations in the deep capillary network were co-localized with intraretinal cystoid spaces (generally, the inner nuclear and plexiform layers).[17]

likewise, in another study conducted by Khotchali et al, cystoid space in DCP was more than SCP, so DCP density was altered more than SCP density in uveitic CME.[18]

According to our findings, intermediate uveitis related refractory macular edema was associated with microvascular changes compared to intermediate uveitis without macular edema. But changes were not in deep layers.

Spaida et al. noted that an important mechanism in the development of CME in retinal vascular disease such as diabetic retinopathy may be DCP ischemia.[19]

All of our patients had intermediate uveitis, thus inflammation of vitreous in these patients may cause ischemia of inner retina and alteration of superficial layer density versus deep layer density.

Although mechanical dislocation of vessels from superficial layers into deep layers may lead to their microvascular changes and refractory macular edema.

Superficial vessels density in parafovea and whole image of macula was significantly lower than in refractory macular edema. These results are consistent with the reports of Tian et al study. They

concluded that superficial vessels density in intermediate uveitis with CME was varied more than deep capillary density and the presence of CME rather than disease entity impacted vessels density of SCP. [20]

Conclusion

In our study, intermediate uveitis related refractory macular edema was associated with microvascular changes compared to intermediate uveitis without macular edema.

Superficial vessels density in parafovea and whole image of macula was significantly lower in refractory macular edema.

Micro-cystic change in inner retina and ischemia may be the cause of alteration in superficial layer density in refractory macular edema.

Low number of patients, lack of choroidal vessels microvascular data, limitation of patients in one type of uveitis (IU) and lack of access to history of onset of disease and treatment were some limitations of our study. We suggest other studies to be planned with all types of uveitis and in the durations of active and inactive inflammation to confirm or decline our findings.

Declarations

Funding:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest:

The Authors declare that there is no conflict of interest.

Ethics approval:

Ethics approval No: IR.TBZMED.REC.1397.573

Consent to participate:

This study was approved by the Ethics Committee of the Tabriz University of Medical Sciences. Written informed consent was obtained and patient confidentiality was safeguarded through study

Consent for publication:

The signed Consent ensures that the Publisher has the Author's permission to publish the relevant Contribution.

Availability of data and material:

The authors confirm that the data supporting the findings of this study are available from the corresponding author on request.

Authors' contributions:

-	Leila Alizadeh	Fardieh Mousavi	Hesam Sadat Hashemi	Masood Bagheri
Concepts	•	•	•	
Design	•		•	
Definition of intellectual content	•	•	•	
Literature search	•	•	•	
Clinical studies	•	•	•	
Data acquisition	•	•	•	•
Data analysis			•	•
Statistical analysis			•	
Manuscript preparation	•	•	•	•
Manuscript review	•	•	•	•

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Tables

Table 1.microvascular structure of macula in patients with intermediate uveitis with/without macular edema

	group	N	Mean ± sd	P value
Superficial density whole	refractory CME	30	41.916 ± 5.366	0.027
	no CME	25	45.776 ± 5.557	
Superficial density fovea	refractory CME	30	17.094 ± 8.277	0.711
	no CME	25	17.938 ± 6.723	
Superficial density parafovea	refractory CME	30	39.027 ± 9.751	0.001
	no CME	25	47.476 ± 6.752	
Deep density whole	refractory CME	30	44.783 ± 6.403	0.906
	no CME	25	45.034 ± 7.242	
Deep density fovea	refractory CME	30	32.938 ± 11.813	0.973
	no CME	25	33.042 ± 8.062	
Deep density parafovea	refractory CME	30	49.950 ± 6.435	0.369
	no CME	25	51.823 ± 6.917	
Whole thicknesses	refractory CME	30	334.50 ± 30.891	0.005
	no CME	25	308.58 ± 27.381	
Parafovea Thickness	refractory CME	30	381.89 ± 46.699	0.000
	no CME	25	331.38 ± 31.509	
Central thickness	refractory CME	30	356.17 ± 137.98	0.001
	no CME	25	256.19 ±	

			35.668	
FAZ	refractory CME	30	0.3349 ± 0.2227	0.586
	no CME	25	0.3063 ± 0.1007	
FAZ perimeter	refractory CME	30	2.2061 ± 0.8561	0.851
	no CME	25	2.1676 ± 0.4180	
Acircularity index	refractory CME	30	1.1426 ± 0.0451	0.104
	no CME	25	1.1173 ± 0.0460	
Foveal vessel density in a 300-μm-wide region around FAZ	refractory CME	30	40.787 ± 11.037	0.202
	no CME	25	45.097 ± 10.156	

Figures

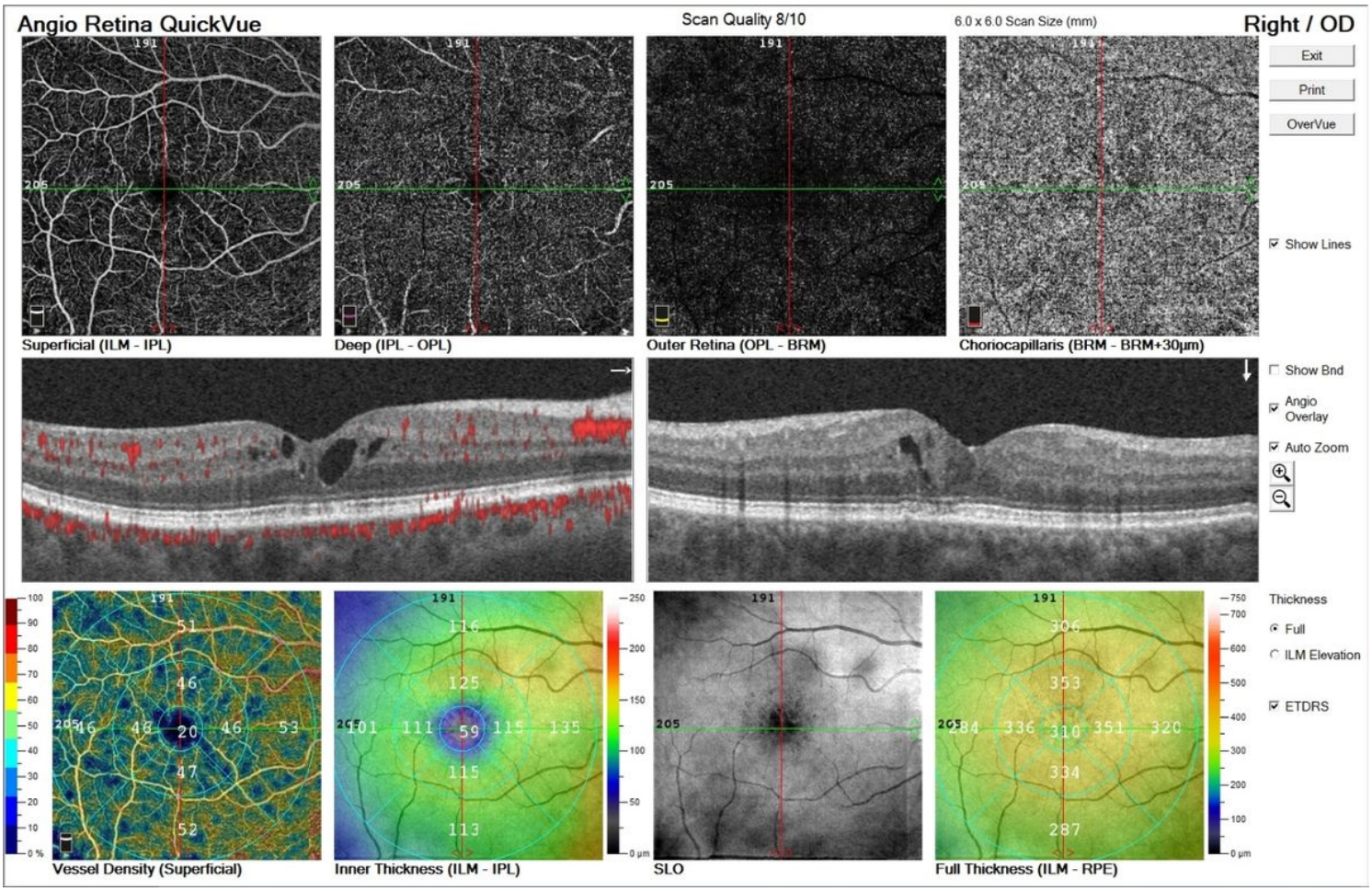

Figure 1

Overview image of OCT angiography in a patient with refractory uveitic macular edema. Top: Superficial-inner retina, deep-inner retina, outer retina and choriocapillaris from left to right respectively Middle: corresponding standard OCT B-scan in horizontal(left) and vertical(right) configuration. Bottom: color encoded image

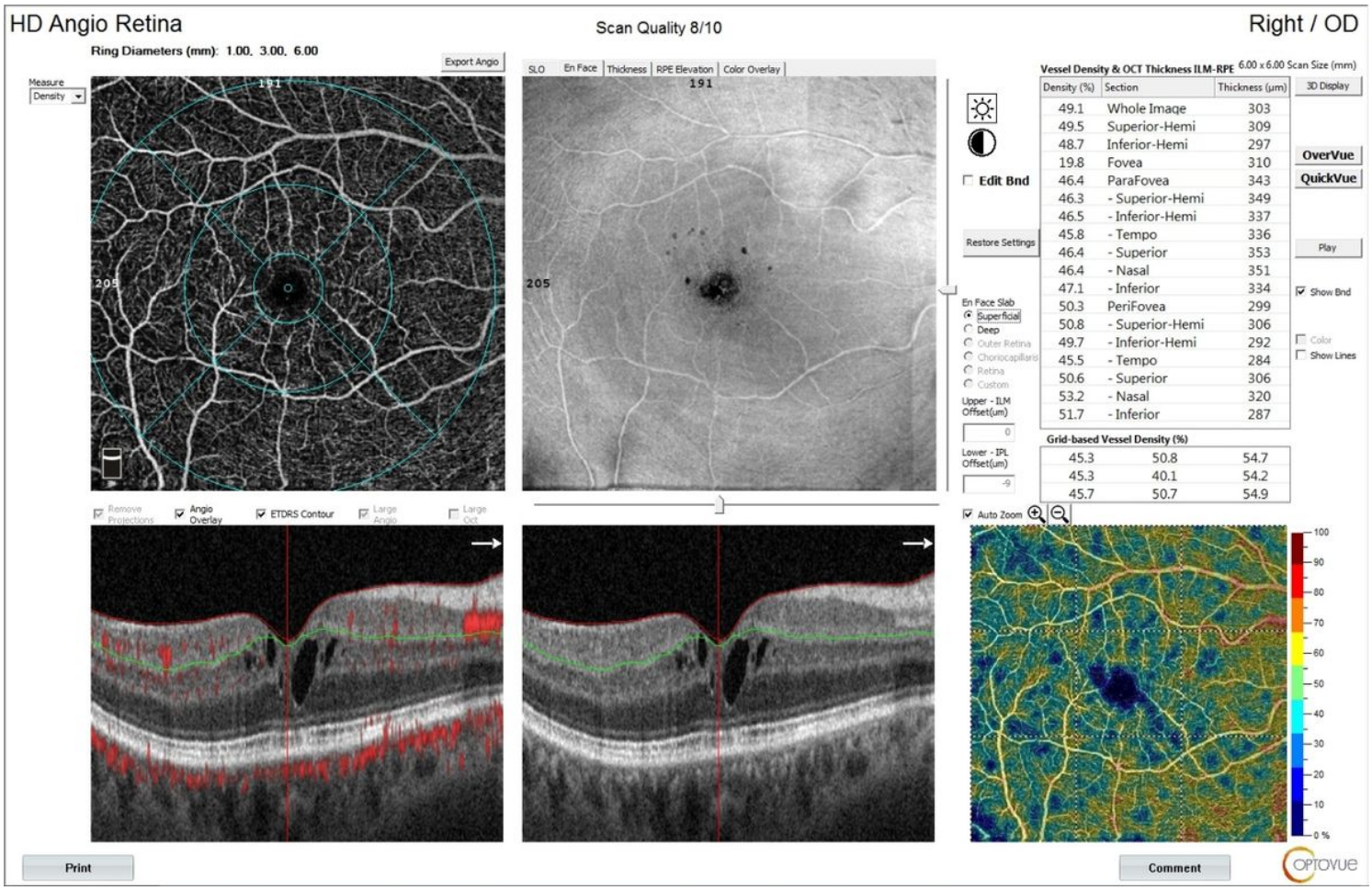

Figure 2

Vascular structure of superficial layer of retina in the same patient with refractory uveitic macular edema. Note the quantitative data in the table.

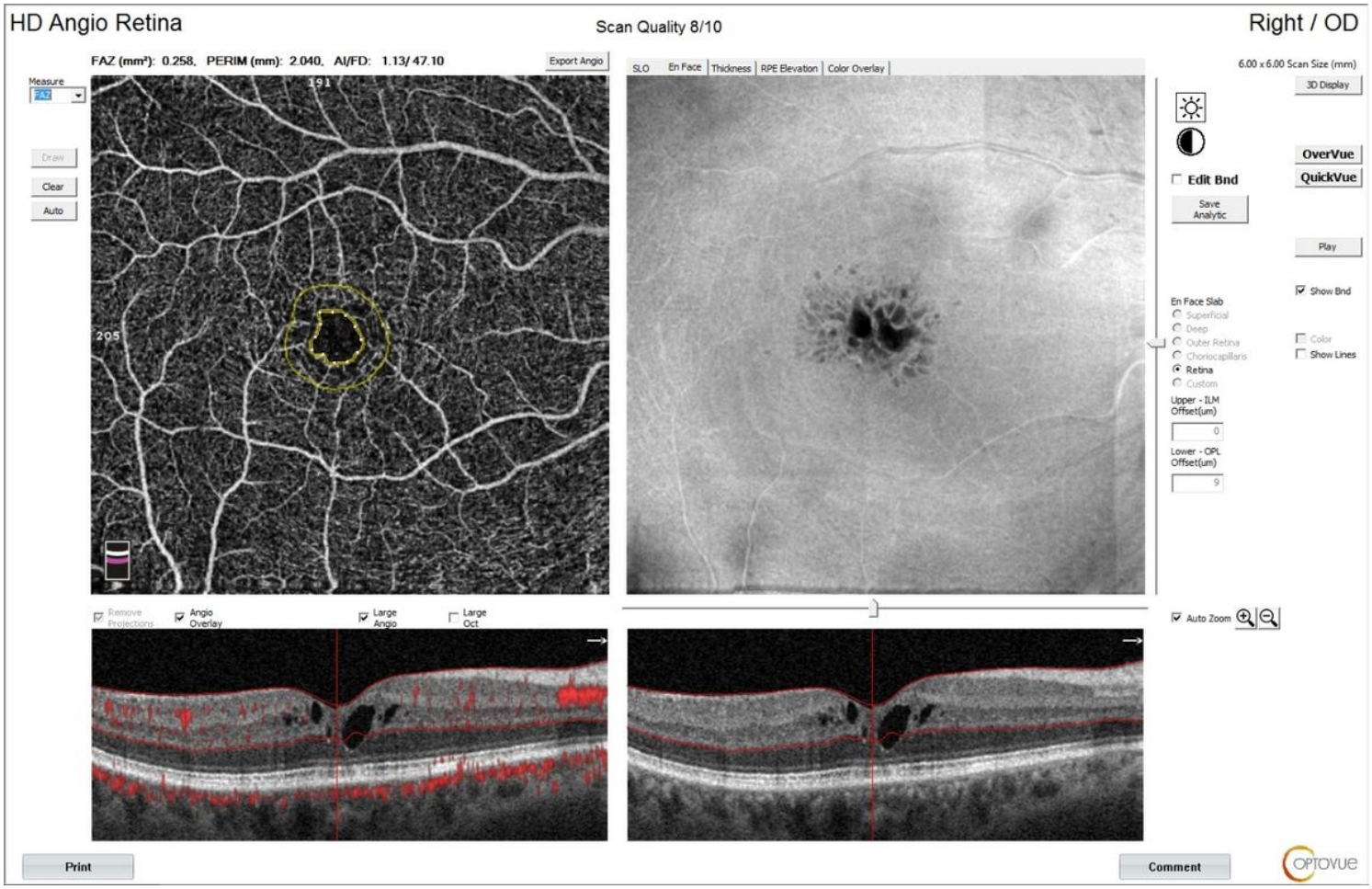

Figure 3

FAZ area in the same patient with refractory uveitic macular edema