

# Accepted Manuscript



Drusen-like Deposits in Young Adults Diagnosed with Systemic Lupus Erythematosus

Alessandro Invernizzi, MD, Laura dell'Arti, MD, Gaia Leone, MD, Daniela Galimberti, MD, Elena Garoli, MD, Gabriella Moroni, MD, Alessandro Santaniello, MD, Aniruddha Agarwal, MD, Francesco Viola, MD

PII: S0002-9394(16)30589-X

DOI: [10.1016/j.ajo.2016.11.014](https://doi.org/10.1016/j.ajo.2016.11.014)

Reference: AJOPHT 9962

To appear in: *American Journal of Ophthalmology*

Received Date: 7 September 2016

Revised Date: 23 November 2016

Accepted Date: 23 November 2016

Please cite this article as: Invernizzi A, dell'Arti L, Leone G, Galimberti D, Garoli E, Moroni G, Santaniello A, Agarwal A, Viola F, Drusen-like Deposits in Young Adults Diagnosed with Systemic Lupus Erythematosus, *American Journal of Ophthalmology* (2017), doi: 10.1016/j.ajo.2016.11.014.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Abstract**

**Purpose:** To determine the prevalence of drusen-like deposits (DLDs) and choroidal changes in patients with Systemic Lupus Erythematosus (SLE), with or without glomerulonephritis. To correlate ocular findings with systemic features.

**Design:** Case-control study

**Methods:** Sixty patients with SLE (18-55 years; 30 with and 30 without SLE-related glomerulonephritis) and 60 age and gender matched healthy controls were enrolled. All patients underwent non-invasive, multimodal imaging that included fundus photography, near-infrared reflectance, blue autofluorescence, blue reflectance, and spectral-domain optical coherence tomography (SD-OCT). Images were analyzed for the prevalence of DLDs. Distribution, size, and number of DLDs were measured. Correlations between ocular findings and systemic features were analyzed. Subfoveal choroidal thickness (SCT) was measured using the SD-OCT.

**Results:** Drusen-like deposits were detected in 40% of SLE subjects and 3.33% of controls ( $P<0.0001$ ). Compared to other techniques, SD-OCT detected the largest number of affected subjects. In eyes with DLDs, small, medium, and large lesions were found in 75%, 50%, and 42% of cases, respectively. Drusen-like deposits were located in the nasal, temporal, inferior, superior, and central regions of the posterior pole in 83%, 75%, 67%, 54%, and 25% eyes, respectively. The prevalence of DLDs in patients with SLE were similar regardless of renal involvement, but patients with glomerulonephritis had more DLDs/eye, larger deposits, and DLDs in >3 quadrants ( $P<0.001$ ,  $P=0.03$ ,  $P=0.009$ , respectively). Subfoveal choroidal thickness was greater in patients with SLE ( $P=0.002$ ).

**Conclusions:** Drusen-like deposits in patients with SLE were independent of renal disease and were best detected with SD-OCT. Lupus-related glomerulonephritis was associated with more fundus abnormalities and a screening SD-OCT should be considered in all patients with SLE. Drusen like deposits in the absence of glomerulonephritis may support the recent proposal that complement alteration is the primary cause for these lesions.

**Title:** Drusen-like Deposits in Young Adults Diagnosed with Systemic Lupus Erythematosus

**Authors:** Alessandro Invernizzi, MD<sup>1-2</sup>, Laura dell'Arti, MD<sup>2</sup>, Gaia Leone, MD<sup>2</sup>, Daniela Galimberti, MD<sup>2</sup>, Elena Garoli, MD<sup>2</sup>, Gabriella Moroni, MD<sup>3</sup>, Alessandro Santaniello, MD<sup>4</sup>, Aniruddha Agarwal, MD,<sup>5</sup> Francesco Viola, MD<sup>2</sup>

1. Eye Clinic, Department of Biomedical and Clinical Science "Luigi Sacco", Luigi Sacco Hospital, University of Milan, Milan, Italy
2. Department of Clinical Sciences and Community Health, University of Milan, Ophthalmological Unit, IRCCS-Cà Granda Foundation – Ospedale Maggiore Policlinico, Via F. Sforza 35, Milan 20122, Italy
3. Department of Clinical Sciences and Community Health, University of Milan, Nephrology Unit, IRCCS-Cà Granda Foundation – Ospedale Maggiore Policlinico, Via F. Sforza 35, Milan 20122, Italy
4. Department of Clinical Sciences and Community Health, University of Milan, Immunological Unit, IRCCS-Cà Granda Foundation – Ospedale Maggiore Policlinico, Via F. Sforza 35, Milan 20122, Italy
5. Advanced Eye Center, Postgraduate Institute of Medical Education and Research, Chandigarh, India

**Running head:** Drusen-like deposits in Systemic Lupus Erythematosus

**Corresponding Author/Address for Reprints:**

Alessandro Invernizzi, MD  
Eye Clinic, Department of Biomedical and Clinical Science "Luigi Sacco",  
Luigi Sacco Hospital, University of Milan  
Via G. B. Grassi 74, 20157 Milano  
Italy  
**Phone:** +39 (02) 39042901  
**Email:** [alessandro.invernizzi@gmail.com](mailto:alessandro.invernizzi@gmail.com)

**Keywords:** drusen, systemic lupus erythematosus, eye, nephritis, retina, optical coherence tomography, SLE

## Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by loss of immune tolerance against nuclear antigens, polyclonal autoantibody production, immune complex deposition, multi-organ damage, and a relapsing/remitting clinical course.<sup>1</sup> As with most autoimmune diseases, there are no specific clinical or laboratory tests to confirm the diagnosis of SLE. Instead, the diagnosis of SLE is based on the presence of at least 4 of the 11 criteria described by the American Rheumatologists Association (ARA).<sup>2</sup> The ARA criteria consist of a number of SLE-related organ disorders such as skin rash, arthritis, nephritis and immune dysfunction.

Although not mentioned in the ARA list, ophthalmologic involvement can occur in 2% to 30% of patients with SLE. Several ocular tissues can be involved, but the retinal vessels are most commonly affected.<sup>3</sup> Early manifestations of retinopathy, such as small intraretinal hemorrhages and cotton wool spots, usually occur prior to the onset of ocular symptoms.<sup>4</sup> Detecting these abnormalities on fundus examination can identify patients at high risk for more advanced disease.<sup>5</sup>

A number of asymptomatic funduscopic changes have been reported to be possible markers for disease activity. Baglio et al. found choroidal alterations and drusen-like deposits (DLDs) on indocyanine green angiography (ICGA) in a small cohort of patients affected by SLE glomerulonephritis. They suggested a possible correlation between these ocular findings and renal involvement.<sup>6</sup> The absence of large confirmatory studies, and the invasive nature and high costs of ICGA may contribute to the rarity of these findings.

During the past few years, non-invasive imaging techniques, particularly fundus autofluorescence (FAF) and spectral domain optical coherence tomography (SD-OCT), have become the gold standards for the detection and characterization of drusen and DLDs both in ocular and systemic conditions.<sup>7-10</sup> The introduction of enhanced-depth imaging (EDI) has improved visualization of the choroid on SD-OCT and enables non-invasive assessment of choroidal structures and measurement of thickness in several diseases including SLE.<sup>11</sup>

The aim of this index study was to assess the prevalence of DLDs and choroidal changes in patients with SLE (with or without renal involvement) using various non-invasive imaging techniques, and to compare them to age and gender-matched healthy controls. Correlation between the ocular findings and the systemic status of the patients, including the ARA criteria, treatment, and the renal involvement, was also determined.

## Methods

In this cross-section, case-control study, sixty patients with SLE that were being treated in the Immunology/Nephrology Unit of the IRCCS-Cà Granda Foundation – Ospedale Maggiore Policlinico, Milan, Italy, and sixty age and gender-matched healthy controls were enrolled. Institutional Review Board approval was obtained and the study adhered to the tenets of the Declaration

of Helsinki. Written informed consent was obtained from all the subjects prior to enrollment in the study.

#### *Inclusion Criteria*

The diagnosis of SLE was based on the presence of at least 4 of the 11 ARA criteria. Among the 60 patients with SLE (cases), 30 had biopsy-proven, SLE-related glomerulonephritis and the remaining 30 had SLE without renal involvement. The American College of Rheumatology (ACR) criteria for glomerulonephritis - detection of persistent proteinuria  $>0.5$  gm/day or  $> 3+$  by dipstick, and/or cellular casts including red cells, hemoglobin, granular, tubular or mixed<sup>12</sup> - were used to rule out renal disease.

Patients with refractive errors less than spherical equivalent of  $\pm 3$  diopters were included in the study. Age-matched control subjects had no known ocular or systemic diseases.

#### *Exclusion Criteria*

Patients with one or more of the following conditions were excluded: history of previous or ongoing ocular or systemic disease known to cause changes in the retina or the choroid other than SLE; history of previously diagnosed SLE-related retinopathy (i.e. small intraretinal hemorrhages and cotton wool spots); media opacities that prevent the acquisition of images that are adequate for analysis; and inability to understand or sign the informed consent. Patients older than 55 years were excluded to avoid the presence of age-related drusen.

#### *Study Procedures*

All patients enrolled into the study underwent complete ocular examinations, including best correct visual acuity (BCVA), anterior segment slit lamp examination, applanation Goldmann tonometry, and a slit lamp funduscopy exam. Non-invasive, multi-imaging studies of the fundus, including color fundus photography (FP) (Canon CR1 Mark II, Canon Inc., Tokyo, Japan), near infrared reflectance (NIR), blue autofluorescence (BAF), blue reflectance (BR), and SD-OCT (Heidelberg Spectralis<sup>®</sup>, Heidelberg Engineering, Heidelberg, Germany) were performed in both eyes. Near infrared reflectance, BAF, and BR images of the 30 central degrees of the retina with a mean ART<sup>®</sup> of 100 frames were obtained after adequate pupillary dilation (tropicamide 1%). The SD-OCT scan pattern consisted of a dense volume ( $30 \times 25^\circ$ ) with a mean ART<sup>®</sup> of 25 frames, 2 single line scans (horizontal and vertical) with a mean ART<sup>®</sup> of 100 frames passing through the fovea, and EDI.

#### *Image Analyses*

One eye of each patient was randomly selected for further analysis. Image analyses were divided into two consecutive steps. In the first part of the analyses, the prevalence of DLDs were determined to establish which

imaging modality had the highest detection sensitivity. The complete set of images from each eye was independently analyzed by two trained graders (A.I. and L.dA.). In cases of disagreement between the two graders, a third grader (F.V.) was asked to adjudicate. When  $\geq 1$  DLDs were detected by at least one imaging modality, the subject was considered to be *positive* for the presence of DLDs and was selected for further analysis. When DLDs were detected in one eye, the contralateral eye was evaluated to determine bilateral involvement.

For each imaging modality, the detection sensitivity for DLDs was calculated by considering multimodal imaging as the *gold standard* (i.e. the number of patients positive for DLDs by each technique was compared to the total number of patients positive for DLDs by multimodal imaging).

Since SD-OCT was the most sensitive technique for detecting DLDs, the second part of the analysis was performed to characterize DLDs on SD-OCT. The scanned area of the posterior pole was divided into 5 smaller areas of interest, superior, temporal, inferior, and nasal zones that were bounded by the intermediate and external rings of the ETDRS grid, and a central zone within the inner ETDRS ring. Each B-scan of the SD-OCT was analyzed to assess the size, location, and number of DLDs. Drusen like deposits were classified into 3 different categories according to their size: small ( $< 50 \mu\text{m}$ ); medium (from 50 to  $100 \mu\text{m}$ ); and large ( $\geq 100 \mu\text{m}$ ). The lesion size was determined with the embedded caliper function by drawing a single line segment parallel to the Bruch's membrane that passed within the elevation of the retinal pigment epithelium (Figure 1).

Subfoveal choroidal thickness was measured with the embedded caliper function by drawing a vertical line segment on the vertical and horizontal EDI-OCT scans through the fovea and calculating a mean value. Two independent graders each measured the subfoveal choroidal thickness twice.

### *Statistical Analysis*

Sensitivities of the different imaging techniques were determined to identify the most suitable technique to detect and characterize DLDs. The Chi Square test was used to compare the prevalence of DLDs in cases and controls. Fisher's Exact test was used to compare patients affected by SLE-related glomerulonephritis and patients without glomerulonephritis for the presence of DLDs, regardless of their size. In eyes where alterations were identified, descriptive statistics were used to represent the distribution of the lesions in the different areas of the posterior pole. Fisher's Exact test was also used to determine whether the number of posterior pole quadrants affected by DLDs and the prevalence of small, medium and large DLDs differed between patients with and without glomerulonephritis.

Given the non-normal distribution of DLDs in the studied population and the small sample size, a Kolmogorov-Smirnov non-parametric test was used to compare the absolute number of DLDs found in eyes from patients with and without glomerulonephritis. A Generalized Linear model (GLM) was used to



correlate the presence of DLDs with systemic features of the patients with SLE, including ARA criteria, complement C3 and C4 depletion (detected at least once in the patient's clinical history), age of disease onset, and disease duration. The Intra-class Correlation Coefficient (ICC) was used to assess inter-observer agreement of choroidal measurements. The Student's t-test was used to compare subfoveal choroidal thickness.

## Results

The mean age of the patients was  $42 \pm 9$  years (range: 19 – 55 years) and 59/60 patients were females. Detailed clinical histories of the patients, including the prevalence of ARA criteria, age of disease onset, duration of disease, C3/C4 levels, and the ongoing treatment at the time of the study are reported in Table 1.

Drusen like deposits were detected by multimodal imaging in 40% (24/60) of patients with SLE and in 3.33% (2/60) of healthy controls ( $P < 0.0001$ ). In patients with DLDs, 70.83% (17/24) of them had bilateral involvement, resulting in bilateral DLDs in 28.33% (17/60) of the entire SLE cohort. None of the controls had bilateral DLDs ( $P = 0.0001$ ). A detailed comparison of ocular findings between cases and controls is reported in Table 2.

The graders were able to detect DLDs with SD-OCT in all the affected patients (100% sensitivity; 24/24 eyes). The sensitivity of the other imaging techniques was lower: NIR, 62% (15/24); FAF, 46% (11/24); FP, 46% (11/24), and BR, 21% (5/24). Multimodal imaging sets from a representative patient with DLDs is shown in Figure 2. On SD-OCT, small DLDs were the most common alteration in patients with SLE (75%; 18/24). Medium DLDs were present in 50% (12/24) of patients and large DLDs were found in 42% (10/24).

All DLDs were located between the retinal pigment epithelium (RPE) and Bruch's membrane. Their appearance ranged from hypo-reflective dots that wrinkled the overlying RPE (small lesions), to distinct hypo-reflective dome-shaped lesions that detached the RPE from the underlying Bruch's membrane (large lesions) (Figure 3).

Drusen like deposits were variably distributed throughout the posterior pole. Nasal and temporal quadrants were the most commonly involved areas (83% (20/24) and 75% (18/24) of the patients with DLDs, respectively); inferior and superior areas were affected in 67% (16/24) and 54% (13/24), respectively. Central macular involvement was found in 25% of patients (6/24) (Figure 4). Similar numbers of patients with and without glomerulonephritis had DLDs (40% (12/30) of eyes in both groups). The total number of DLDs per affected eye, however, was significantly higher in patients with renal disease ( $P = 0.001$ ). Among patients with SLE-related glomerulonephritis, DLDs were more widely distributed (involving more than 3 posterior pole quadrants) compared to SLE patients without renal disease ( $P = 0.009$ ). No significant differences in the prevalence of small or medium DLDs were observed when comparing SLE patients with and without renal involvement. The number of

subjects with large DLDs, however, was significantly higher in patients with glomerulonephritis ( $P=0.03$ ). Ocular findings among SLE patients with and without renal involvement are compared in Table 3.

Good agreement regarding the measurement of subfoveal choroidal thickness ( $ICC=0.92$ ) was seen between the two graders. The mean subfoveal choroidal thickness (SCT) was significantly greater in patients with SLE ( $362.7 \pm 142.2 \mu\text{m}$ ) compared to controls ( $296.5 \pm 83.4 \mu\text{m}$ ) ( $P=0.002$ ). No significant differences were found between the choroidal thickness of SLE patients with or without glomerulonephritis (Table 2 and 3). No significant differences were found in the SCT of SLE patients treated with systemic corticosteroids at the time of the study ( $355 \pm 147.6 \mu\text{m}$ ) compared to those not receiving steroids ( $383.9 \pm 128.1 \mu\text{m}$ ;  $P=0.49$ ). Five percent of patients affected by SLE (3/60) showed signs of a chronic retinal pigment epitheliopathy (small serous RPE detachments, shallow subretinal fluid pockets), but none were seen in controls. No significant correlations were found between the presence of DLDs and any of the ARA criteria, C3-C4 depletion, disease duration, age of onset, and method of treatment (all  $P>0.05$ ).

## Discussion

Non-invasive multimodal imaging of the fundus demonstrated the presence of DLDs in a significantly higher percentage of young adults affected by SLE compared to healthy controls. These had been previously identified with fluorescein and ICG angiography in a small group of patients affected by SLE-related glomerulonephritis<sup>6</sup> but not in patients who did not have glomerulonephritis. The authors concluded that DLDs occur only in SLE patients with kidney disease and may be a sign of renal involvement.

To the best of our knowledge, ours represents the first report of DLDs in young SLE patients without kidney involvement. According to the results of our study, patients without renal disease that had been previously reported to show no ocular alterations,<sup>6</sup> are actually affected by smaller and less numerous DLDs compared to the patients with renal involvement. Newer imaging techniques with higher resolutions than FA and ICGA are able to detect these microscopic alterations. Detailed tomographic scanning of each retinal layer with SD-OCT enables identification of RPE alterations that could not be detected previously (Figure 5). This is consistent with previous reports in the literature.<sup>13</sup> The presence of DLDs in patients with glomerulonephritis, either related to SLE<sup>6</sup> or another etiology,<sup>10,14</sup> is thought to be related to the anatomical similarities between the glomerulus and the choriocapillaris/Bruch's membrane/retinal pigment epithelium complex.<sup>15</sup>

Detection of DLDs in similar proportions of patients with and without nephritis, however, calls for a more detailed explanation. Several histopathological investigations have demonstrated the presence of complement components in age-related drusen as well as in glomerulonephritis-associated DLDs.<sup>16-18</sup> The same authors suggest a possible role of complement activation/deposition or complement pathway abnormalities in the formation of drusen and DLDs.



Since complement activation and depletion is a hallmark of SLE disease, even in the absence of clinically detectable renal involvement, complement factors could play a major role in the development of DLDs in SLE patients. Low CH50 and C3 levels have been associated with histopathologically proven, but clinically undetectable, glomerulonephritis in patients with SLE, an entity called Silent Lupus Nephritis.<sup>19</sup> Such patients may resemble the subset of patients with DLDs but without clinically relevant renal disease in our population.

These reports, together with our results, suggest that SLE-related complement abnormalities are a risk factor for DLDs. Clinically detectable renal involvement may only be an adjunctive risk factor, or a concomitant SLE manifestation, for a more aggressive ocular disease that is characterized by numerous, large, widely spread lesions.

Our study found a peculiar distribution of DLDs throughout the posterior pole in SLE patients. Topographic analysis showed foveal sparing, with only a quarter of the DLDs found within the central ETDRS subfield. This ring-shaped distribution differs from the centripetal distribution usually found with typical age-related drusen.<sup>20</sup> This suggests that drusen and DLDs may be due to different underlying mechanisms. Age-related drusen develop because Bruch's membrane thickens due to lipid and protein accumulation.<sup>21</sup> This aging process does not spare the center of the macula and frequently leads to subfoveal lesions.

If deposition of blood-born complement factors constitutes the primary mechanism of DLD development, their disposition could be highly influenced by flow within the choriocapillaris.<sup>22</sup> Filling of the choriocapillaris begins in the macula and progresses radially towards the periphery in a wavelike manner.<sup>23</sup> This centripetal blood flow pattern may be responsible for the peculiar perifoveal distribution of the lesions and the relative sparing of the central high-flow region. Further studies are needed to completely explain the distribution of DLDs.

Subfoveal choroidal thickness was greater in our SLE patients than in controls, which differs from the findings of Altinkaynak et al.<sup>11</sup> More than sixty percent of our SLE patients were receiving systemic corticosteroids at the time of the study. Drug-induced choroidal thickening, as it occurs in patients with central serous chorioretinopathy taking corticosteroids,<sup>24,25</sup> seems unlikely in our cases since there was no significant difference in SCT between treated and untreated SLE patients. Considering the well-known relationship between choroidal thickness and systemic inflammatory conditions, a low grade, subclinical inflammation could be considered responsible for the choroidal thickening.<sup>26</sup> Despite the theory that complement activation contributes to the formation of DLDs, we did not find a correlation between any of the ARA criteria (apart from the kidney involvement) or a history of complement depletion, and the presence of DLDs in our subjects. This may be due to the systemic indicators that we chose to evaluate the disease activity and level of complement depletion in our study. For example, clinical features including C3

and C4 depletion were graded in a binary manner only (i.e. present/absent), with no consideration for the duration of the changes, the nature of the measurement, or of the alteration itself. This may constitute a limitation of our study.

Other limitations of the study include a limited sample size and the absence of immune-histochemical data related to the complement deposition found in the renal biopsies. The identification of complement factors in the glomeruli may strongly correlate with the presence of DLDs as suggested by recent studies.<sup>18</sup> We also did not perform genetic studies in our patients, so we could not determine the presence of AMD-related polymorphisms<sup>27</sup> that could be correlated with the development of DLDs. Finally, only those lesions located in the central area of the retina (ETDRS grid) were included as 30° SD-OCT scans were used for the analyses. Since wide-field OCT was not available at the time of this study, lesions outside the posterior pole could not be assessed. Involvement of the macula is of primary interest to clinicians, but analyses of the mid-peripheral retina could provide valuable and clinically meaningful information for both nephrologists and ophthalmologists.

In conclusion, our findings offer a novel insight into the effects of SLE on the retina and choroid. Until a correlation between systemic SLE features and DLDs is identified, not only patients with renal involvement but all SLE patients should be considered at risk for DLDs. The correlation between SLE-related DLDs and the development of complications such as choroidal neovascularization or RPE atrophy has not been established. In other conditions, it has been suggested that similar lesions may increase the chances of developing sight-threatening complications.<sup>28,29</sup> Systematic screening of the fundus with non-invasive, high-resolution imaging techniques such as SD-OCT should be considered to detect DLDs in patient with SLE. Additional studies that focus on complement abnormalities and genetics in SLE patients are needed to confirm and expand upon our results. Additional data might determine if a correlation exists between worsening of DLDs and renal involvement, and if a link exists between SLE and AMD.

#### **Acknowledgments/Disclosure**

**Founding Support:** None

**Financial Disclosures:** No financial disclosures.

## References

1. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011; 365(22):2110-21.
2. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25:1271-7.
3. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. *Autoimmune Dis*. 2012;2012:290898.
4. Ushiyama O, Ushiyama K, Koarada S, et al. Retinal disease in patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2000; 59(9):705-8.
5. Stafford-Brady FJ, Urowitz MB, Gladman DD, Easterbrook M. Lupus retinopathy. Patterns, associations, and prognosis. *Arthritis Rheum*. 1988; 31(9):1105-10.
6. Baglio V, Gharbiya M, Balacco-Gabrieli C, et al. Choroidopathy in patients with systemic lupus erythematosus with or without nephropathy. *J Nephrol*. 2011;24(4):522-9.
7. Kanagasingam Y, Bhuiyan A, Abràmoff MD, et al. Progress on retinal image analysis for age related macular degeneration. *Prog Retin Eye Res*. 2014;38:20-42.
8. Yi K, Mujat M, Park BH, et al. Spectral domain optical coherence tomography for quantitative evaluation of drusen and associated structural changes in non-neovascular age-related macular degeneration. *Br J Ophthalmol*. 2009;93(2):176-81.
9. Adhi M, Read SP, Liu JJ, et al. High-speed ultrahigh-resolution OCT of Bruch's membrane in membranoproliferative glomerulonephritis type 2. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45(6):614-7.
10. Lally DR, Baumal C. Subretinal drusenoid deposits associated with complement-mediated IgA nephropathy. *JAMA Ophthalmol*. 2014;132(6):775-7.

11. Altinkaynak H, Duru N, Uysal BS, et al. Choroidal Thickness in Patients with Systemic Lupus Erythematosus Analyzed by Spectral-domain Optical Coherence Tomography. *Ocul Immunol Inflamm*. 2015;1-7.
12. Hahn BH, McMahon M, Wilkinson A, et al. American College of Rheumatology Guidelines for Screening, Case Definition, Treatment and Management of Lupus Nephritis. *Arthritis care & research*. 2012;64(6):797-808.
13. Schlanitz FG, Ahlers C, Sacu S, et al. Performance of drusen detection by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2010;51(12):6715-21.
14. D'souza Y, Short CD, McLeod D, Bonshek RE. Long-term follow-up of drusen-like lesions in patients with type II mesangiocapillary glomerulonephritis. *Br J Ophthalmol*. 2008;92(7):950-3.
15. Duvall J, Tso MO. Cellular mechanisms of resolution of drusen after laser coagulation. An experimental study. *Arch Ophthalmol*. 1985;103(5):694-703.
16. Mullins RF, Aptsiauri N, Hageman GS. Structure and composition of drusen associated with glomerulonephritis: implications for the role of complement activation in drusen biogenesis. *Eye* 2001;15(Pt 3):390-5.
17. Savige J, Amos L, Ierino F, et al. Retinal disease in the C3 glomerulopathies and the risk of impaired vision. *Ophthalmic Genet*. 2016:1-8.
18. Dalvin LA, Fervenza FC, Sethi S, Pulido JS. Shedding light on fundus drusen associated with membranoproliferative glomerulonephritis: breaking stereotypes of types I, II, and III. *Retin Cases Brief Rep*. 2016;10(1):72-8.
19. Ishizaki J, Saito K, Nawata M, et al. Low complements and high titre of anti-Sm antibody as predictors of histopathologically proven silent lupus nephritis without abnormal urinalysis in patients with systemic lupus erythematosus. *Rheumatology* 2015;54(3):405-12.
20. Farsiu S, Chiu SJ, O'Connell RV, et al; Quantitative classification of eyes with and without intermediate age-related macular degeneration using optical coherence tomography. *Ophthalmology*. 2014;121(1):162-72.

21. Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. *Invest Ophthalmol Vis Sci.* 2013;54(14):ORSF68-80.
22. Hayreh SS. Vascular pattern of the choriocapillaris. *Exp Eye Res.* 1974;19(1):101-4.
23. Flower RW. Extraction of choriocapillaris hemodynamic data from ICG fluorescence angiograms. *Invest Ophthalmol Vis Sci.* 1993;34(9):2720-9.
24. Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis. *Prog Retin Eye Res.* 2015;48:82-118.
25. Yang L, Jonas JB, Wei W. Optical coherence tomography-assisted enhanced depth imaging of central serous chorioretinopathy. *Invest Ophthalmol Vis Sci.* 2013;54(7):4659-65.
26. Ersan I, Kilic S, Arikan S, Kara S, Işik S, Gencer B, Ogretmen Z. Evaluation of Macular Ganglion Cell-inner Plexiform Layer and Choroid in Psoriasis Patients Using Enhanced Depth Imaging Spectral Domain Optical Coherence Tomography. *Ocul Immunol Inflamm.* 2016 Mar 25:1-5. [Epub ahead of print]
27. Hoffman JD, van Grinsven MJ, Li C, Brantley M Jr, McGrath J, Agarwal A, Scott WK, Schwartz SG, Kovach J, Pericak-Vance M, Sanchez CI, Haines JL. Genetic Association Analysis of Drusen Progression. *Invest Ophthalmol Vis Sci.* 2016;57(4):2225-31.
28. Leys A, Vanrenterghem Y, Van Damme B, et al. Fundus changes in membranoproliferative glomerulonephritis type II. A fluorescein angiographic study of 23 patients. *Graefes Arch Clin Exp Ophthalmol.* 1991;229(5):406-10.
29. Leys A, Michielsen B, Leys M, Vanrenterghem Y, Missotten L, Van Damme B. Subretinal neovascular membranes associated with chronic membranoproliferative glomerulonephritis type II. *Graefes Arch Clin Exp Ophthalmol.* 1990;228(6):499-504.

## Figure Legends

### **Figure 1. Drusen-like deposits (DLDs) size assessment technique on spectral-domain optical coherence tomography (SD-OCT) scan.**

Measurement of DLD size is divided into two steps. First, the borders of the retinal pigment epithelium (RPE) detachment (black arrowheads), representing the deposits' lateral boundaries, and Bruch's Membrane (white arrowheads) were identified

(Left). Following this, a linear segment parallel to Bruch's membrane was drawn

between the previously identified RPE borders using the Heyex Eye Explorer® linear caliper measurement tool (Right).

### **Figure 2 Multimodal imaging set in a patient diagnosed with Systemic Lupus Erythematosus (SLE) showing Drusen-like deposits temporal to the fovea.**

In the fundus color pictures (Top-left), DLDs are visible as multiple yellowish lesions of different sizes affecting the temporal region of the posterior pole.

The same area shows a grainy appearance on Blue Autofluorescence (Topmiddle) with the lesions appearing as multiple hypo-fluorescent grains when compared to the surrounding retina. A smaller number of hyper-

reflective dots corresponds to the DLDs on the blue reflectance image (Top Right). On the near infrared reflectance image (Bottom Left), a mix of hyper/hypo reflective changes are visible in the areas affected by DLDs. The

horizontal Spectral Domain Optical Coherence tomography scan (Bottom Right), clearly shows the presence of multiple DLDs that wrinkle the overlying retinal pigment epithelium in the temporal region of the posterior pole. These DLDs spare the fovea.

### **Figure 3. Systemic Lupus Erythematosus (SLE)-related Drusen-like deposits (DLDs) of different sizes as they appear on Spectral Domain Optical Coherence Tomography (SD-OCT) scans.**

An SD-OCT scan shows the presence of different sized DLDs throughout the posterior pole (Top Row) and some of the lesions are visible beneath the fovea. Subfoveal lesions are unusual since central macular involvement was found in only 25% of the subjects affected by DLDs. (Bottom Row) The SD-OCT shows small (Left), medium (Middle) and large (Right) DLDs, which correspond to  $<50 \mu\text{m}$ ,  $50 \text{ to } 100 \mu\text{m}$ , and  $\geq 100 \mu\text{m}$  lesions according to the proposed classification.

### **Figure 4. Drusen-like deposits (DLDs) distribution across the posterior pole in patients affected by Systemic Lupus Erythematosus (SLE).**

The percentage of eyes with DLDs in each quadrant is reported. Regions outside the fovea correspond to the intermediate and the external quadrants of the ETDRS grid, whereas the central region is represented by the foveal ETDRS sector. A ring shaped localization of the lesions is clearly visible along with partial foveal sparing.

### **Figure 5. Multimodal Imaging set showing Drusen-like deposits (DLDs) affecting both eyes in a patient diagnosed with Systemic Lupus Erythematosus (SLE).**



In the color fundus photos (Top/Third Row, left column), DLDs are seen as multiple yellowish lesions of different sizes spread across the posterior pole, but mainly located in the temporal region. DLDs appear hyper-autofluorescent on blue autofluorescence (Top/Third Row, Central column). A mix of hyper/hypo reflective granular changes are visible on blue reflectance (Top/Third row, right column) and near infrared reflectance (Second/Bottom row, left column). Spectral-domain optical coherence tomography (SD-OCT) scans encompass the fovea, whose location is represented by green arrows on near infrared reflectance Images, clearly show a sparing of the foveal region with the DLDs mainly located in the temporal region. Inferior scans performed along the black arrows, demonstrate several small DLDs (white arrowheads) that wrinkle the overlying retinal pigment epithelium, but are barely visible with the other imaging modalities (Second and Bottom row).

**Table 1. Clinical Features of patients with systemic lupus erythematosus**

<b>Age (years) *</b>	42.43 ± 9.07	(19-55)
<b>Sex (M:F)</b>	1:59	
<b>Disease onset age (years) *</b>	25.06 ± 8.68	(10-48)
<b>Disease Duration (years) *</b>	17.48 ± 9.10	(1-33)
<b>ARA Criteria<sup>#</sup></b>		
1 – Malar Rash	50%	(30/60)
2 – Discoid Rash	18.33%	(11/60)
3 – Photosensitivity	51.66%	(31/60)
4 – Oral ulcers	5%	(5/60)
5 – Arthritis	58.33%	(35/60)
6 – Serositis	8.33%	(5/60)
7 – Renal disorder	50%	(30/60)
8 – Neurologic disorder	5%	(3/60)
9 – Hematologic disorder	56.66%	(34/60)
10 – ANA positivity	96.66%	(58/60)
11a – Anti DNA Ab	95%	(57/60)
11b – Anti ENA Ab	61.66%	(37/60)
<b>C3<sup>#</sup></b>	85%	(51/60)
<b>C4<sup>#</sup></b>	76.66%	(46/60)
<b>Hydroxychloroquine<sup>#</sup></b>	88.33%	(53/60)
Cumulative Dose (g) *	728.09 ± 696.50	(0-2920)
<b>Corticosteroids<sup>#§</sup></b>	63.33%	(38/60)
<b>Immunosuppressive Drugs<sup>#§</sup></b>	60%	(36/60)

ARA=American Reumathologists Association; ANA= Anti-Nucleous Antibody

\* Mean ± SD (range)

# Prevalence: % (number of subjects/n)

§ Therapy at the time the study was performed

Table 2. Ocular findings in patients with systemic lupus erythematosus compared to age- and gender-matched controls

	<b>SLE patients</b>	<b>Controls</b>	<b>P Value</b>
<b>Subjects with DLDs</b>	40% (24/60)	3.33% (2/60)	<b>p&lt;0.0001</b>
<b>Bilateral DLDs</b>	28.33% (17/60)	0/60	<b>p=0.0001</b>
<b>Retinal pigment epitheliopathy</b>	5% (3/60)	0/60	p=0.242
<b>Subfoveal choroidal thickness (mean <math>\pm</math> SD)</b>	362.7 $\pm$ 142.2 $\mu$ m	296.5 $\pm$ 83.4 $\mu$ m	<b>p=0.002</b>

SLE=Systemic Lupus Erythematosus; DLDs=Drusen-like deposits

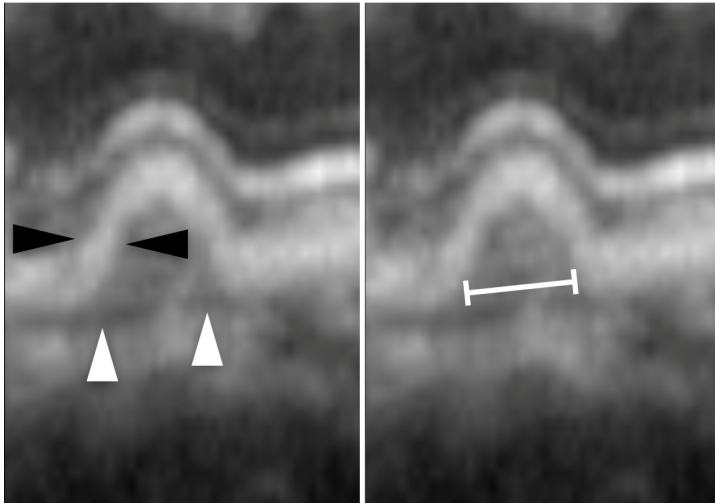
Table 3. Comparison between Drusen-Like Deposits' features in Systemic Lupus Erythematosus patients with and without glomerulonephritis

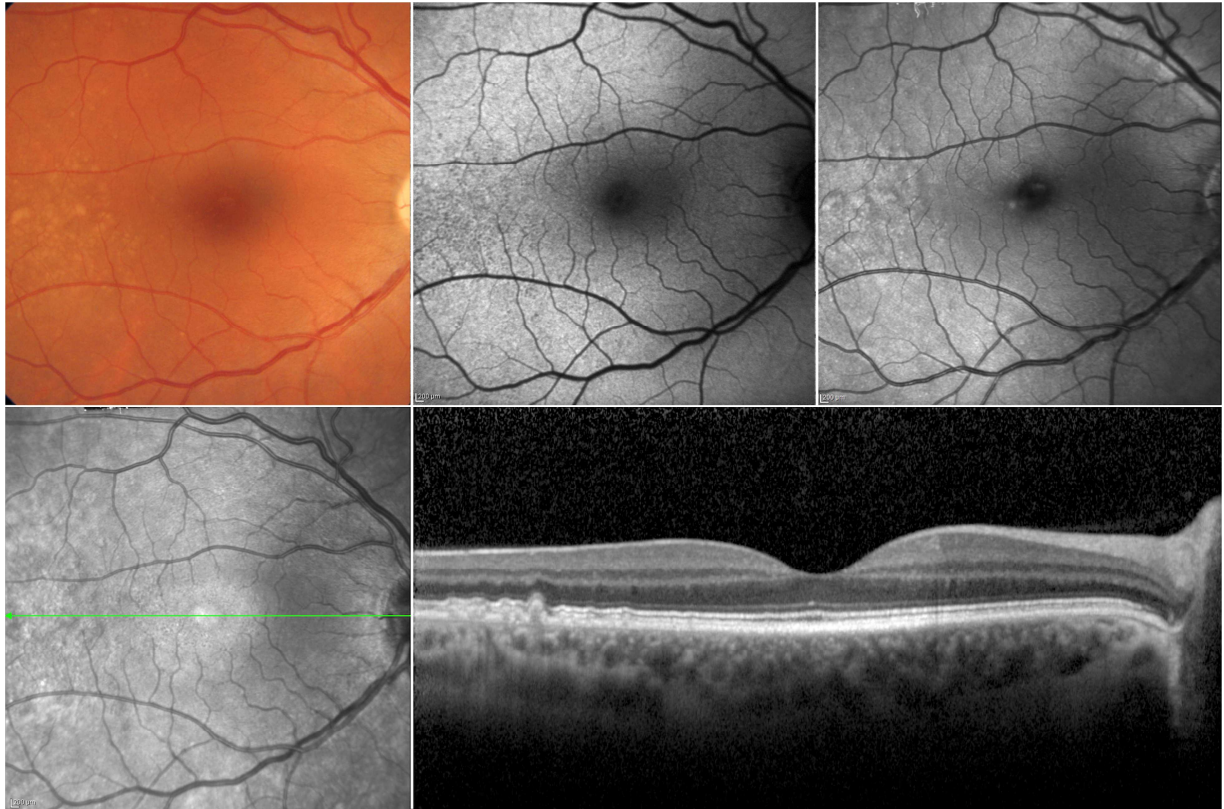
	<b>SLE patients with renal involvement</b>	<b>SLE patients without renal involvement</b>	<b>P Value</b>
<b>Subjects with DLDs<sup>#</sup></b>	12/30	12/30	1
<b>DLDs type*</b>			
- Small Deposits	10/12	8/12	0.640
- Medium Deposits	5/12	7/12	0.684
- Large Deposits	8/12	2/12	<b>0.036</b>
<b>More than 3/5 quadrants involved*</b>	7/12	1/12	<b>0.009</b>
<b>Number of DLDs/eye (median, range)*</b>	9.5 (6-125)	4.5 (1-11)	<b>0.001</b>
<b>Bilateral DLDs<sup>#</sup></b>	8/30	9/30	1
<b>Retinal pigment epitheliopathy<sup>#</sup></b>	0/30	3/30	0.237
<b>Choroidal thickness (mean <math>\pm</math> SD)<sup>#</sup></b>	337.6 $\pm$ 93.2 $\mu$ m	387.8 $\pm$ 176.4 $\mu$ m	0.174

SLE= Systemic Lupus Erythematosus; DLDs=Drusen Like Deposits

<sup>#</sup> Statistics performed on the total SLE population (n=60)

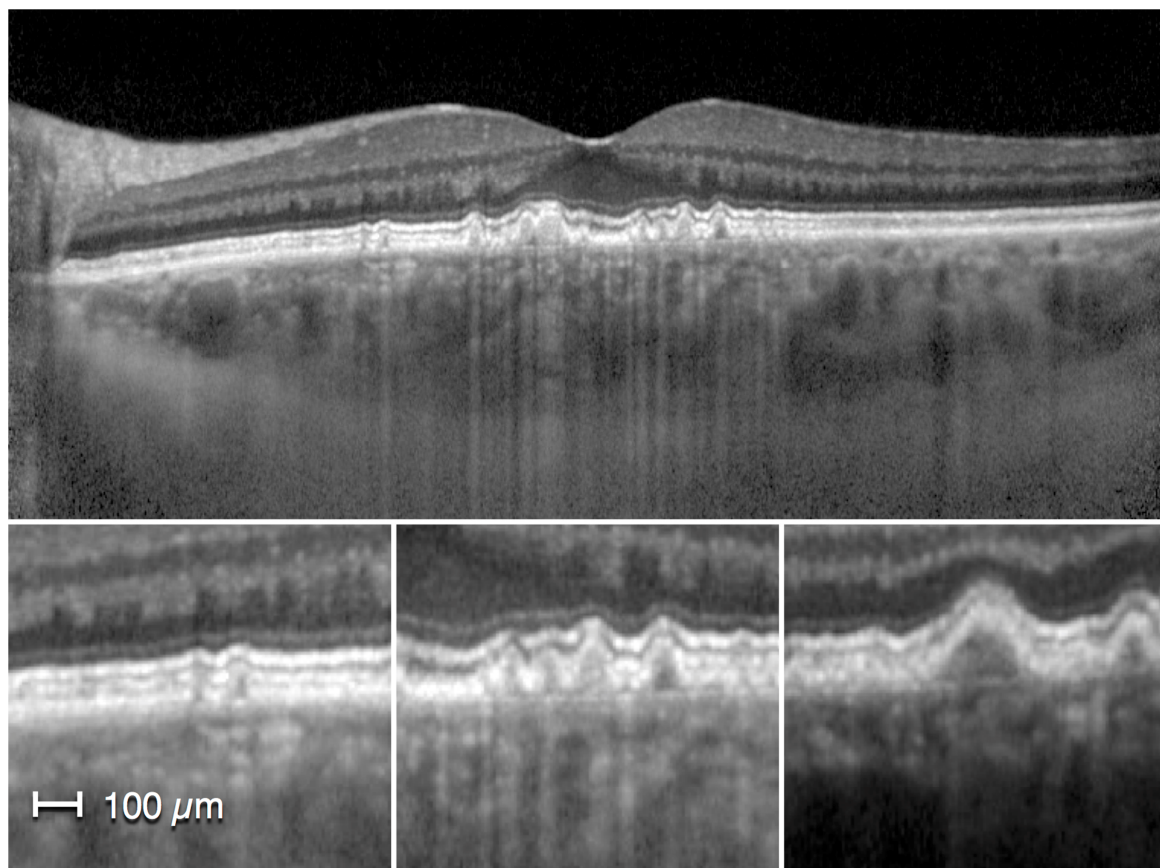
\* Statistics performed on the subset of patients affected by DLDs (n=24)



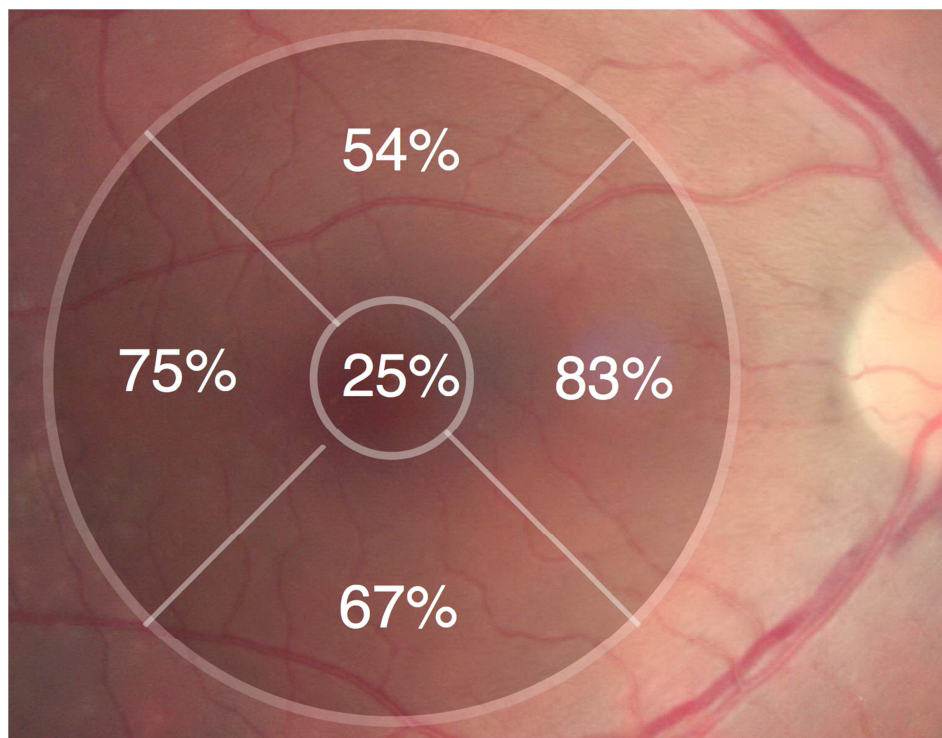


ACCEPTED MANUSCRIPT

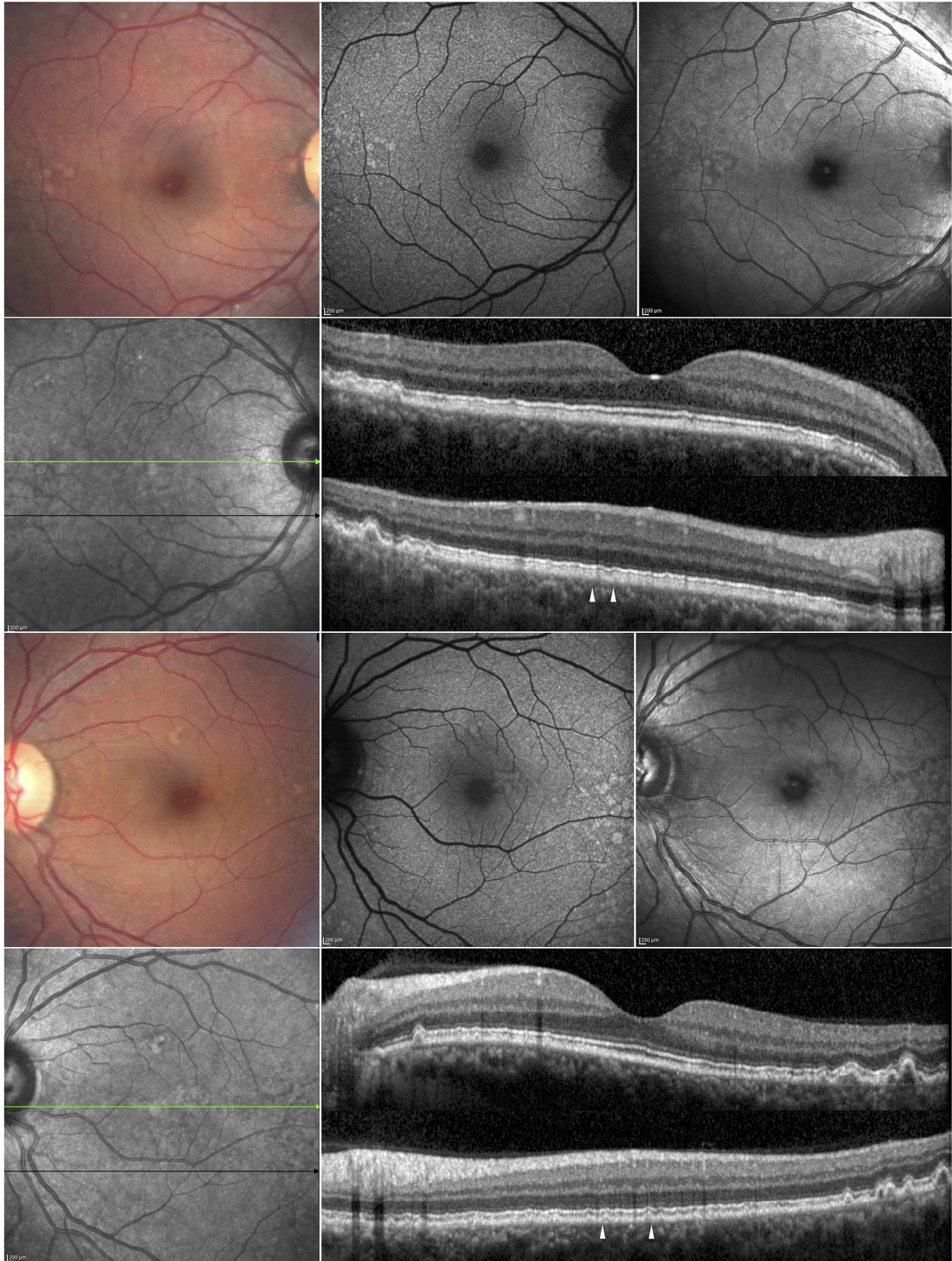




ACCEPTED



ACCEPTED MANUSCRIPT



## Table of Contents

A multimodal imaging study was conducted on a cohort of young patients affected by Systemic Lupus Erythematosus (SLE), with or without glomerulonephritis and healthy controls. Drusen-like deposits (DLDs) were identified in a large percentage of SLE patients regardless the renal involvement. Spectral Domain Optical Coherence Tomography resulted the most suitable technique for the detection DLDs. The presence of DLDs in SLE patients may support the proposed relationship existing between complement disturbances and drusen formation.