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Research Paper

Optical coherence tomography angiography features in Waldenström macroglobulinemia patients without Hyperviscosity syndrome: A pilot prospective study

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ABSTRACT

Purpose: To evaluate the retinal vessel density (VD) with optical coherence tomography angiography (OCTA) in asymptomatic patients affected by Waldenström macroglobulinemia (WM) without hyperviscosity syndrome (HVS) and to highlight the presence of microvascular damage in theese clinically asymptomatic WD patients.
Design: Prospective study.
Methods: A total of 43 eyes from 43 WM patients (24 females, 19 males, mean age 55.1 ± 13.6 years) were enrolled from January 2023 to December 2023 in the Eye Clinic of the University of Naples Federico II. Along with WM patients, 40 healthy subjects (HS) (20 females, 20 males, mean age 52.3 ± 15.6 years) with a normal ophthalmic examination and no history of intraocular surgery or retinal pathologic features were included as control group All patients and controls underwent OCTA
Results: The two groups were not significantly different for age and sex Visual acuity examination showed no statistically significant difference in BCVA between controls and patients Compared to HS, WD patients showed lower VD values in the SCP in the whole image (47.95 ± 5.17% vs. 52.99 ± 2.52 %; $p < 0.001$), as well as in the parafovea (53.01 ± 6.69% vs. 55.30 ± 2.61 %; $p = 0.002$), and fovea (21.38 ± 9.01% vs. 30.31 ± 5.84 %; $p < 0.0001$). On the other hand, in the DCP VD values were significantly higher in patients compared to controls in the whole image (55.82 ± 8.07% vs. 50.83 ± 5.46 %; $p = 0.005$), as well as in the parafovea (56.76 ± 6.26% vs. 52.59 ± 5.46 %; $p = 0.0001$), and fovea (38.75 ± 8.59% vs. 33.43 ± 8.68 %; $p < 0.0001$).
Conclusion: The finding that OCTA confirmed the presence of widespread microvascular damage in WD patients clinically silent. Thus, OCTA is a safe rapid imaging technique that could represent a valid biomarker of systemic vascular dysfunction.

1. Introduction

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by the presence of immunoglobulin M (IgM) monoclonal protein. The physical manifestations of the disorder are hepatomegaly (20 %), splenomegaly (15 %), and lymphadenopathy (15 %) and hyperviscosity syndrome (10 %−30 %) [1,2]. The most common presenting symptom is fatigue related to a normocytic anemia. The condition virtually progresses from an IgM monoclonal gammopathy of undetermined significance (MGUS through Smouldering Macroglobulinemia and IgM Disorder.[2] The median age at diagnosis is 71 years, with a higher incidence among caucasians whites (4.1 per million per year) than in African origin (1.8 per million per year) [3]. Presence of IgM monoclonal protein associated with ≥10 % clonal lymphocytic/linfoplasmacytic cells in bone marrow confirms the diagnosis. The International Prognostic Scoring System for Waldenström Macroglobulinemia is to be used for patients who require treatment. These criteria include: the presence of immunoglobulin M level greater than 4500 mg/dl, bone marrow infiltration with 70 % or greater lymphoplasmacytic lymphoma, beta 2 microglobulin >4 mg/L or greater

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and albumin <3.5 g/dl [4-8]. Even among patients presenting with an IgM greater than 6000 mg/dl the median time to initial therapy was 6.9 years [5]. Current treatment options include Rituximab, alone or in combination with Cyclophosphamide and Dexamethasone (RCd regimen), Proteosome Inhibitors, alone (Vd regimen), in combination with Rituximab (RVd regimen), Carlfizomib-Rituximab-dexamethasone regimen, Ixazomib-Rituximab-dexamethasone regimen) of with Cyclophosphamide; BTK inhibitors (Ibrutinib, Zanubrutinib, Acalabrutinib) and Bendamustine [9].

Therefore, the disorder can be completely asymptomatic with low serum IgM (< 4500 mg/dl) and that does not require immediate therapy, or it can involve several organs and tissues, eyes included. Indeed, the characteristics caused the IgM serum protein make clinical manifestations peculiar, ranging from hyperviscosity syndrome (HVS), peripheral neuropathy, hemolytic anemia to immune complex vasculitis [9-12]. Ocular manifestations occur only in WD patients with HVS and include vein occlusions, retinal hemorrhages, and varying degrees of paraneoplastic retinopathy [13-15].

The aim of this prospective study was to evaluate, with Optical coherence tomography angiography (OCTA), retinal vessel density (VD) in asymptomatic patients WM without HVS, to highlight the presence of microvascular damage in theese clinically asymptomatic WD patients.

2. Methods

The present study was a prospective, observational, cohort study. The study protocol was registered on clinicaltrial.gov (NCT05809851). The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. Written informed consent was obtained from all subjects enrolled in the study.

2.1 A total of 43 eyes from 43 WM patients (24 females, 19 males, mean age 55.1 ± 13.6 years) were enrolled from January 2023 to December 2023 in the Eye Clinic of the University of Naples "Federico II". The patient group was screened for asymptomatic HVS as part of the routine examination conducted in Hematology Unit, of the University of Naples Federico II, for all cases diagnosed with IGM monoclonal gammopathy. Each subject underwent an evaluation of best corrected visual acuity (BCVA) according to the Early Treatment of Diabetic Retinopathy Study (ETDRS), intraocular pressure measurement, slit-lamp biomicroscopy, fundus examination with a + 90 D lens and indirect ophthalmoscopy, multicolor images, spectral domain (SD)-OCT (Spectralis + HRA; Heidelberg Engineering, Heidelberg, Germany), and OCTA (RTVue XR Avanti, Optovue, Inc., Freemont, CA, USA). Along with WM patients, 40 healthy subjects (HS) (20 females, 20 males, mean age 52.3 ± 15.6 years) with a normal ophthalmic examination and no history of intraocular surgery or retinal pathologic features were included as control group (Table 1).

Only one eye for each participant was randomly selected and included in the analysis. The primary outcome of this study was the vessel density near the macula as measured by OCTA in the WM group, as compared with the control group. Spectral domain (SD)-OCT parameters, such as ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL), was considered as secondary outcome measures, as well as clinical variables, including BCVA and retinal findings. The diagnosis of WM was set and revised according to WHO 2022-HAEM5; all patients were screened with complete physical examination, serum biochemistry, quantitative test for IgG, IgA, and IgM, serum protein electrophoresis, serum immunofixation to validate the presence of monoclonal IgM, serum β2 microglobulin, LDH and bone marrow biopsy (to evaluate and confirm the presence of monoclonal lymphoplasmacytic infiltrate and mutational analysis of MYD88 and CXCR4). Mean value of M protein was 2,02 g/dl (range 0,22–4,49 g/dl). None of the included patients had signs of HVS or required treatment at the time of evaluation.

Exclusion criteria were the presence of another systemic comorbidities, clinically relevant opacities of the optic media, low-quality OCTA images, myopia greater than 6 diopters, history of intraocular surgery, evidence of vitreoretinal and macular disease, uveitis, diabetic retinopathy, congenital eye disorder, and other ocular pathologic features (e.g., combined retinal vein and artery occlusive disease).

2.2 Spectral Domain Optical Coherence Tomography All the patients were examined using spectral domain-OCT (SD-OCT) (software RTVue XR version 2017.1.0.151, Optovue Inc., Fremont, CA, USA). The optic nerve head (ONH) analysis measures the disc area, the rim area, and the cup-to-disc ratio and was used to assess the RNFL thickness, calculated along a 3.45-mm diameter circle around the optic disc. The GCC thickness was obtained from a 7 × 7 mm grid of the macula centered 1-mm temporal to the fovea. The GCC thickness is the distance from the internal limiting membrane to the outer boundary of the inner plexiform layer [16].

2.3. OCTA images were acquired with the Angiovue System (RTVue XR Avanti, Optovue, Inc., Freemont, CA, USA), which is based on split-spectrum amplitude de-correlation system (SSADA). The instrument has an A-scan rate of 70,000 scans per second with a tissue axial resolution of 5 μm and a 15 μm beam width. Each B-scan contained 304 A-scans. Two consecutive B-scans were captured at a fixed position before proceeding to the next sampling location. Size volumes were recorded and the B-scan images were compared with each other to calculate decorrelation in the images. Blood flowing through vessels could cause a change in reflectance over time and results in localized areas of flow decorrelation between frames. The spectrum of the light source was split into multiple component parts to decrease the noise present in the image; each part was used to perform the de-correlation step and the results of all the split spectra were averaged. An image of the blood flow contained in a given tissue region can be obtained by examining the projection image [17]. The projection artifact removal software was used. The OCTA device included the 3-dimensional (3D) projection artifact removal (PAR) algorithm to remove projection artifacts for improving depth resolution on an OCTA signal in order to ensure correct visualization of the SCP and DCP [17]. Cross-sectional registered reflectance intensity images and flow images were summarized and viewed as an en face maximum flow projection from the inner limiting layer to the retinal epithelial pigment. The macular capillary network was visualized in scans centered on the fovea by performing a 6 × 6 mm scan over the macular region. Vessel density (VD) was defined as the percentage area occupied by the large vessels and microvasculature in the analyzed region [18]. The OCTA software, according to the ETDRS classification of diabetic retinopathy, analyzed the macular region divided in whole image, fovea, and parafovea. For each eye analyzed, the software (AngioAnalytic™) automatically calculated vessel density in different vascular networks of the retina: the SCP and DCP. Poor-quality images with a signal strength index (that reflects OCT image quality) of less than 40 or registered image sets with residual motion artefacts were excluded from the analysis.

2.4 Statistical analysis was performed with the Statistical Package for Social Sciences (Version 25 for Windows; SPSS Inc, Chicago, Ill, USA). The Chi-squared test was used to determine differences in terms of

Table 1
Demographic and ocular characteristics of Waldestr öm (WM) group and controls.

	WM group	Control group
Eyes (n.)	40	40
Gender (male/female)	19/24	20/20
Age (years)	55.1 ± 13.6	52.3 ± 15.6
BCVA, logMAR	0.03 ± 0.09	0.02 ± 0.04
Axial length (mm)	23.3 ± 0.1	23.2 ± 03
IOP (mmHg)	13.9 ± 2.4	13.6 ± 2.1
SSI	83.5 ± 2.1	84.1 ± 2.3
Desease duration (months)	18 ± 1.3	–

Data are expressed as mean ± SD.
BCVA: best-corrected visual acuity; logMAR: logarithm of the minimum angle of resolution; IOP: intraocular pressure; SSI: signal strength index.

sex. Student's *t*-test analysis for independent samples was used to compare structural SD-OCT and OCTA parameters between patients and controls. The multiple linear regression model was used to evaluate the relationship between SD-OCT and OCTA parameters in the WM group. The agreement between two observers (G.C. and E.M) in the measurement of SD-OCT and OCTA parameters was assessed using the intraclass correlation coefficient. A p value of < 0.001 was considered statistically significant.

3. Results

The two groups were not significantly different for age (55.1 ± 13.6 and 52.3 ± 15.6 for WD and HS, respectively; $p = 0.62$) and sex (male/female= 19/20 and 24/20 for WD and HS, respectively; $p = 0.30$). Visual acuity examination showed no statistically significant difference in BCVA between controls and patients (0.02 ± 0.04 logMar vs. 0.03 ± 0.09 logMar; $p = 0.29$).

Compared to HS, WD patients showed lower VD values in the SCP in the whole image (47.95 ± 5.17% vs. 52.99 ± 2.52 %; $p < 0.001$), as well as in the parafovea (53.01 ± 6.69% vs. 55.30 ± 2.61 %; $p = 0.002$), and fovea (21.38 ± 9.01% vs. 30.31 ± 5.84 %; $p < 0.0001$). On the other hand, in the DCP VD values were significantly higher in patients compared to controls in the whole image (55.82 ± 8.07% vs. 50.83 ± 5.46 %; $p = 0.005$), as well as in the parafovea (56.76 ± 6.26% vs. 52.59 ± 5.46 %; $p = 0.0001$), and fovea (38.75 ± 8.59% vs. 33.43 ± 8.68 %; $p < 0.0001$). The structural SD-OCT showed no significant difference in GCC average ($p = 0.309$), and in RNFL average parameters ($p = 0.212$) in the WM group compared to the control group. A complete list of the between group analysis regarding SD-OCT and OCTA values is available in Table 2, while an example of the OCTA analysis is shown in Fig. 1. No significant relationship was found between GCC and RNFL average thickness and OCTA parameters. (Table 3)

4. Discussion

To the best of our knowledge, this is the first study that investigated macular vessel density changes with OCTA in asymptomatic WM patients without HVS. We found a complex and heterogeneous involvement of VD in this condition, with a different behavior between the SCP and DCP. In particular, we found in the SCP a lower VD in patients compared to controls, while an increase in VD at the level of the DCP was found in our study population. Previous studies involved only patients affect by Hyperviscosity syndrome (HVS) that occurr in 10–30 % of WD patients [11]. Serum viscosity relates with immunoglobulin levels, but the concentration of Ig required to significantly increase viscosity depends on the type of paraprotein. IgM is pentameric and very large in size (970 kDA), and serum viscosity can increase significantly with IgM levels as low as 3 g/dL, and IgM levels of 6 g/dL or higher are associated with rapid development of hyperviscosity, with a median time to symptomatic HVS of 3 months [12]. Symptomatic hyperviscosity is not common in patients with an IgM concentration lower than 4000 mg/dl, and viscosity measurements are not necessary in patients whose IgM levels are below that threshold. The ocular symptoms of hyperviscosity are mainly due to the rupture of venous channels [12]. The pathology seems to progress from venous dilation to peripheral retinal hemorrhages, observed by indirect ophthalmoscopy. Central venous dilation, increased tortuosity, central hemorrhages, disc edema, and venous sausaging are observed in advanced stages of HVS. In according with these finding, previous studies showed intraretinal hemorrhages or subretinal serous detachments due to an increase of macroglobulin concentration, resulting in a decrease of blood flow to the retina and an increase of intravascular pressure within the retinal venous circulation [19-21].

However, Sargues et al. have previously detected morfological alterations of the superficial and deep plexuses on the OCTA evaluation of patients affected by WM disease, even in absence of HVS [22].

According to them, we hypothesize that the increased recruitment of microvascular units in DCP, in response to the reduction of VD in the SCP, could lead to an increase in hydrostatic pressure at deeper levels. This change in the hydrostatic pressure could lead to marked capillary congestion and vascular dilatation, and also to the weakening of their resistance to transmural pressure In line with this speculation, in other retino-vascular disorders characterized by vessel tortuosity and dilatation, such as retinal vein occlusion, vascular congestion was mainly observed in the DCP. Indeed the DCP is characterized by a large number of small capillaries connected to the SCP through multiple vertical anastomoses. This change in the hydrostatic pressure could lead to marked capillary congestion

All patients enrolled in the WM group of this study had no visual acuity reduction, no visual symptoms and their ocular examination proved unremarkable. They also had no history of eye symptoms during their admission. The presence of microvascular changes on OCT imaging in otherwise healthy and asymptotic eyes of Waldenström Macroglobulinemia patients has great scientific relevance, as it points out the need to screen patients for possible microvascular involvement at diagnosis, before the onset of clinical manifestations and advanced endothelial damage. This might support the hypothesis of widespread microvascular damage that could be clinically silent.

In conclusion, this non-invasive imaging technique could represent a valid biomarker of systemic vascular dysfunction. The early identification of this condition in asymptomatic patients guarantees the possibility of a better quality of life and autonomy in cancer patients already subjected to screening and/or long-life treatments. However our study has some limitations, for example the small number of patients examined, particularly due to the rarity of the pathology.

Longitudinal studies on larger cohorts are needed to detect the possible progression of retinal vascular alterations on long-term follow-up.

Table 2
Differences in OCT angiography and SD-OCT parameters between Waldestr öm (WM) group and healthy subjects.

	WM group	Healthy subjects	P value
OCTA parameters			
SCP (%)			
Whole image	47.95 ± 5.17	52.99 ± 2.52	<0.001
Parafovea	53.01 ± 6.69	55.30 ± 2.61	<0.001
Fovea	21.38 ± 9.01	30.31 ± 5.84	<0.001
DCP (%)			
Whole image	55.82 ± 8.07	50.83 ± 5.46	<0.001
Parafovea	56.76 ± 6.26	52.59 ± 5.46	<0.001
Fovea	38.75 ± 8.59	34.43 ± 8.68	<0.001
FAZ area (mm^2)	0.220 ± 0.09	0.223 ± 0.07	0.883
SD-OCT parameters			
GCC average (μm)	99.20 ± 5.81	100.77 ± 6.15	0.309
RNFL average (μm)	98.47 ± 6.64	100.92 ± 5.06	0.012

Data are expressed as mean ± SD.
SCP: superficial capillary plexus; DCP: deep capillary plexus; RPC: radial peripapillary capillary plexus; FAZ: foveal avascular zone; GCC: ganglion cell complex; RNFL: retinal nerve fiber layer.
Student's *t*-test for independent samples.
Statistical significance P value <0.001.

Compliance with ethical standards

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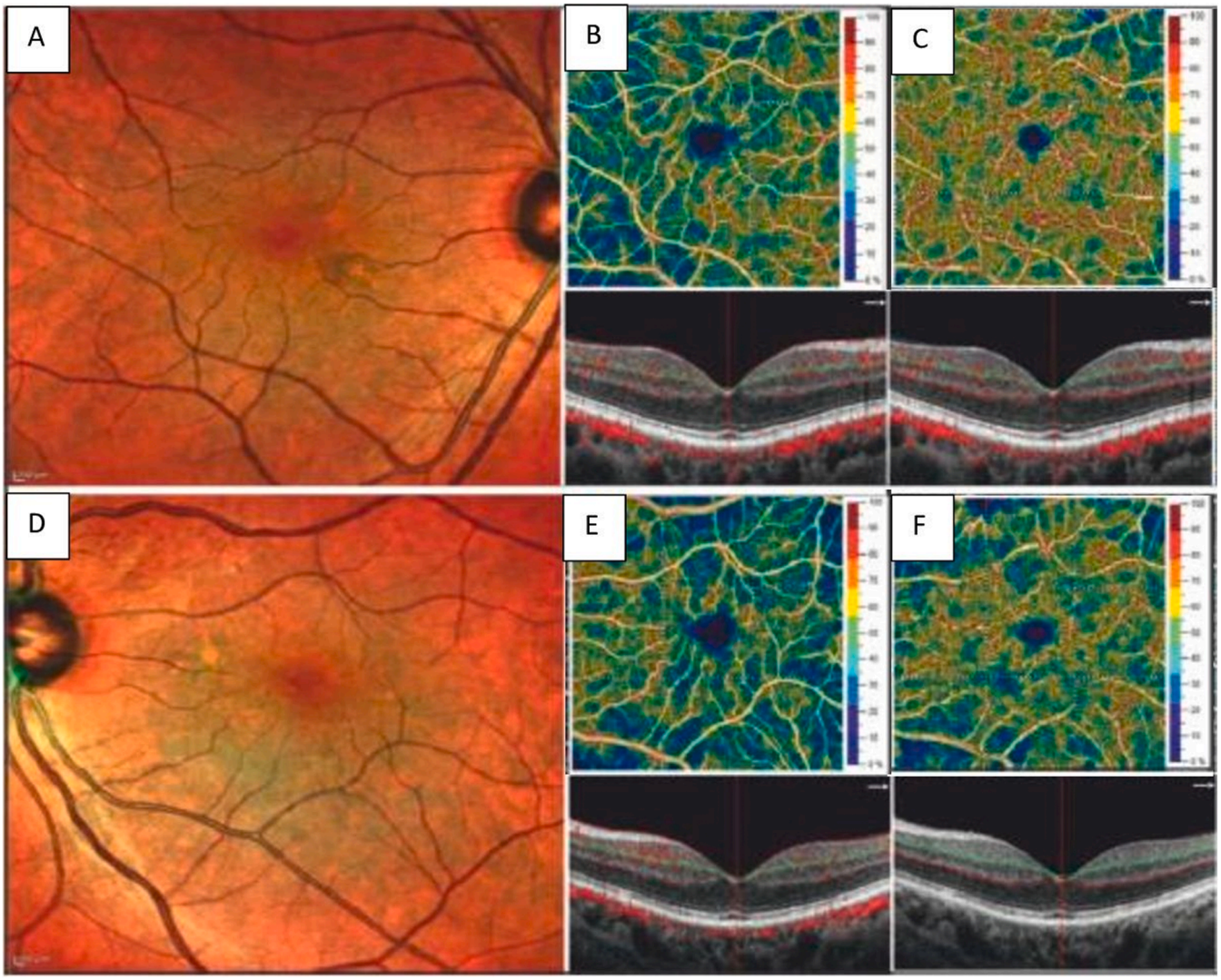

Fig. 1. Right eye (A-C) of a patient affected by waldestrom macroglobulinemia (male, 65 years old) shows at multicolor imaging, a mild increased tortuosity of retinal vessels (A), a slight reduction of vessel density in superficial capillary plexus at OCTA (B) and a marked increased in vessel density of foveal deep capillary plexus at OCTA (C). Left eye (D-F) of a healty control patient (male, 68 years old) shows at multicolor imaging, a slight increasing tortuosity of retinal vessels (D), a normal vessel density in superficial and deep capillary plexus at OCTA (E-F).

Table 3
Multiple linear regression model between SD-OCT and OCTA parameters in WM group.

	r	ANOVA p value	β	p value
GCC average	0.712	0.057		
SCP whole image			0.178	0.830
SCP parafovea			−0.771	0.378
SCP fovea			−0.165	0.550
DCP whole image			2.166	0.028
DPC parafovea			−1.911	0.012
DCP fovea			−0.479	0.269
RNFL average	0.758	0.058		
SCP whole image			0.851	0.217
SCP parafovea			−0.959	0.412
SCP fovea			0.200	0.377
DCP whole image			2.055	0.280
DPC parafovea			−1.423	0.021
DCP fovea			- 0.321	0.796

SCP: superficial capillary plexus; DCP: deep capillary plexus; GCC: ganglion cell comples; RNFL: retinal nerve fiber layer.
Multiple linear regression model; statistical significance $P < 0.001$.

CRediT authorship contribution statement

Gilda Cennamo: Writing – original draft, Methodology, Conceptualization. **Michele Rinaldi:** Writing – original draft, Conceptualization. **Alessandro Severino:** Formal analysis, Data curation. **Laura De Fazio:** Formal analysis, Data curation. **Emanuele Malvone:** Formal analysis, Data curation. **Vincenzo Martinelli:** Writing – review & editing, Conceptualization. **Ciro Costagliola:** Writing – review & editing, Validation, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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