Retinal Morphological Alterations in Polycythemia Vera: An Optical Coherence Tomography Angiography Study

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Research Article

Abstract

Purpose

Investigation of retinal morphological alterations in patients with polycythemia vera (PV) using optical coherence tomography angiography (OCTA).

Materials and Methods

Thirty PV patients (group 1) who were followed-up at Afyonkarahisar Health Sciences University Hospital, Department of Hematology, and 30 normal subjects (group 2) who applied to Ophthalmology Department for routine eye examination were enrolled in this cross-sectional, single-centered study. Following a comprehensive ophthalmological examination, all participants underwent spectral-domain OCTA examination with Angio Retina mode (6x6 mm). Data were compared between groups for statistical significance.

RESULTS

The male-to-female ratio was 1:1. Mean ages were 46.97±3.20 and 47.42±2.55 years in groups 1 and 2, respectively (*P*. 0.350). Compared to group 2, group 1 had higher values of superficial whole, parafoveal, deep foveal, perifoveal region vascular density, foveal avascular zone perimeter, and foveal vascular density in 300 μm wide regions around foveal avascular zone values, although there were no statistically significant differences. Further, group 1 had statistically non-significantly decreased flow values and foveal avascular zone area compared to group 2. The superficial foveal vascular density was statistically significantly higher in group 1 than in group 2 (*P*. 0.032).

CONCLUSION

For the first time, the present study has revealed association of PV with substantial increase in the vascular density almost all around the foveal region. This suggests consideration of potential hyperviscosity impact on the vessel density during macular microcirculation assessment of patients with PV.

Introduction

Polycythemia vera (PV) is officially classified by the World Health Organization (WHO) classification scheme as a major form of myeloproliferative neoplasms (MPN) [1]. The WHO MPN category has seven sub-categories. However, the term "MPN" typically applies to the three JAK2 mutation-enriched clinic-pathological entities, that is, PV, essential thrombocythemia, and primary myelofibrosis. Diagnosis of PV also includes existence of the JAK2 mutation, in addition to the increased hemoglobin/hematocrit at the threshold level defined by the 2016 WHO revised criteria (>16.5 g/dL/49 % for males and >16 g/dL/48 % for females) [1]. Initially, PV presents as isolated erythrocytosis, leukocytosis, thrombocytosis, or some combination thereof, along with splenomegaly or myelofibrosis, and it may take years for true

panmyelopathy to appear [2]. Primary polycythemia, that is, PV is associated with excessive erythrocytes in the bone marrow independent of another cause [3]. Typically, clinical features of PV include: mild-to-moderate degrees of splenomegaly on and constitutional symptoms such as fatigue and pruritus; symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms such as headache, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia; thrombotic and bleeding complications; and risk of leukemic transformation or fibrotic progression [3,4]. Ophthalmological manifestations of PV, in particular, vary from monocular vision loss due to retinal ischemia, papilledema to combined retinal vein occlusion and anterior ischemic optic neuropathy [5-7]. Preventing thromboembolic complications and alleviating symptoms is the current treatment target in PV [8].

The ophthalmological evaluation of PV patients involves fluorescein angiography which is used to visualize retinal vessels and thus to measure the vessel flow in relation to hematological diseases. However, the fluorescein angiography is unable to distinguish or quantify capillary networks in different retinal layers, and as an invasive technique, its repeated use is constrained. Contrastingly, optical coherence tomography angiography (OCTA, Optovue, Inc., Fremont, CA) is a novel non-invasive imaging technique that has recently been implemented. This technique visualizes retinal and choroid capillary networks, and foveal avascular zone (FAZ) without exogenous dye. Identification of retinal ischemic diseases with clinically undetectable fundus lesions is also possible [9]. Optical coherence tomography angiography can produce three dimensional and *en face* imaging of retinal capillary networks thanks to its split spectrum amplitude-decorrelation angiography property. Quantitative data of the retinal vasculature and its thickness and foveal avascular zone area can be measured automatically using the AngioAnalytics program. Optical coherence tomography angiography is increasingly widely used in the diagnosis and evaluation of various vascular-associated retinal or choroidal diseases, including diabetic retinopathy, choroidal neovascularization, and retinal vein occlusion [10-12].

The present study was designed to quantify the OCTA parameters of retinal morphology, including retinal vascular density, FAZ area and central foveal thickness of PV patients, and to compare the data with normal subjects.

Materials And Methods

Participants

Thirty PV patients (Group 1) who were followed-up at Afyonkarahisar Health Sciences University Hospital, Department of Hematology, and 30 normal subjects (Group 2) who applied to our Ophthalmology Department for routine eye examination were enrolled in this cross-sectional, single-centered study. All procedures were carried out according to the tenets of the Helsinki Declaration. The approval of the board of institutional review was received from the Afyonkarahisar Health Sciences University Ethics Committee. Formal informed consent was obtained prior to the study.

Ophthalmological Examination and Optical coherence Tomography Angiography Acquisition

A thorough ophthalmological examination including measurements of the best-corrected visual acuity and Goldmann applanation tonometry intraocular pressure, anterior and posterior segment slit-lamp biomicroscopy were carried out. All participants underwent spectral-domain OCTA scanning in Angio Retina mode (6x6 mm) under normal conditions by the same clinician. Eye movement artefacts were minimized by an eye-tracking mode and eliminated by a motion correction technology. All scans were reviewed to ensure proper segmentation and image quality (Quality Index ≥7) and scans of low quality were omitted. AngioVue Analytics, RTVue-XR version 2017.1.0.155 program automatically quantified the vessel density in superficial retinal layer (superficial capillary plexus, SCP) and deep retinal layer (deep capillary plexus, DCP). Central macular thickness-defined as the average thickness of the central 1 mm^2 fovea region, the parafovea macula thickness, the average retinal thickness of the 6x6 mm region and the superior and inferior hemifields were also quantified automatically by the AngioVue Analytics program. The flow area of the 3 mm diameter circle was determined. Meanwhile the FAZ, FAZ perimeter (PERIM), and foveal vessel density were also obtained from the software's FAZ mode in 300 μm wide regions around FAZ (FD-300).

Statistical Analysis

The SPSS software (Version 18, SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Corp., Redmond, Washington, USA) were used to conduct statistical analysis. All parameters were analyzed for distribution by the Shapiro-Wilk test. And, since the data were identified in a normal distribution, an independent sample *t*-test was used in the data analysis. *P*-values of less than 0.05 were considered statistically significant.

Results

There was a male-to-female ratio of 1:1 among the 60 participants. The mean ages for male and female PV patients were 49±5.15 years and 46.21±2.25 years, respectively. While the mean age of all PV patients was 46.97±3.20 years, normal subjects had 47.42±2.55 years **(*P*: 0.350).** The demographic features of the respective study groups are shown in **Table 1.**

Table 2 shows alterations in the retinal vascular density of the respective study groups. Patients with PV had statistically non-significant increases in the vascular density in superficial whole, parafoveal, deep foveal, and perifoveal region relative to normal subjects. Statistically non-significant decreases in flow values as well as in the FAZ region were also observed in patients with PV relative to normal subjects **(Table 3 and 4).** Besides, Patients with PV were associated with statistically non-significant increases in PERIM and FD-300 parameters **(Table 4).** Moreover, in comparison to normal subjects, patients with PV were associated with a statistically significantly increased vascular density in the superficial foveal area **(*P*: 0.032)(Figure 1).**

Discussion

Polycythemia vera is commonly known clinical entity resulting from primary hyperplasia of erythroblastic elements of the bone marrow. This disease is seldom detected by the internist, and far more seldom by the ophthalmologist, as vision is occasionally impaired. Nevertheless, the fundus examination is likely to reveal early characteristic lesions of significance in the diagnosis. In view of this, the present study was intended to decode the conundrum regarding PV and the consequent retinal morphological alterations by implementing the novel non-invasive OCTA technique. Increased vascular density was recorded in almost all central retina, in particular foveal region due to PV-related hematic hyperviscosity.

Investigation and comparison of viscosity and coagulation including activated protein C resistance between 87 central retinal vein occlusion patients and the age-matched, population-based control group conducted by Williamson et al [13]., recorded marked reductions in both choroid and retinal blood flow in central retinal vein occlusion patients. Consistently, the present study revealed reductions in flow values and in the FAZ region in PV patients, although the results were not substantial. Ocular symptoms of PV are either due to hyperviscosity or thrombosis [14]. If untreated, PV can be life-threatening due to cardiovascular thrombotic events or PV transition to myelofibrosis, leukemia, or myelodysplastic syndromes [15]. For this reason, PV management is generally designed to prevent thrombotic incidents and to maintain a regular hematocrit level by periodic phlebotomy. In view of this, Dhrami-Gavazi et al [16]., documented a JAK2 mutation patient with central retinal artery occlusion and ipsilateral middle cerebral artery stroke. This also demonstrates the impact of hematic hyperviscosity, as seen in the current study involving PV patients.

Investigation of plasmapheresis effects on hyperviscosity syndrome-related retinopathy and retinal hemodynamic parameters in patients with Waldenström's macroglobulinemia carried out by Menke et al [17]., concluded that hyperviscosity might cause a specific type of retinopathy with retinal vein occlusion-like appearance, although the retinal blood flow remains at normal levels. Following therapy, patients developed reduction in venous diameter, and subsequent increase in the retinal venous blood flow velocity. Despite this, focal vascular constrictions revealed by slit-lamp biomicroscopy and indirect ophthalmoscopy prior to the plasmapheresis were not associated with substantial change following therapy. Likewise, PV patients participating in the present study were associated with reductions in microcirculation parameters and increases in the PERIM and FD-300 parameters with negligible differences contrary to normal subjects, respectively. All these findings indicate sluggishness of the retinal microcirculatory blood flow mainly attributable to hematic hyperviscosity, related to higher hematocrit in PV.

The study reported by Crowe et al [18]., in which the retinal vessel diameter was plotted against relative serum viscosity, showed a consistent relationship between these two parameters. The viscosity decreased directly in relation to the retinal vessel diameter in both arteries and veins. Corresponding findings with which PV patients were associated with significant increase in vascular density in almost all central retina, especially in superficial foveal region relative to normal subjects were revealed in the present study. Optical coherence tomography angiography scanning, as is understood, includes the image acquisition and processing of an erythrocyte motion contrast within the vessel. We proposed that

different measurement values could be obtained for hyperviscosity syndrome, including PV, particularly in the foveal region. As revealed in the present study, only superficial foveal vascular density values increased significantly as compared to normal subjects.

The key drawbacks of the present study are the limited sample size and cross-sectional design of the analysis. Further trials with a wider population considering the effects of PV before and after therapy and a longer follow-up duration may also be worthwhile.

Conclusions

For the first time, the present study revealed association of PV with substantial increase in the vascular density around the foveal region. These findings suggest consideration of possible hyperviscosity impact on the vessel density during macular microcirculation assessment in patients with PV.

Declarations

- *Funding:* Authors declare no public or private financial support or involvement whatsoever in the products, methods or materials referred to in this manuscript.
- *Conflicts of interest/Competing Interests:* The authors claim no conflict of interest.
- *Financial Interest:* Both 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.
- *Consent to participate:* Informed consent was obtained from all individual participants included in the study.
- *Authors' contributions:* All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Muberra AKDOGAN], [Mustafa DOGAN], [Anar Alizada], [Mehmet Cem SABANER], [Hamidu Hamisi GOBEKA], and [Filiz Yavasoglu]. The first draft of the manuscript was written by [Muberra AKDOGAN, Hamidu Hamisi GOBEKA] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
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- *Clinical Trials Registration:* Not applicable.

- *Gels and Blots/ Image Manipulation:* Not applicable.

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Tables

Table 1
Demographic features of the respective study groups

	Polycythemia vera patients (N:30)	Normal subjects (N:30)	P-value
Age (year)	46.97 ± 3.20	47.42 ± 2.55	0.350[*]
Gender (M:F ratio)	14:16	15:15	0.883[▯]
Intraocular pressure (mmHg)	14.06 ± 2.81	13.71 ± 2.38	0.159[*]
BCVA (logMAR)	0.0 ± 0.0	0.0 ± 0.0	1.000[*]
Axial length (mm)	21.58 ± 2.09	21.19 ± 1.49	0.206[*]
*: Independent t-test results, [▯]: Chi-Square test results, BCVA: Best-corrected visual acuity.			

Table 2

Comparison of the retinal vascular density parameters between polycythemia vera patients and normal subjects

Parameters	Groups	N	Mean density values (%)	*P*-value*
Whole superficial	Group 1	30	51.7 ± 2.8	0.468
	Group 2	30	50.8 ± 3.5	
Foveal superficial	Group 1	30	23.2 ± 4.5	0.032
	Group 2	30	19.1 ± 5.8	
Parafoveal superficial	Group 1	30	53.4 ± 2.4	0.692
	Group 2	30	53.0 ± 4.1	
Perifoveal superficial	Group 1	30	52.4 ± 1.2	0.304
	Group 2	30	53.3 ± 3.1	
Whole deep	Group 1	30	55.3 ± 2.4	0.694
	Group 2	30	54.8 ± 3.9	
Foveal deep	Group 1	30	41.4 ± 3.1	0.752
	Group 2	30	40.7 ± 5.0	
Parafoveal deep	Group 1	30	56.7 ± 2.1	0.426
	Group 2	30	57.4 ± 3.3	
Perifoveal deep	Group 1	30	56.9 ± 1.7	0.369
	Group 2	30	55.8 ± 4.4	

*: Independent sample t-test results: P < 0.05 was considered statistically significant and was indicated as bold. Group 1: Polycythemia vera patients, Group 2: Normal subjects.

Table 3

Comparison of the outer retinal and choroidal flow values between polycythemia vera patients and normal subjects

Parameters	Groups	N	Mean flow area values (%)	*P*-value*
Outer retinal flow area	Group 1	30	8.60 ± 1.04	0.751
	Group 2	30	8.97 ± 9.68	
Choroidal flow area	Group 1	30	18.73 ± 0.72	0.092
	Group 2	30	19.15 ± 0.51	

*: Independent sample t-test results: P < 0.05 was considered statistically significant. Group 1: Polycythemia vera patients, Group 2: Normal subjects.

Table 4. Comparison of the foveal avascular zone parameters between polycythemia vera patients and normal subjects

Parameters	Groups	N	Mean values	*P*-value*
FAZ area (mm^2)	Group 1	30	0.27 ± 0.64	0.529
	Group 2	30	0.29 ± 0.14	
PERIM (mm)	Group 1	30	2.26 ± 0.37	0.209
	Group 2	30	2.07 ± 0.49	
FD-300 Area (%)	Group 1	30	53.93 ± 2.34	0.914
	Group 2	30	53.85 ± 4.06	

*: Independent sample t-test results: P < 0.05 was considered statistically sigificant. FAZ: foveal avascular zone, PERIM: FAZ perimeter in mm, FD-300: vessel density 300μm from the fovea. Group 1: Polycythemia vera patients, Group 2: Normal subjects
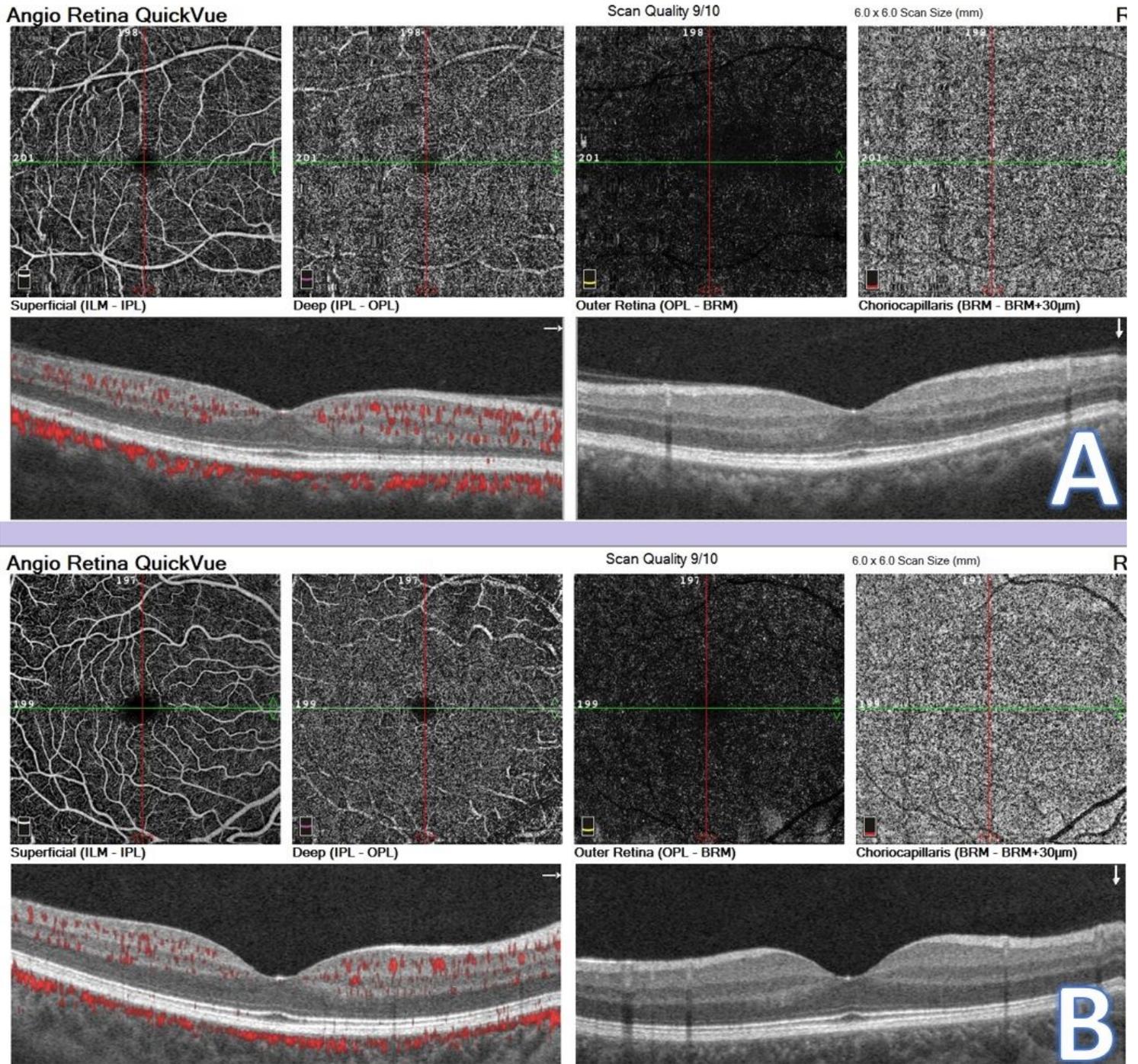
Figures

Figure 1

Illustrative OCTA comparison of a polycythemia vera patient (A) and normal subject (B).