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ORIGINAL ARTICLE

Pearl necklace sign and other optical coherence tomography findings in retinal vein occlusion at the first visit

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Abstract

Purpose: In patients with retinal vein occlusion (RVO), the presence of pearl necklace sign is often overlooked; however, this sign should be sought among optical coherence tomography (OCT) findings. Our aim is to evaluate retrospectively the presence of pearl necklace sign and other OCT (findings in patients with RVO at their first visit. Furthermore, to reveal any association between pearl necklace sign and other OCT findings.

Methods: In this retrospective cross-sectional study, OCT features of the patients with RVO who were examined between 2009 and 2019 were analyzed. Only the OCT findings at the first visit were taken into consideration. Both treatment-naïve patients and patients previously treated elsewhere were included in the study. OCT findings, particularly the pearl necklace sign (circular localization of the hyperreflective dots (HRDs) around the inner retinal cyst wall or the sensory retinal detachment wall) were looked for.

Results: The study population was 100 eyes of 100 patients with RVO. The pearl necklace sign was found in 20 of 100 eyes with RVO (20%). The presence of the pearl necklace sign and serous retinal detachment had a statistically significant connection (P = 0.026). Moreover, the pearl necklace sign group was shown to have statistically higher HRDs than the other groups (P = 0.002).

Conclusion: Even though the common OCT findings were meticulously elaborated in many of the previous studies, pearl necklace sign has not been particularly looked for in eyes with RVO. Overall, pearl necklace sign was present in 20% of 100 patients with RVO in this single-visit OCT study. This ratio makes us think that the pearl necklace sign actually accompanies RVO more often than previously thought.

Keywords: Hyperreflective dot; pearl necklace sign; retinal vein occlusion; spectral domain optical coherence tomography.

Retinal vein occlusion (RVO) is the second most common retinal vascular disease following the diabetic retinopathy[1] and as a subtype, branch RVO (BRVO) is 4–6 times more common than the central RVO (CRVO).[2]

When RVO occurs, increased intravascular pressure may cause the blood–retina barrier breakdown and macular edema may ensue due to the vascular permeability. Furthermore, retinal perfusion may also be impaired and

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ischemia in various magnitudes may occur.[3] The presence of increased leukocyte adhesion and intraretinal leukocyte migration are suggestive of inflammation during the course of retina vein occlusion.[4] In addition, increased vitreous levels of VEGF or PEDF, and adhesion molecules such as ICAM-1 support the inflammatory mechanism. However, relationship between the inflammation and the degree of clinical severity is still not fully understood.

Optical coherence tomography (OCT) is a non-invasive imaging method that is frequently used to evaluate the macular changes and accompanying vitreoretinal interface abnormalities in many diseases. Various OCT findings were reported in eyes with RVO such as cystoid edema,[5] serous retinal detachment (SRD),[6] hyperreflective dots (HRDs),[7] and intraretinal haemorrhage.[8] Gelman et al.[9] were the first to coin the term of pearl necklace sign in the literature and argued that it was formed as a result of collection of the HRDs either around the inner retinal cyst wall or the sensory retinal detachment wall. The pearl necklace appearance was shown to be replaced by hard exudates in eyes with diabetic macular edema.[10] Activated microglial cells,[11] hard exudates, and microaneurysm may appear as HRDs which can be the precursor of pearl necklace sign.[12]

In this single-visit retrospective cross-sectional study, the presence of pearl necklace sign was particularly looked for in patients with RVO with the help of spectral domain OCT.

Materials and Methods

This cross-sectional, single visit study included OCT analysis of 100 eyes which were diagnosed with RVO at their first visit. These eyes were evaluated by two retinal specialists (Saatci O.and Oner F.H) at the Ophthalmology Department of Dokuz Eylül University between January 2009 and May 2019, and these eyes were both treatment-naïve and previously treated at the time of diagnosis. Spectral domain OCT (Heidelberg Spectralis HRA/OCT) was performed and star-pattern cross sections passing through the fovea were taken into consideration. HRDs were defined as the presence of focal hyperreflective material scattered in outer and inner retinal layers in at least one scan passing through the fovea and the OCT scan harboring the most HRDs in number was taken into consideration for the quantification. (Adapted from Coscas et al.[13,14]). Two blinded ophthalmologists counted the HRDs, and the mean was considered. Pearl necklace sign was assumed to be present whenever the HRDs were lined up either around the inner retinal cyst wall or the sensory retinal detachment wall.[9] When there was fluid accumulation under the sensory retina, this was considered SRD.[15]

Vitreomacular abnormalities were assessed in accordance with the International vitreomacular traction (VMT) Study Group data.[16] The files of the patients were screened to obtain the demographic data and previous treatment history in cases who were previously treated elsewhere. The examinations were conducted by two medical retina specialists (Karatas E. and Ipek S.C). The study was carried out by the ophthalmology clinic, and all stages of the study were carried out with the permission of the ethics committee of our hospital.

*Ferit Hakan Oner unfortunately passed away in August 2020 during the manuscript preparation.

Statıstical Analysis

The necessary corrections and error checks were conducted when the obtained data were transmitted to the IBM SPSS 21.0 program in a computer setting. Mean and standard deviation are used to represent regularly distributed values, while median (interquartile range: 25–75%) is used to represent non-normally distributed variables. For the examination of continuous variables, the Mann–Whitney U-test was employed for nonparametric data and the Student's t-test for parametrically distributed data in independent samples. When the requirements for the normality of distributions or homogeneity of variances could not be satisfied, Kruskal–Wallis analysis was used.

Results

A hundred eyes of 100 patients were included in the study. The demographic and initial clinical characteristics of the patients are summarized in Table 1.

The mean central macula thickness (CMT) was 465.87 (Range: 120–1082±222 µm).

While mean CMT for treatment-naïve patients was 499±223

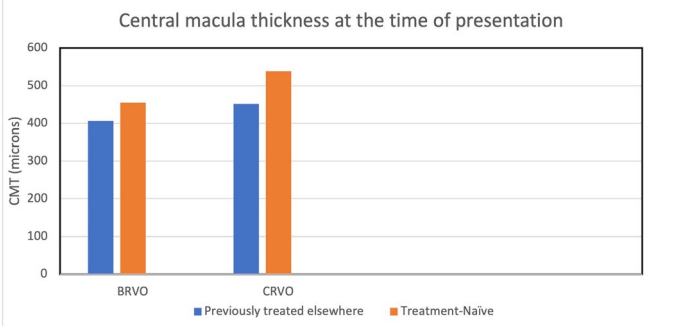

Fig. 1. Mean CMT (Central macula thickness (microns, µm)) at the time of first visit; BRVO*: Branch retinal vein occlusion; CRVO**: Central retinal vein occlusion.

Table 1. Demographic and clinical characteristics of the patients with retinal vein occlusion

Age (years, avg.±SD)	**65.65±12**
Gender (n, woman: man)	50:50
Laterality	54 right eyes, 46 left eyes
Subtype (n)	48 CRVO
	52 BRVO
Pearl necklace sign (n)	20 (in total)
Subtype (n) (CRVO related- BRVO related)	9 and 11
Subgroup (n) (around the intraretinal cyst-surrounding the serous retinal detachment)	14 and 6
Hyperreflective retinal dots (n) (BRVO related-CRVO related)	7.27±5.28, 6.02±6.08
Treatment-naïve (n) (BRVO related- CRVO related)	54 (25–29)
Follow-up (months, avg.±SD)	50.03±30.6

n: Quantity in number.

μm, it was 426±217 μm in eyes previously treated elsewhere. There was no statistically significant difference between these two groups (P=0.07). No statistically significant difference in terms of CMT was also found between eyes with BRVO and eyes with CRVO (P=0.1). Figure 1 illustrates the mean CMT changes of the study eyes.

The pearl necklace sign was noted in 20 of 100 eyes with RVO (20%). Of these, 14 surrounded the intraretinal cysts (seven in BRVO eyes and seven in CRVO eyes) and the remaining 6 surrounded the SRD (four in BRVO eyes and two in CRVO eyes) (Figs. 2 and 3). While no difference with regard to age or gender was found in the eyes where the pearl necklace sign was observed, the number of HRDs was found to be statistically more compared to eyes without pearl necklace sign (P=0.002). No statistical difference was observed between the treatment-naïve and previously treated eyes in terms of pearl necklace sign (P=0.7).

The mean CMT in 20 eyes with the pearl necklace sign was 511±146.77 microns, whereas mean CMT was 458±232.56 microns in 80 eyes without pearl necklace sign. However, this was not statistically significant (P=0.5). All SD-OCT findings are summarized in Table 2.

SRD was present in 51 of 100 eyes (51%). The average height of SRD was 112.36 microns (Range; 0–801±156.08 microns). No statistical difference was found with regard to age and gender (P=0.39 and P=0.4 respectively). On the other hand, mean CMT and the number of HRDs were found to be statistically significantly higher in eyes with SRD when compared to eyes without SRD (P<0.05). There was no statistical difference in terms of the height of SRD between BRVO eyes and CRVO eyes (P=0.6, P=0.7, respectively). There was a statistically significant relationship between the presence of the pearl necklace sign and SRD (P=0.026). Again, a significant statistical correlation was found among the SRD and interdigitation zone defect (IZ), ellipsoid zone (EZ) defect, and external limiting membrane (ELM) defect (P<0.05, P=0.004, and P=0.005, respectively). The presence of SRD was statistically higher in treatment-naïve eyes at

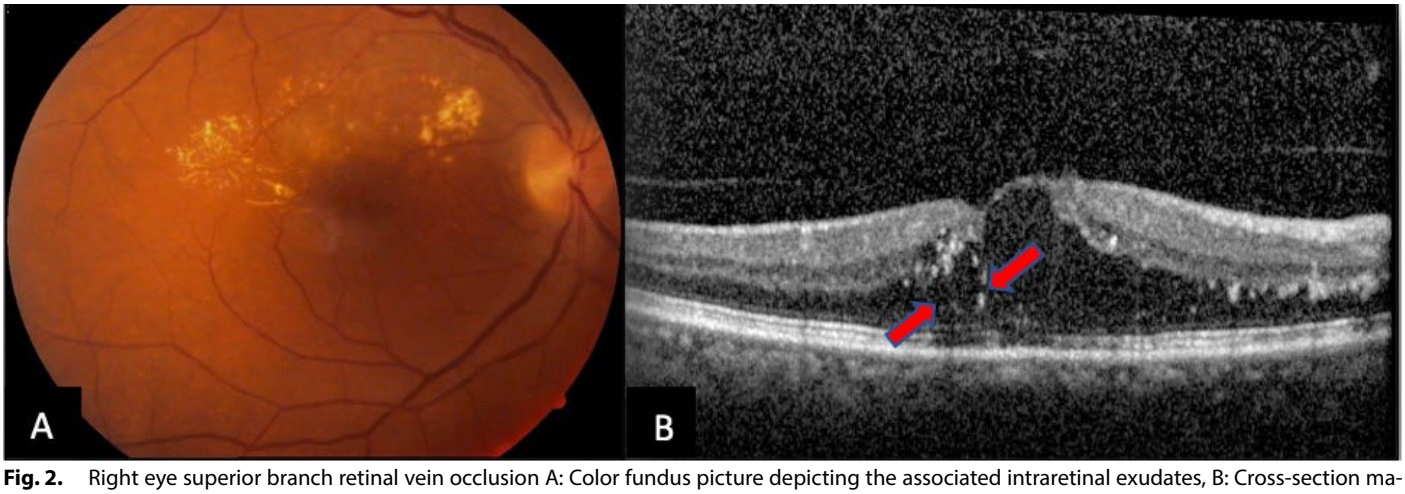

Fig. 2. Right eye superior branch retinal vein occlusion A: Color fundus picture depicting the associated intraretinal exudates, B: Cross-section macular OCT showing the intraretinal cysts, hyperreflective dots, and the appearance of pearl necklace sign (between the red arrows)

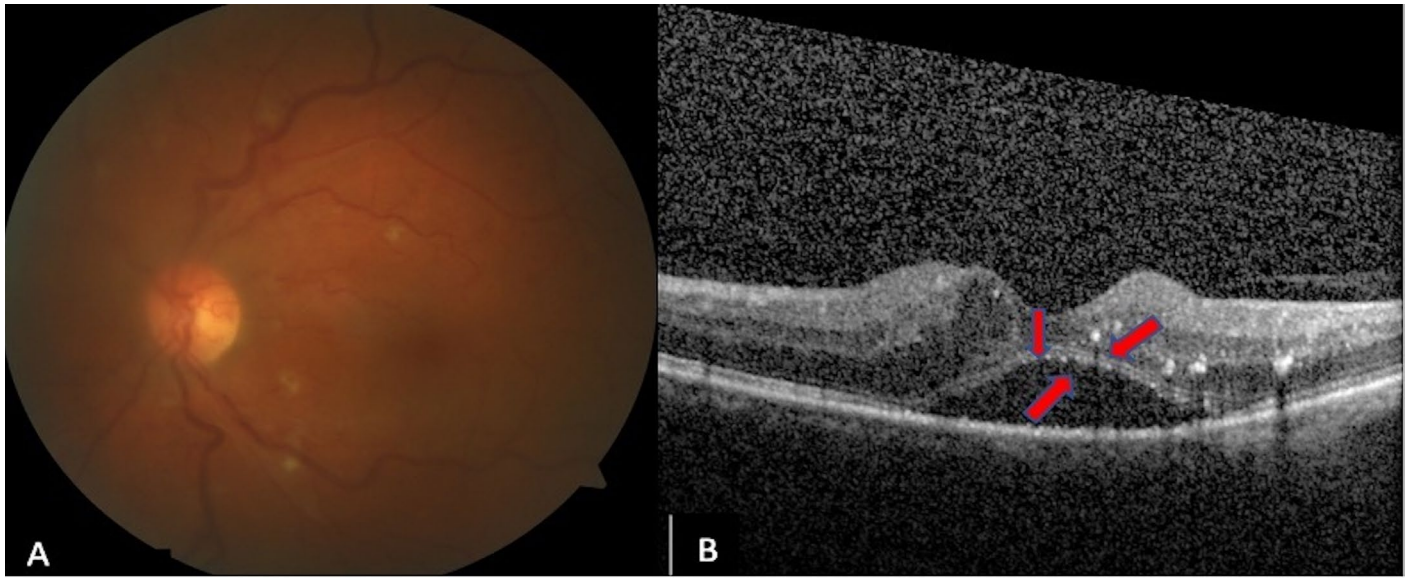

Fig. 3. Left eye central retinal vein occlusion A: Color fundus picture depicting the hard and soft exudates and tortuous veins B: Cross-section macular OCT showing the serous retinal detachment and the accompanying pearl necklace (red arrows)

Table 2. SD-OCT findings in the study eyes (n*, %**)

	BRVO (52 eyes)	SRVO (48 eyes)	TOTAL (100 eyes)
Serous retinal detachment	24 (%46)	27 (%43)	51 (%51)
Pearl necklace sign	11 (%21)	9 (%18)	20 (%20)
Epiretinal membrane	7 (%13)	9 (%18)	16 (%16)
Vitreomacular adhesion	4 (%7)	4 (%8)	8 (%8)
Vitreomacular traction	-	2 (%4)	2 (%2)
Interdigitation zone defect	34 (%65)	32 (%66)	66 (%66)
Ellipsoid zone defect	32 (%61)	31 (%64)	63 (%63)
External limitant membrane defect	31(%59)	30 (%62)	61 (%61)

n*: number of eyes, % **: Percentage of the eyes.

the time of diagnosis (P=0.01). No relationship was found among SRD and vitreomacular interface pathologies (VMA, VMT, epiretinal membrane [ERM]; P=0.1, 0.1, and 0.9, respectively).

The number of foveal HRDs counted within the 1500 microns was found to be 6.66 (Range; 0–24±5.68). The number of HRDs according to the type of vein occlusion and treatment status is shown in Figure 4. HRDs were slightly more in eyes with BRVO (7.27±5.28) when compared to CRVO eyes (6.02±6.08), but there was no significant difference between these groups (P=0.09).

There was abnormal ELM in 61 eyes (61%), the EZ defect in 63 eyes (63%), and the IZ abnormality in 66 eyes (66%). In eyes with EZ defect, ELM abnormality was present in 59% and IZ abnormality in 62%. The number of HRDs in eyes with ELM and IZ abnormality was found to be statistically significantly higher than eyes which did not have any ELM or IZ defect. (P=0.025 and P=0.005, respectively).

Vitreoretinal interface disorder was detected in 26 eyes (26%). ERM was detected in 16 eyes (16%), vitreoretinal adhesion in 8 eyes (8%), and VMT in 2 eyes (2%). The mean age of patients with ERM was found to be higher

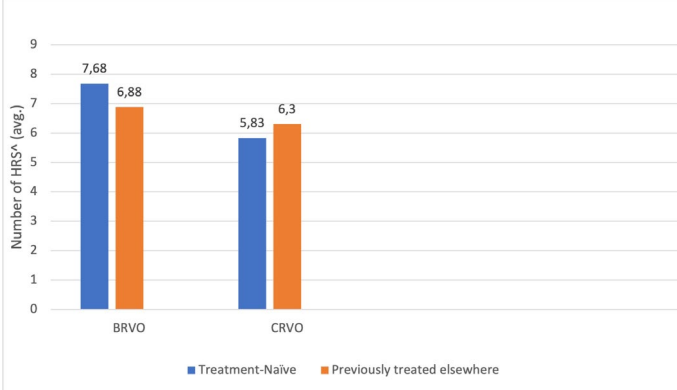

Fig. 4. A number of hyperreflective dots (HRD^) according to subgroups. BRVO*: Branch retinal vein occlusion; CRVO**: Central retinal vein occlusion.

than the other groups (P=0.049). There was no statistically significant difference between the treatment-naïve group and the previously treated group in terms of vitreoretinal interface disorders (for VMT, VMA, and ERM (P=0.1, 0.6, and 0.3, respectively).

Discussion

RVO is a chronic condition that may have a serious impact on the vision. Nowadays, OCT findings play a very important role in the diagnosis and treatment of the patients as OCT enables the clinicians to perform qualitative and quantitative analyses of the retinal layers. Moreover, morphological changes can also be ascertained.

The pearl necklace sign is the distribution of HRDs in a ring-like distribution either around the inner retinal cysts or sensory retinal detachment wall. First, Gelman et al.[9] described the pearl necklace sign in 21 eyes of 20 patients with exudative maculopathy with various causes such as age-related macular degeneration, chronic diabetic macular edema, retinal arterial macroaneurysm, and Coats disease and only two of 21 eyes had BRVO. Pearl necklace sign is associated with the chronic vascular leakage and accepted as the lipid-laden macrophages accompanying the chronic cystoid macular edema.[9] Since it may represent an ongoing cicatrizing process, it is thought that the presence of this finding, especially when subfoveal, may have a negative effect on the visual acuity. Histopathological reports have shown that the HRDs forming the pearl necklace sign were stained with oil red-O and were often concentrated near the deep capillary plexus at the outer retinal layers.[16] In addition, lipid-laden macrophages and apolipoprotein-B have also been detected in retinal vessels and have been associated with the macrophages clearing the lipids inside the tissue.[16] Deposits forming the pearl necklace sign are separately localized with distinct borders and this distribution supports the fact that they are most likely the lipid-laden macrophages and thereby accompany the diseases characterized with severe exudation. Ajay et al.[10] in their retrospective study showed that pearl necklace sign was present in 35 of 267 eyes (13%) with diabetic macular edema. In most of these eyes, the pearl necklace appearance was replaced by hard exudates with intravitreal anti-VEGF treatment. Strikingly, three eyes with subfoveal pearl necklace sign at the time of treatment initiation experienced dramatic visual decline of 20 letters or more despite having the intravitreal injections. Therefore, they concluded that subfoveally located pearl necklace formation might end up with a permanent photoreceptor layer damage and irreversible vision loss. Ipek and Saatci[17] reported the presence of pearl necklace sign in an eye with retinal arterial macroaneurysm together with the intraretinal fluid accumulation. Ramtohul and Denis[18] described the pearl necklace sign in an eye with combined hamartoma of the retina and retinal pigment epithelium. They speculated that this finding was related to possible microglial activation. In the present study, the absence of a significant difference between the treatment-naïve group and the non-treatment-naïve group with regard to inner retinal layer pearl necklace formation suggests us that this might be an indicator for the edema recurrence and inadequate treatment outcome. As HRDs are believed to be the activated glial cells and deemed as an inflammation marker, anti-inflammatory treatment alternatives may be more beneficial.[11] The relationship between the SRD and the pearl necklace sign was also evident in our study and might also implicate outer retinal layer damage. As the current study was a cross-sectional single visit study, we could not look for the clinical and anatomic outcome with the treatment.

Conclusion

Meticulous OCT assessment at the first visit carries out a paramount importance as some of the OCT findings such as the pearl necklace sign may imply a guarded visual prognosis and even affect the treatment choice of the physician. Although SRD and HRDs are well-known, pearl necklace sign is relatively less known. In light of our paper, we want to point out the importance of the pearl-necklace sign in eyes with RVO and to help to increase the awareness of this important OCT sign.

Ethics Committee Approval: This study was approved by Dokuz Eylul University Hospital of Medicine Ethics Committee (date: 30.06.2022; number: E-91930332-099-301459).

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