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Original Article

Prevalence of Serous Macular Detachment in Recurrent Macular Edema Secondary to Retinal Vein Occlusion

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Abstract

Objectives: To evaluate the prevalence of serous macular detachment (SMD) accompanying recurrent cystoid macular edema (CME) in patients initially treated for CME secondary to retinal vein occlusion (RVO) with accompanying SMD, and discuss the factors that affect the prevalence.

Materials and Methods: We retrospectively evaluated the medical records of 71 patients with RVO-associated CME and SMD who achieved complete anatomical resolution after treatment with either a single dexamethasone implant or three loading doses of ranibizumab and developed recurrent CME during follow-up.

Results: Initial treatment was a single intravitreal dexamethasone implant in 45 patients (63.4%) (Group 1) and three loading doses of intravitreal ranibizumab in 26 patients (36.6%) (Group 2). The mean time to CME recurrence was 4.7±0.8 months (range, 4-7 months) and was similar in both groups (p=0.984). At the time of CME recurrence, SMD was present in 41 patients (57.7%) and absent in 30 patients (42.3%). SMD was present in 27 (60.0%) of the 45 Group 1 patients and 14 (53.8%) of the 26 Group 2 patients (p=0.613). SMD was present in 48.8% of branch RVO and 71.4% of central RVO patients at the time of recurrence (p<0.001).

Conclusion: SMD accompanied recurrent CME in only 57.7% of patients previously treated for CME and SMD and seems to be more frequent in patients with central RVO. Initial intravitreal treatment choice of either ranibizumab or dexamethasone implant did not affect the prevalence of concurrent SMD in patients with recurrent CME.

Keywords: Cystoid macular edema, optical coherence tomography, serous macular detachment, Branch retinal vein occlusion, central retinal vein occlusion

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Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder, and cystoid macular edema (CME) is the main cause of vision loss in these patients.[1] Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents (ranibizumab, bevacizumab, and aflibercept) and steroids (triamcinolone acetonide and sustained-release dexamethasone implant) has been found to be effective in the treatment of macular edema secondary to RVO.[2,3,4,5,6]

Serous macular detachment (SMD) has been defined as a triangular hyporeflective cavity between the outer retinal layers and retinal pigment epithelium detected with optical coherence tomography (OCT) and is thought to be strongly associated with inflammation.[7,8] It may accompany certain retinal disorders such as RVO, diabetic macular edema, Behçet's disease, postoperative cystoid macular edema, and Coats' disease.[7,8,9,10,11] After the clinical use of OCT in daily practice, it is recognized that SMD is more common than previously thought, and has been reported up to 80% of patients with RVO.[7,12,13] However, no study has investigated the incidence of SMD in recurrent CME secondary to RVO and the factors associated with the incidence of SMD during recurrence.

The aim of the present study was to evaluate the incidence of SMD in patients with recurrent CME secondary to RVO who were initially treated for CME with accompanying SMD and achieved complete anatomical resolution either with a single dose of dexamethasone implant or three loading doses of ranibizumab, and to discuss the factors that affect the prevalance of SMD in these patients.

Materials and Methods

We retrospectively reviewed the medical records of treatment-naive patients who were admitted to the retina department of a single tertiary hospital between June 2013 and June 2017 with an initial diagnosis of CME and accompanying SMD secondary to RVO. The study adhered to the tenets of the Declaration of Helsinki and was carried out upon approval of the Ethics Committee of Numune Training and Research Hospital. Treatment-naive patients who were followed-up for at least 12 months and met the following criteria were included in the study: had CME and SMD secondary to branch RVO (BRVO) or central RVO (CRVO), showed complete anatomical resolution at 3 months after intravitreal injection of either a single dose of sustained-release dexamethasone implant (Ozurdex®) or three monthly loading doses of ranibizumab, and developed CME recurrence detected with spectral domain OCT.

The data collected from the patients' files included past medical and ophthalmic history; demographic data including age and sex; clinical data including the type of RVO (BRVO or CRVO), initial treatment for CME (single intravitreal dexamethasone implant [Group 1] or three monthly ranibizumab injections [Group 2]), logMAR visual acuity, anterior and posterior segment findings on slit-lamp examination, intraocular pressure (IOP) measured by noncontact tonometry, and spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) findings (presence or absence of CME and/or SMD and central macular thickness [CMT]) at each follow-up visit. Patients with a history of previous intraocular surgery and those with evidence of ocular disorders such as diabetic retinopathy, age-related macular degeneration, retinal dystrophies, retinal arterial occlusion, uveitis, vitreoretinal interface disorders, and glaucoma were excluded from the study. Patients whose IOP exceeded 21 mmHg at any point during follow-up and those who were treated with macular or panretinal photocoagulation during follow-up were also excluded.

Statistical analyses were performed using SPSS for Windows version 22.0 (IBM Corp, Armonk, NY, USA). Normal distribution of the variables was tested using visual (histogram and probability graphs) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). Descriptive statistics were expressed as frequency and percentage for categorical variables, whereas quantitative data were expressed as mean ± standard error of mean for normally distributed variables and median (minimum-maximum) for non-normally distributed data. Categorical variables were analyzed by Pearson chi-square test and Fisher's exact test. For the variables that were not normally distributed, Mann-Whitney U test was used to compare two independent groups, Wilcoxon signed rank tests for two dependent groups and Friedman test for three dependent groups. If a significant difference was detected among three dependent groups, post hoc analysis was performed using Wilcoxon signed-rank test with Bonferroni correction. A probability level of $p<0.05$ was considered statistically significant.

Results

A total of 71 eligible patients (37 men, 34 women) with a mean age of 61.4±11.6 years (34-81 years) and a diagnosis of BRVO in 43 (60.6%) and CRVO in 28 (39.4%) were included in the study. The right eye was involved in 36 patients (50.7%) and the left eye in 35 patients (49.3%). Initial treatment was a single intravitreal dexamethasone implant in 45 patients (63.4%) (Group 1) and three loading doses of intravitreal ranibizumab in 26 patients (36.6%) (Group 2). There was no statistically significant difference between the groups with regard to gender distribution ($p=0.209$) or type of RVO ($p=0.898$). However, the mean age was higher in Group 1 than Group 2 ($p<0.001$) (Table 1). Pre-treatment best corrected visual acuity (BCVA) was significantly worse among Group 1 patients when compared to Group 2 (1.29±0.44 and 0.85±0.40 logMAR, respectively; $p<0.001$). Pre-treatment CMT was thicker in Group 1 than Group 2, but the difference was not statistically significant (689.6±166.7 µm and 613.2±163.8 µm, respectively; $p=0.059$).

Following complete anatomical resolution of CME and SMD at 3 months after intravitreal therapy, CME recurred at 4 months in 36 patients (50.7%), at 5 months in 23 patients (32.4%), at 6 months in patients 9 (12.7%), and at 7 months in 3 patients (4.2%), with a mean time of 4.7±0.8 months (range: 4-7 months). The mean time to recurrence was 5.0±0.9 months

(range: 4-7 months) in BRVO patients and 4.3±0.5 months (range: 4-5 months) in CRVO patients (p=0.001). Recurrence times in Group 1 and 2 patients are shown in detail in Table 2 and the mean duration of recurrence was similar for both groups (p=0.984). The patients' mean BCVA and CMT prior to treatment, at 3 months, and at the time of CME recurrence differed significantly (p<0.001 for all) (Table 3).

At the time of CME recurrence, SMD was present in 41 patients (57.7%). SMD was present in 21 (48.8%) of the 43 BRVO patients and 20 (71.4%) of the 28 CRVO patients (p<0.001) and in 27 (60.0%) of the 45 Group 1 patients and 14 (53.8%) of the 26 Group 2 patients (p=0.613) at the time of recurrence.

Discussion

The most common reason for decreased vision in patients with RVO is CME, which is frequently associated with SMD in these patients.[13] However, the pathogenesis of SMD in RVO is still not clearly understood.[13,14,15,16] The occlusion of retinal venous outflow in RVO leads to increased intravascular pressure, particularly in postcapillary venules and capillaries. Venous obstruction also leads to capillary nonperfusion and tissue ischemia, resulting in the production of certain cytokines that enhance vascular permeability. Park et al.[17] reported that aqueous VEGF levels are higher in patients with SMD associated with BRVO compared with patiets without SMD. Thus, it is well known that increased intravascular pressure and vascular

Table 1. Clinical and demographic characteristics of the study population.

	Group 1 (n=45)	Group 2 (n=26)	p
Age (years) Mean ± SD (range)	65.8 ± 9.2 (41-81)	53.8 ± 11.7 (34-73)	<0.001[a]
Gender			
Male, n (%)	26 (57.8%)	11 (42.3%)	0.209b
Female, n (%)	19 (42.2%)	15 (57.7%)	
Type of RVO			
BRVO, n (%)	27 (60.0%)	16 (61.5%)	0.898[b]
CRVO, n (%)	18 (40.0%)	10 (38.5%)	

SD: Standard deviation, RVO: Retinal vein occlusion, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, [a]Mann-Whitney U test, [b]Chi-square test

Table 2. The recurrence time of the study groups

	Group 1 (n=45)	Group 2 (n=26)	p
Timing of recurrence, n (%)			
Month 4	23 (51.2)	13 (50.1)	0.989[a]
Month 5	14 (31.1)	9 (34.6)	
Month 6	6 (13.3)	3 (11.5)	
Month 7	2 (4.4)	1 (3.8)	
Mean time to recurrence (months), mean ± SD (range)	4.7±0.9 (4-7)	4.7±0.8 (4-7)	0.984[b]

SD: Standard deviation, [a]Chi-square test, [b]Mann-Whitney U test

Table 3. Best corrected visual acuity and central macular thickness of patients before treatment, at 3 months, and at time of recurrence

	Pretreatment	Month 3	During recurrence	p*
BCVA (logMAR), mean ± SD (range)	1.13±0.47 (0.30-1.80)	0.33±0.31 (0-1.50)	0.72±0.44 (0.05-1.80)	<0.001
CMT (µm), mean ± SD (range)	661.6±168.6 (331-1,048)	244.6±32.2 (207-270)	531.6±171.8 (285-1,084)	<0.001

BCVA: Best corrected visual acuity, CMT: Central macular thickness, *Friedman Test
Post-hoc comparisons: BCVA: Pretreatment-Month 3 p<0.001, Pretreatment-During recurrence p<0.001, Month 3-During recurrence p<0.001, CMT: Pretreatment-Month 3 p<0.001, Pretreatment-During recurrence p=0.011, Month 3-During recurrence p<0.001

permeability in RVO have important roles in the development of CME and SMD. However, many studies have demonstrated that the pathogenesis of SMD secondary to RVO is not only related to increased intravascular pressure and vascular permeability, but it is presumably multifactorial and also related to inflammation.[16,18,19] Noma et al.[16] reported that vitreous levels of inflammatory factors such as soluble vascular endothelial growth factor receptor-2 and soluble intercellular adhesion molecule-1 were higher and the anti-inflammatory pigment epithelium-derived factor were lower in CRVO patients with SMD, suggesting a role of inflammation in SMD. Dacheva et al.[20] measured the vitreous levels of interleukin 6, monocyte chemoattractant protein-1, and VEGF-A and concluded that inflammatory cytokines were more often correlated with morphological changes (CMT, thickness of the neurosensory retina, extent of SMD, and disintegrity of ellipsoid zone) assessed by OCT, whereas VEGF-A did not correlate with CRVO-associated changes in OCT. Therefore, anti-VEGF therapy alone may not be sufficient to decrease the inflammatory response in CRVO patients with SMD.

Intravitreal anti-VEGF agents and corticosteroids are the main treatment options for the treatment of CME secondary to BRVO and CRVO.[3,4,5,6] Gallego-Pinazo et al.[21] compared the efficacy of intravitreal ranibizumab in the treatment of CME due to BRVO with and without SMD and found that CME improved significantly after a mean of 5 intravitreal ranibizumab injections over a median follow-up of 12.5 months in the patients with SMD and after a mean of 4.3 injections over a median follow-up of 10.4 months in patients without SMD. Although triamcinolone acetonide is the first intravitreal corticosteroid reported to be effective in the treatment of CME and SMD secondary to RVO, sustained-release dexamethasone implant (Ozurdex®) is the preferred intravitreal steroid recently because it has fewer adverse effects compared to triamcinolone acetonide.[4] Maggio et al.[22] determined in their study that Ozurdex® was a safe and effective option for the treatment of RVO-related CME, but the presence of SMD and macular ischemia were negatively associated with visual outcomes. In a study by Elbay et al.[23], CME and SMD regressed after a single intravitreal injection of dexamethasone implant in 23 of 24 patients with SMD secondary to nonischemic CRVO. However, 20 patients relapsed within 5.45±1.45 months and 17 of them had SMD. Karacorlu et al.[6] reported that CME and SMD secondary to CRVO recurred in 50% of patients at 6 months and SMD was again present in all eyes during recurrence. Contrary to these studies, SMD was present in only 57.7% of patients with recurrent CME in our study. The prevalence of SMD during recurrence appeared to be similar for both the dexamethasone and ranibizumab groups in our study. As SMD is a well-known inflammatory biomarker and corticosteroids may have a more prominent anti-inflammatory effect compared to anti-VEGF agents, we would have expected to find a lower SMD prevalence in patients treated with dexamethasone implant. However, we must note that the patients in the dexamethasone group were older and had a lower pretreatment BCVA, probably having more severe disease, which in turn might cause bias in the interpretation of the results.

We evaluated the medical records of patients at 3 months after a single injection of sustained-release dexamethasone implant or a loading dose (three monthly injections) of ranibizumab as first-line therapy in treatment-naive patients with CME and SMD secondary to RVO. If patients exhibited complete anatomical resolution of CME and SMD at 3 months, we continued to examine OCT findings from monthly follow-up visits in order to detect the signs of CME recurrence, such as increased CMT and the appearance of intraretinal cysts. At the time of recurrence, we noted whether SMD was present. In our study, SMD was present during recurrence in only 57.7% of patients who had CME and SMD before treatment. However, the SMD incidence would be lower if the follow-up interval was shorter than one month and higher if it was longer than one month, probably due to the increased amount of CME and further decreased anti-inflammatory effects of intravitreal agents. Thus, it can be speculated that it is important to prevent the occurrence of SMD with timely retreatment in order to achieve better anatomical and functional outcomes. The study data are limited up to the time of first CME recurrence, and the treatment choice at recurrence and the functional and anatomical results of treatment were beyond the scope of the current study.

Study Limitations

This was a preliminary study to evaluate the prevalence of SMD in patients with recurrent CME secondary to RVO who were initially treated for CME with an accompanying SMD and determine the factors affecting the occurrence of SMD in these patients. However, the study has some limitations, including the small sample size and its retrospective nature. In addition, the treatment groups differed in age and some baseline clinical characteristics such as BCVA, which makes interpreting the results difficult and potentially introduces bias. Furthermore, we did not differentiate ischemic and nonischemic RVO, which may affect the results.

Conclusion

In conclusion, this study suggests that SMD seems to be more frequent in patients with recurrent CME secondary to CRVO when compared to BRVO. The choice of initial intravitreal treatment with either ranibizumab or dexamethasone implant did not affect the prevalence of SMD in recurrent CME. However, longer-term prospective studies including a larger number of patients with similar pretreatment baseline characteristics are needed to reach a more accurate and definitive conclusion.

Ethics

Ethics Committee Approval: It was approved by the Ankara Numune Hospital Ethics Committee.

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.Ş., S.D., P.Y., Concept: M.A.Ş., Design: M.A.Ş., Data Collection or Processing: M.A.Ş., F.B.T., S.D., Analysis or Interpretation: M.A.Ş., F.B.T., S.D., Literature Search: M.A.Ş., F.B.T.,S.D., Writing: M.A.Ş.

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