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TITLE PAGE

Title: OUTER RETINAL LAYER DETERIORATION PATTERNS IN EYES WITH DIABETIC SEROUS MACULAR DETACHMENT

Short Title: Outer retinal deterioration in SMD

Authors: Furkan Kirik[1], MD; M. Giray Ersoz[2*], MD, FEBO; Furkan Atalay[1], MD; Ersin Akbulut[1], MD, FEBO; Mehmet Kucuk[1], MD; Arif Koytak[1], MD; Hakan Ozdemir[1], MD

1 Bezmialem Vakif University, Faculty of Medicine, Department of Ophthalmology, Istanbul, Türkiye

2 Biruni University, Faculty of Medicine, Department of Ophthalmology, Istanbul, Türkiye

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* **Corresponding author:** M. Giray Ersoz, MD, FEBO

Biruni University, Faculty of Medicine, Department of Ophthalmology

Gültepe Mah., Halkalı Cd., No: 99, 34295, Küçükçekmece / Istanbul / Türkiye

Phone: +90 505 855 50 84; E-mail: m.girayersoz@gmail.com

Key words: diabetic macular edema; diffuse; disruption of retinal outer layers; ellipsoid zone; external limiting membrane; fistula; outer retinal layer; patch; serous macular detachment; wedge

Summary: In eyes with diabetic serous macular detachment, five outer retinal layer deterioration patterns with distinct clinical and anatomical characteristics were identified by OCT imaging: DIFFUSE, PATCH, WEDGE, FISTULA and SMD-DROL. WEDGE was associated with better visual acuity, whereas DIFFUSE linked to higher risk of ELM/EZ alterations.

ABSTRACT

Purpose: To classify the outer retinal layer (ORL) deterioration patterns in eyes with diabetic serous macular detachment (SMD), and to determine their impact on visual and anatomical prognosis.

Methods: In this retrospective case series, optical coherence tomography images of patients with diabetic macular edema between January 2015 and June 2024 were reviewed. Eyes exhibiting SMD were evaluated for ORL integrity, and five different ORL deterioration patterns were identified according to their structural characteristics: DIFFUSE, PATCH, WEDGE, FISTULA, and SMD-DROL. The relationship of these patterns with best-corrected visual acuity (BCVA), and post-treatment external limiting membrane (ELM) and ellipsoid zone (EZ) status was analyzed with regression models.

Results: A total of 1018 eyes of 592 patients were reviewed, and 168 eyes of 131 patients exhibited at least one ORL deterioration pattern. WEDGE was the most common pattern (31.75%), while DIFFUSE was the least detected (5.29%). WEDGE was associated with better BCVA, as well as with a decreased risk of alterations in the ELM/EZ ($p<0.001$). ELM/EZ alterations were observed in all eyes with the DIFFUSE, and post-treatment ELM alteration width was associated with poorer visual outcome ($p<0.05$).

Conclusion: Diabetic SMD may present various ORL deterioration patterns associated with heterogeneous clinical and anatomical outcomes.

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes mellitus (DM).[1] The increased vascular permeability and disruption of the blood-retina barrier in DR lead to fluid extravasation into the intraretinal and/or subretinal space, causing DME.[2] Serous macular detachment (SMD) refers to dome-shaped subretinal fluid accumulation in the space between the neurosensory retina and the retinal pigment epithelium, which can occur in various retinal pathologies, including DR.[3-7] While some authors accept SMD as a separate type of DME, it has been proposed in recent years that SMD should be considered an adjunctive finding.[3, 8, 9] The coexistence with other types of DME, and its occurrence beneath the neurosensory retina are features that render SMD as an adjunctive finding in DME.[10, 11]

In addition to DME, several imaging biomarkers have been shown to affect visual prognosis in patients with DR.[12, 13] Among these structural changes detectable by OCT, the deterioration of the outer retinal layers (ORL), including the external limiting membrane (ELM), and ellipsoid zone (EZ) have been closely associated with visual function.[12-15] However, the prognostic significance of SMD secondary to DR remains controversial.[14-17] One reason for this may be the lack of detailed assessment of ORL deteriorations that are coexistent with SMD. Moreover, the space that occurs between the neurosensory retina and the RPE in SMD may potentially allow for the evaluation of ORL from a different aspect. In this context, there is a need to identify and address the ORL deterioration patterns that accompany SMD. To the best of our knowledge, there is no study that explores ORL deterioration patterns in diabetic SMD and classifies them according to OCT imaging features.

This study aimed to evaluate the ORL deterioration patterns in eyes with diabetic SMD, classify these patterns based on their structural characteristics, and determine their impact on visual prognosis.

METHODS

In this single-center, retrospective case series the medical records and SD-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) images of patients who were recommended intravitreal injection treatment for DME between January 2015 and June 2024 were assessed. Both the fovea-centered horizontal single-line and raster scans (25 B-scans) were evaluated by a retinal specialist (FK) for the presence of diabetic SMD in all eyes. In images with diabetic SMD, the structural integrity of the ORL located beneath the outer nuclear layer (from the ELM to the RPE) was evaluated by two experienced retinal specialists

(FK, GE). Images with loss or disruption of ELM and/or EZ above the SMD were considered as ORL deterioration and included in this study. In images where there was disagreement between the observers regarding the ORL status, a third retinal expert (HO) was consulted, and the images were included or excluded based on this expert's assessment. Eyes were excluded if there were other causes of SMD (e.g., retinal vein occlusion [RVO], age-related macular degeneration), if the SMD was due to vitreomacular interface disease, or if pathologies such as cataract or vitreous hemorrhage interfered with macular OCT imaging.

Based on the features of ELM and/or EZ alterations detected in eyes with diabetic SMD, five different ORL deterioration patterns were identified (Fig. 1):

1. ***DIFFUSE****:* Characterized by a ≥1000-micron-wide absence of the EZ in the subfoveal region (central macula). In this pattern, the ELM remains intact along with the EZ defect (Fig 1A and B).
2. ***PATCH****:* Characterized by a focal absence of the EZ <1000 microns in width, which does not meet the definition of the DIFFUSE pattern described above. In this pattern, the ELM remains intact along the EZ defect as well (Fig 1C and D).
3. ***WEDGE:*** Characterized by an intraretinal cystic cavity extending to the ELM, along with an intact ELM and a continuous EZ at the apex of the lesion. At the base, an angular shape gap of an 'inverted V' appears between the photoreceptor columns. In this pattern, although changes in EZ intensity may be observed at the apex of the lesion, there is no full-thickness EZ loss (discontinuation), unlike in the DIFFUSE and PATCH (Fig 1E and F).
4. ***FISTULA****:* Characterized by a full-thickness ORL aperture that causes a connection between the SMD and an intraretinal cystic cavity, the lesion area shows neither EZ nor ELM integrity (Fig 1G and H). This finding has been reported previously in the eyes with DME and RVO.[18-20]
5. ***DISORGANISATION OF RETINAL OUTER LAYERS (DROL):*** Characterized by a deterioration where the ORL remains intact, yet the ELM and EZ cannot be delineated separately and the typical anatomical organization of the ORL is absent (Fig 1I and J). Since this pattern differs from the DROL described in the literature for eyes with macular edema without SMD, it will be referred to as ***SMD-DROL*** throughout the article.[21, 22]

Untreated eyes (patient-related; treatment rejection or missing) or eyes without OCT imaging at follow-up with regression of SMD after treatment were excluded in the post-treatment evaluation. Both baseline and post-SMD foveal volumes (central 1 mm ETDRS subfield)

were quantified using the automated segmentation module of the Spectralis SD-OCT (HEYEX; Heidelberg Engineering, Heidelberg, Germany). Baseline SMD height and foveal neurosensory retinal thickness (NRT) at both baseline and post-SMD visits were measured by an experienced retinal specialist (F.K.) using the built-in caliper function of the device. The horizontal width of post-SMD ELM and EZ alterations was measured in the same manner by two masked ophthalmologists (M.K. and F.A.) who were masked to the ORL deterioration pattern types, and the mean of their independent measurements was used as the final value for analysis. The OCT scans from the follow-up where SMD regressed (post-SMD) were evaluated by the same experienced retinal specialists (F.K. and M.E.) according to EZ and ELM status. Post-treatment ELM and EZ status were categorized as follows: 1- Intact (structural integrity preserved, no change in reflectivity), 2- Disruption (structural integrity preserved, but reflectivity altered) and 3- Loss (complete loss of structural integrity) (Fig 2).
In OCT images with SMD, the presence of intraretinal cysts extending to the ELM and the presence of hyperreflective material within these cysts were recorded in relation to ORL deterioration patterns. The best-corrected visual acuities (BCVA) at baseline and the post-treatment visit when SMD had regressed, and the duration of SMD were obtained from the medical records.

Statistical Analysis

Statistical analyses were carried out with Stata 19.0 (StataCorp LLC, College Station, TX, USA). Categorical variables are presented as frequencies (%) and continuous variables as median (minimum–maximum). Distributional assumptions were examined visually with histograms and Q-Q plots. Inter-rater agreement for the ELM and EZ alteration measurements was assessed using the intraclass correlation coefficient (ICC). Several right-skewed anatomical measurements, including baseline and post-SMD NRT and foveal volume, SMD height at the baseline visit, and the ELM and EZ alteration measurements at the post-SMD visit, were natural log-transformed with only the ELM and EZ alteration measurements increased by a constant of 1 μm prior to transformation. For the interaction analyses the log-transformed (ln) ELM and EZ alterations measurements were mean-centered while the other transformed covariates remained in their original scale because collinearity was assessed using the variance inflation factor (VIF) and all VIF values were <4. Visual acuities were converted to logMAR for statistical analysis and presented with their Snellen equivalents.

Within-eye changes from baseline to the post-SMD visit were examined with the Wilcoxon signed-rank test. The effect of the ORL deterioration patterns on BCVA (in logMAR) was

assessed using a linear mixed-effects model with a random intercept for eye, fixed effects for visit, the ORL deterioration patterns and their visit-by-pattern interaction terms, and potential anatomical confounders (baseline and post-SMD log-transformed NRT and foveal volume, post-SMD mean-centered log-transformed ELM and EZ alteration widths, baseline SMD height, and duration of SMD). Model parameters were estimated by maximum likelihood using cluster-robust standard errors. The joint effect of the visit-by-pattern interaction terms was evaluated with a Wald χ^2 test. Changes in BCVA were expressed as ETDRS letters, and for regression analyses, coefficients for predictors associated with these changes were also converted to and presented as their ETDRS letter equivalents.

To explore the combined influence of the ORL deterioration patterns on the baseline and post-SMD NRT and foveal volume, a multivariate analysis of variance (MANOVA) was first performed, adjusted for age and sex. Multivariate significance was assessed using Wilks' lambda statistic. When the global test reached significance, each outcome was re-examined in separate ordinary least-squares regressions, also adjusted for age and sex, and fitted with heteroskedasticity-consistent standard errors; and the overall contribution of the five patterns was summarised with a Wald F statistic.

The association of post-treatment ELM and EZ status with ORL deterioration patterns was evaluated with a univariate generalized ordinal logistic regression model. Due to perfect separation in some variables, multivariate analyses employed a Bayesian ordinal logistic regression model estimated via the random-walk Metropolis–Hastings algorithm (12,500 iterations: 2,500 burn-in, 10,000 sampling) and adjusted for baseline foveal NRT and foveal volume. Variables with $p<0.20$ in univariate analyses were included in the multivariate model. Regression results were presented as coefficients (β) or odds ratio (OR) with 95% confidence intervals (95% CI) and p-values, while Bayesian results are presented as multivariate posterior (MP) means, standard deviations (SD), and 95% credible intervals (CrI). A p-value <0.05 was considered statistically significant; for Bayesian models, significance was determined when the 95% CrI did not include 0.

RESULTS

A total of 8892 medical records and SD-OCT imaging sessions from 1018 eyes of 592 patients diagnosed with DME were evaluated. Among these, 307 eyes of 216 patients exhibited SMD at any visit. 168 eyes of 131 patients with at least one ORL deterioration pattern were included in this study. Based on the predefined patterns, DIFFUSE was observed in 10 eyes, PATCH in 25, WEDGE in 60, FISTULA in 40 and SMD-DROL in 54. Twenty-

one eyes showed more than one pattern. The median age was 58 (48–72) years, and 75 (57.25%) of the patients were male (Table 1). Post-SMD analyses were performed in 148 eyes with follow-up SD-OCT images in which SMD regressed after intravitreal treatment. Snellen equivalent of the median BCVA was 20/63 (20/25 – 20/2000) at baseline and 20/50 (20/20 – 20/2000) at the post-SMD visit (p:0.002). At the post-SMD visit, foveal NRT and foveal volume had decreased significantly (both p<0.001). The median baseline SMD height was 150 μm (48–530), and the median time to SMD regression was 16 weeks (4–31.3) (Table 1). The inter-rater reliability for the ELM alteration measurements was 0.93 (95 % CI 0.90–0.95), and for the EZ alteration measurements it was 0.91 (95 % CI 0.88–0.94).

In a linear mixed-effects regression with a random intercept for eye, BCVA (in logMAR) was modeled as a function of visit (baseline vs. post-SMD), ORL deterioration patterns, their interaction, and anatomical covariates. The model was significant (Wald $\chi^2(17)$:154.99, p<0.001), while the overall effect of visit was non-significant (β:0.021, p:0.846). Among the ORL deterioration patterns, presence of the WEDGE was independently linked to better BCVA (β:-0.266, corresponding to approximately +13.3 ETDRS letters, p:0.017), whereas presence of DROL showed a borderline association (β:-0.193, corresponding to approximately +9.7 ETDRS letters, p:0.097). No significant differences were observed for the other patterns, and none of the pattern-by-visit interactions reached significance (joint Wald $\chi^2(5)$:5.47, p:0.361). Of the anatomical factors, wider ELM alteration and greater SMD height (both log-transformed) were associated with worse BCVA (β:0.060, corresponding to approximately -3.0 ETDRS letters per ln-unit, p<0.001; β:0.125, corresponding to approximately -6.3 ETDRS letters per ln-unit, p:0.024, respectively). Foveal NRT and volume, EZ alteration width and duration of SMD had no independent effect (p>0.05) (Table 2).

The association between post-treatment ELM/EZ status and ORL deterioration patterns was first analyzed with univariate generalized ordinal logistic regression model. Notably, no eye with DIFFUSE had an intact ELM at the post-SMD follow-up. In the univariate model, DIFFUSE was found to increase the risk of ELM loss (OR: 25.04, 95% CI: 4.940 – 126.965). Although PATCH and SMD-DROL increased the risk of ELM disruption (OR: 4.22, 95% CI: 1.352 – 13.183, and OR: 2.29, 95% CI: 1.092 – 4.782, respectively), there was no association with ELM loss (p:0.994, and p:0.857, respectively). Conversely, the WEDGE reduced the risk of both ELM disruption and loss (OR: 0.15, 95% CI: 0.070 – 0.311, and OR: 0.04, 95% CI: 0.006 – 0.375, respectively). Due to perfect separation between DIFFUSE and ELM alterations, a multivariate model assessing the relationship between ORL deterioration

patterns and post-treatment ELM status was built using a Bayesian ordinal logistic regression model adjusted for baseline log-transformed NRT and foveal volume. In the multivariate model including DIFFUSE, PATCH, WEDGE, and SMD-DROL patterns, DIFFUSE increased the risk of ELM alterations (MPM: 3.31 ± 0.95, 95% CrI: 1.543 – 5.272), and WEDGE was negatively associated (MPM: -1.65 ± 0.55, 95% CrI: -2.736 – -0.573) (Table 3). At the post-SMD follow-up, EZ loss was observed in all eyes with the DIFFUSE, and EZ disruption or loss was observed in all eyes with PATCH. The univariate model revealed that PATCH increased the risk of EZ loss (OR: 3.63, 95% CI: 1.410 – 9.340). In contrast, the WEDGE reduced the risk of both EZ disruption and loss (OR: 0.22, 95% CI: 0.072 – 0.672). Although the univariate model for the SMD-DROL was statistically significant (p:0.036, model significance), the association between SMD-DROL and increased risk of EZ alterations (intact vs. disruption or loss) was marginally significant (OR: 7.76, 95% CI: 0.993 – 60.630). In the multivariate Bayesian ordinal logistic regression model adjusted for baseline log-transformed NRT and foveal volume, the DIFFUSE (due to perfect separation) and the FISTULA (due to non-significance in the univariate analysis) patterns were excluded. The WEDGE demonstrated a negative association with EZ alterations (MPM: -1.92 ± 0.48, 95% CrI: -2.843 – -0.951). Although the PATCH showed a high risk for EZ disruption or loss, the result was marginally non-significant (MPM: 0.96 ± 0.51, 95% CrI: -0.066 – 2.058) (Table 3). MANOVA of the log-transformed baseline and post-SMD NRT and foveal volume confirmed a global effect of ORL deterioration patterns (Wilks' λ:0.651, $p<0.001$). Pattern-specific multivariate tests were significant for DIFFUSE (p:0.021) and FISTULA (p:0.033), while PATCH (p: 0.051) and DROL (p: 0.063) showed borderline effects. Follow-up robust ordinary least-squares models showed that the overall pattern effect remained significant for baseline NRT (p:0.008), post-SMD NRT (p:0.010) and baseline foveal volume (p:0.004), whereas the post-SMD foveal volume model did not reach significance (p:0.074). At the single-contrast level, PATCH pattern tended to have a thinner baseline NRT (β:-0.248, p:0.070), while a weak opposite trend was observed for WEDGE at the post-SMD visit (β:0.189, p:0.085). Post-SMD NRT was significantly greater in FISTULA (β:0.253, p:0.021). Baseline foveal volume was larger in DROL eyes (β:0.162, p:0.002) and showed a borderline increase in FISTULA eyes (β:0.101, p:0.074). No pattern differences persisted in foveal volume at the post-SMD visit (Table 4).

The presence of intraretinal cysts extending to the ELM was completely associated with both WEDGE and FISTULA due to the definitional criteria, whereas it was less in DIFFUSE

compared to the others. The highest frequency of intracystic hyperreflective material was observed in the PATCH and FISTULA (Table 5).

DISCUSSION

In this study, five different ORL deterioration patterns were identified in eyes with diabetic SMD, each thoroughly characterized, along with their structural and functional outcomes. Eyes with the WEDGE pattern had better BCVA both at baseline and at the post-SMD visit compared to the other deterioration patterns, and this pattern was less associated with ELM/EZ alterations. In contrast, ELM and EZ alterations were more pronounced in DIFFUSE and PATCH patterns. FISTULA was associated with greater post-SMD NRT, whereas SMD-DROL had larger baseline foveal volume. Wider post-SMD ELM alteration and higher baseline SMD height were linked to worse BCVA. Based on these findings, evaluating the presence of SMD in conjunction with other biomarkers, such as ORL deterioration patterns, rather than individually, may provide valuable information about the prognosis of patients with DME.

SMD has been reported to be present in 15-31% of eyes with DME.[3, 7, 18] Controversial results have been reported regarding the prognostic implications of diabetic SMD. Some studies suggest that the presence of SMD may have a favorable therapeutic response, whereas others show no significant association.[7, 16, 22, 23] The controversial results may be explained by the tendency to consider SMD as a unique entity and neglect the potential ORL alterations known to be closely related to visual function that may accompany diabetic SMD. Indeed, some authors have even stated that it is not feasible to evaluate the EZ when SMD is present.[10] However, this study demonstrated that various ORL deterioration patterns accompanying SMD may be associated with different functional and structural outcomes. Accordingly, it may be useful to assess the presence of SMD in conjunction with coexisting ORL findings or potentially categorize different ORL deterioration patterns to better understand their prognostic implications. To the best our knowledge, this is the first study to classify ORL deterioration patterns in eyes with diabetic SMD.

In some eyes, a type of ORL deterioration was observed that led to a connection between the intraretinal cystic space and the SMD due to a full-thickness discontinuity with a hyper-transmission defect. This lesion was named FISTULA because it represents a pathological connection between two cavities. While previous limited case series, such as the study by Ota

et al.[18] in 9 of 28 DME eyes, attributed this connection to ELM barrier damage from subretinal fluid and exudation, similar finding in RVO-related macular edema have been linked to increased intraretinal cyst volume and Müller cell traction.[20] In our cohort, 40 eyes exhibited FISTULA-type ORL deterioration. Although earlier studies suggested an association between FISTULA and poor visual function, presented findings did not show a significant link with BCVA.[19] This discrepancy may be due to preserved central vision in some cases, resulting from the parafoveal location of FISTULA, and the restoration observed in the ORL after treatment. Moreover, the absence of a significant relationship between FISTULA and post-treatment ELM/EZ integrity implies that this focal ORL discontinuity might not be permanent.[24] In many cases, the hyperreflective material within intraretinal cysts supports the hypothesis that lipids and proteins in the extravasated fluid contribute to temporary ORL damage.

In contrast to the ORL discontinuity seen in FISTULA, some eyes exhibited a non-full-thickness, angular-shaped deterioration in the ORL at the base of an intraretinal cystic cavity extending to the ELM. Named WEDGE for its characteristic OCT appearance, this lesion did not feature the full ORL discontinuity seen in FISTULA, nor the distinct boundaries of EZ interruption observed in DIFFUSE or PATCH. To our knowledge, a similar lesion accompanying SMD has not been previously described. The alterations of the ORL caused by the intraretinal cystic cavity extending to the ELM was previously described by Nair et al.[25] as "Plume sign". However, this finding has not been associated with SMD. In addition, the fact that hyperreflective cyst content, which is one of the primary criteria of the Plume sign, was less frequent in the WEDGE characteristically differentiates the two lesions. Clinically, the WEDGE was more benign than the other patterns, was associated with better baseline and post-treatment visual function and fewer ELM/EZ damage.

In retinal vascular pathologies such as DR and RVO, the condition in which the inner retinal structures are disorganized and the boundaries of these layers cannot be distinguished is defined as DRIL.[22, 26] Ischemic microvascular damage has been emphasized for the mechanism of DRIL and has been associated with poor visual prognosis.[27] Recently, the term DROL has also emerged to describe similar pathology in the outer retina. However, there is no consensus in the literature regarding DROL. Vujosevic et al. defined "DROL" and "DROL plus" primarily as ELM and EZ loss or disruption.[21] In RVO cases, Bemme et al., and in DME cases, Sardana et al., have similarly described DROL as ELM and EZ disruption.[22, 28] The SMD-DROL preferred in this study differs from previous definitions because it is

characterized by the loss of recognizable anatomical boundaries among the ORL rather than ELM/EZ loss. In other words, it is similar to DRIL, but it is observed in the outer retina and co-occurs with SMD. According to the findings, SMD-DROL was not associated with ELM disruption or loss in the multivariate model and had no significant impact on BCVA. These findings may suggest that SMD-DROL may not be as poor prognostic biomarker as DRIL.

ELM or EZ alterations have previously been shown to be associated with poor visual outcomes in retinal diseases.[15, 29] Unlike WEDGE, some eyes exhibited focal or extended EZ loss overlying the SMD. In this study, focal EZ defects <1000 μm were termed as PATCH and EZ defects involving the subfoveal area and ≥1000 μm were termed as DIFFUSE. Although these two subtypes are relatively uncommon in the study population, DIFFUSE has been highly associated with ELM/EZ abnormalities. Because all eyes with DIFFUSE presented with EZ loss and ELM disruption at the post-SMD visit. Although the linear mixed-effects model did not demonstrate a significant direct effect of the DIFFUSE pattern on BCVA, wider ELM alteration was linked to worse BCVA. Considering the significant relationship between DIFFUSE and post-SMD ELM alteration, these findings indicate that the extent of pattern-induced ELM damage, rather than the mere presence of the pattern, is the primary determinant of BCVA. Accordingly, the DIFFUSE pattern may be indirectly related to poorer BCVA. As for PATCH, it was more frequently found to be associated with disruption of the EZ and ELM. In both findings, although the ELM on the SMD seemed to be intact, loss of ELM was detected after treatment. It is considered that this situation can be explained by the ELM maintaining its anatomical barrier function but losing its hyperreflective characteristic on OCT and, most likely, functional properties.[30] Additionally, PATCH showed no significant baseline effect on BCVA, and its time interaction indicated a borderline marginally significant trend toward greater visual improvement following SMD regression. It is considered that the different BCVA trends between PATCH and DIFFUSE are related to the extent of ELM damage, because the small, local ORL alteration in PATCH can partially recover after SMD regression, whereas the broader ORL damage in DIFFUSE often persists after SMD resolves and therefore limits visual recovery.

In this study, the relationships between ORL deterioration patterns and both baseline and post-SMD NRT and foveal volume were assessed using MANOVA and multivariable models adjusted for age and sex. The global MANOVA revealed a strong overall pattern effect on foveal metrics, indicating that these patterns can influence foveal anatomy. Although

DIFFUSE did not correlate with any single foveal metric in the adjusted regressions, it showed the highest pattern-specific significance in MANOVA, suggesting that its presence may be linked to multidimensional structural involvement rather than isolated increases or decreases in individual foveal parameters. For PATCH, the borderline pattern-specific significance and a borderline negative baseline NRT coefficient point to a tendency toward thinner initial NRT. WEDGE, previously associated with better visual prognosis and limited ELM/EZ alteration, showed no significant impact on foveal measurements, supporting the hypothesis that it represents a comparatively benign prognostic profile. FISTULA, which implies a connection between intraretinal and subretinal fluid spaces, was the only pattern significantly associated with increased post-SMD NRT and reached significance in the pattern-specific analysis; this may indicate residual intraretinal fluid even after SMD regression. SMD-DROL displayed borderline pattern-specific significance and was significantly linked to greater baseline foveal volume, which may reflect transient disorganization in the ELM and deeper retinal layers caused by widespread foveal edema. Despite these interpretations, the underlying pathophysiological mechanisms remain unclear, as many of these patterns are newly described and have never before been analyzed this comprehensively. Moreover, although neither foveal NRT nor volume showed a significant association with visual function in the linear mixed-effects model, the study included only SMD eyes with documented ORL deterioration; the exclusion of control eyes without pathological ORL changes may have limited the ability to detect an effect of foveal metrics on visual function.

Although some ORL deterioration patterns were observed less frequently, the strengths of the study include a large case series, the specific definition of ORL deterioration patterns associated with SMD, and the assessment of both structural and functional outcomes. In addition, several findings are novel, and the confusion surrounding previously described lesions such as DROL was addressed. However, the study has limitations. It was retrospective and single-center, with relatively small sample sizes for some patterns. Furthermore, the spacing between raster scan slices may have led to missing retinal abnormalities between the OCT images, and while all images were evaluated by retinal specialists, the characteristics of the tissue between slices remain unknown. Dense retinal-scanning protocols, such as horizontal and vertical raster as well as radial scans, would also be valuable for defining the full extent of each pattern and for performing detailed two-dimensional mapping and analysis. Another major limitation of this study is that the relationship between macular ischemia and

the identified patterns could not be assessed. Because demonstrating macular ischemia could both clarify the mechanisms underlying these patterns and exert a significant influence on visual function, it should be regarded as a key variable in future investigations. Finally, other OCT biomarkers like DRIL and hyperreflective dots, as well as structural changes in patients with recurrent SMD after treatment, were not examined.

In conclusion, this study demonstrates that diabetic SMD does not present as a homogeneous clinical entity but can manifest with various ORL deterioration patterns. Each pattern may have a distinct clinical and structural presentation, suggesting that evaluation of ORL deterioration in eyes with SMD may provide additional prognostic information. Future prospective and multicenter longitudinal studies conducted with large cohorts, utilizing denser macular imaging, assessing macular ischemia and investigating additional OCT biomarkers, may provide valuable information about the prevalence, structural characteristics and prognostic impact of these defined ORL deterioration patterns.

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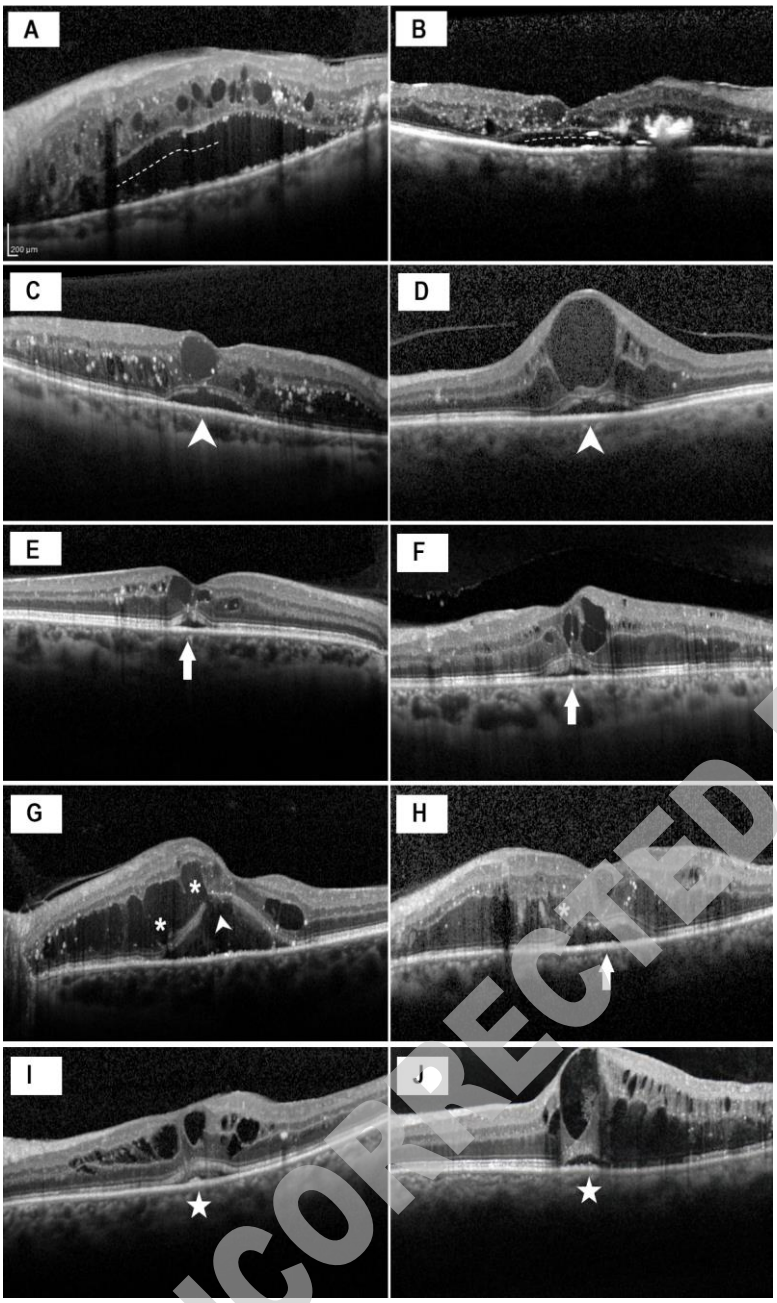
FIGURE LEGENDS

Fig. 1. Representative spectral domain-optical coherence (SD-OCT) images of outer retinal layer deterioration patterns in eyes with diabetic serous macular detachment (SMD). **A** and **B** illustrate the DIFFUSE pattern, characterized by a subfoveal absence of the ellipsoid zone (EZ) extending ≥1000 μm with an intact external limiting membrane (ELM) (dashed lines). **C** and **D** show the PATCH pattern, characterized by a focal (<1000 μm) EZ loss with preserved ELM (white arrowheads). **E** and **F** display the WEDGE pattern, featuring an intraretinal cyst extending to the ELM, a continuous EZ at the lesion apex, and an angular, inverted V-shaped gap at its base (white arrows). **G** presents two FISTULA patterns (asterisks) alongside a focal PATCH pattern with localized EZ loss (white arrowhead). **H** shows a FISTULA pattern (asterisk) combined with a foveal intraretinal cyst whose base exhibits a WEDGE pattern (white arrow). **I** and **J** show SMD-DROL, characterized by a loss of normal outer retinal layer architecture, where the focal outer retinal hypo- and hyperreflective bands are indistinguishable (white stars).

Fig. 2. OCT images from eyes with diabetic serous macular detachment accompanied by outer retinal layer deterioration patterns, showing pre-treatment scans and post-treatment follow-up images acquired after serous macular detachment (SMD) regression. In an eye with the DIFFUSE pattern pre-treatment (**A**), both ELM and EZ loss occurred at post-treatment follow-up (**B**). In an eye exhibiting the PATCH pattern (**C**), post-treatment ELM disruption and EZ loss were observed (**D**). In an eye with the WEDGE pattern (**E**), after SMD regressed with treatment (**F**). In an eye with FISTULA at baseline (**G**), post-treatment restoration with intact ELM and EZ was observed (**H**). **I** highlight the pre-treatment SMD-DROL, with **J** demonstrating intact ELM and EZ disruption following intravitreal treatment.



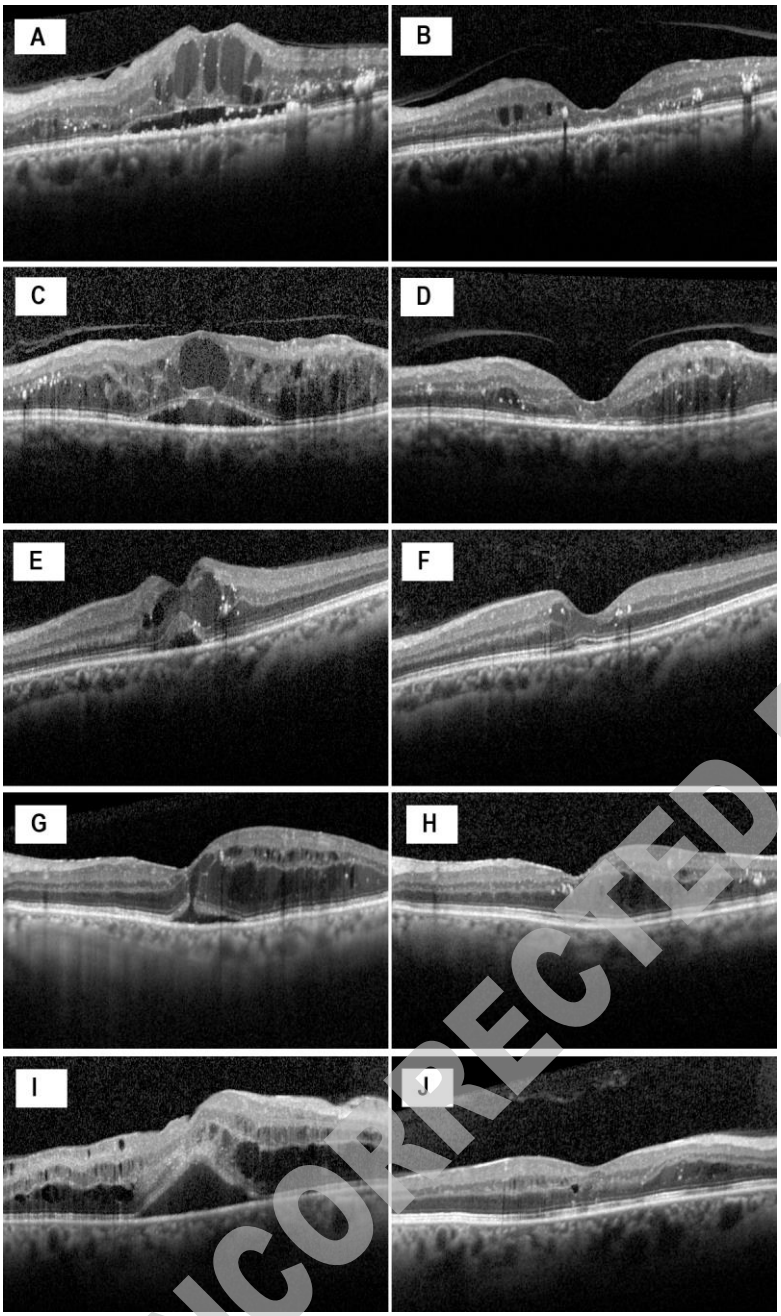


Table 1. Clinical and imaging characteristics of eyes at the baseline and the visit after serous macular detachment regression (post-SMD).

Age, *years* (N:131)	55
median (min–max)	(48 – 70)
Sex (N: 131)	57 / 74
Female/Male (%)	(43.51 / 56.49)
Baseline BCVA, *Snellen* (n:168)	20/63[a]

median (min–max)		(20/25 – 20/2000)
Post-SMD BCVA, *Snellen* (n:148)		20/50[a]
median (min–max)		(20/20 – 20/2000)
Baseline foveal volume, mm^3 (n:168)		0.42[b]
median (min–max)		(0.21 – 0.83)
Post-SMD foveal volume, mm^3 (n:148)		0.24[b]
median (min–max)		(0.12 – 0.57)
Baseline NRT, *µm* (n:168)		338[c]
median (min–max)		(100 – 726)
Post-SMD NRT, *µm* (n:148)		231[c]
median (min–max)		(84 – 608)
Baseline SMD height, *µm* (n:168)		150
median (min–max)		(48 – 530)
Duration to SMD regression, *weeks* (n:148)		16
median (min–max)		(4 – 31.3)
ORL deterioration patterns (*168 eyes – 189 observed patterns*[*])	**DIFFUSE**	10 (5.29)
	PATCH	25 (13.23)
	WEDGE	60 (31.75)
	FISTULA	40 (21.16)
	DROL	54 (28.57)
Post-SMD ELM status (n:148)	**Disruption (%)**	56 (37.84)
	Loss (%)	27 (18.24)
Post-SMD EZ status (n:148)	**Disruption (%)**	77 (52.03)
	Loss (%)	55 (37.16)
Post-SMD ELM alteration width, *µm* (n:148)		129.50
median (min–max)		(0 – 3010)
Post-SMD EZ alteration width, *µm* (n:148)		421
median (min–max)		(0 – 2116)

[a]: Snellen visual acuities were converted to logMAR for statistical analysis. The logMAR equivalents of the baseline and post-SMD median (min–max) BCVA were 0.50 (0.10–2.00) and 0.40 (0.00–2.00), respectively, corresponding to approximately +5 ETDRS letters of improvement (Wilcoxon signed-rank test, **p: 0.002**).

[b]: Wilcoxon signed-rank for analysis of change in foveal volume after the SMD regression, **p<0.001**

[c]: Wilcoxon signed-rank for analysis of change in foveal NRT after the SMD regression, **p<0.001**

min: minimum; max: maximum; BCVA: best-corrected visual acuity; SMD: serous macular detachment; NRT: neurosensory retinal thickness; ORL: outer retinal layer; DROL: disorganization of retinal outer layers; ELM: external limiting membrane, EZ: ellipsoid zone.

*: More than one outer retinal layer deterioration pattern was observed in 21 eyes. Bold p-values indicate statistical significance.

Table 2: Linear mixed-effects regression of best-corrected visual acuity (in logMAR) on visit, outer retinal layer deterioration patterns, and anatomical covariates (maximum-likelihood estimation with cluster-robust standard errors).

Predictor	β coeff (95% CI) [≈ ETDRS letters equivalent†]	*p*
Visit (post-SMD vs. baseline)	0.021 (-0.192 – 0.234) [-1.1; -11.7 – 9.6]	0.846
DIFFUSE	0.234 (-0.085 – 0.553) [-11.7; -27.7 – 4.2]	0.150
PATCH	-0.120 (-0.375 – 0.136) [6.0; -6.8 – 18.8]	0.358
WEDGE	-0.266 (-0.486 – -0.047) [13.3; 2.4 – 24.3]	**0.017**
FISTULA	-0.108 (-0.364 – 0.149) [5.4; -7.4 – 18.2]	0.412
SMD-DROL	-0.193 (-0.422 – 0.035) [9.7; -1.8 – 21.1]	0.097
Visit # DIFFUSE	0.027 (-0.276 – 0.330) [-1.3; -16.5 – 13.8]	0.861
Visit # PATCH	-0.200 (-0.403 – 0.003) [10.0; -0.1 – 20.2]	0.053
Visit # WEDGE	-0.131 (-0.342 – 0.080) [6.5; -4.0 – 17.1]	0.224
Visit # FISTULA	-0.124 (-0.352 – 0.104) [6.2; -5.2 – 17.6]	0.285
Visit # SMD-DROL	-0.003 (-0.194 – 0.188) [0.1; -9.4 – 9.7]	0.977
NRT*	0.008 (-0134 – 0.151)	0.909

	[-0.4; -7.5 – 6.7]	
Foveal volume*	-0.038 (-0.247 – 0.172)	0.724
	[1.9; -8.6 – 12.3]	
ELM alteration width*	0.060 (0.039 – 0.081)	**<0.001**
	[-3.0; -4.0 – -1.9]	
EZ alteration width*	0.007 (-0.024 – 0.038)	0.661
	[-0.3; -1.9 – 1.2]	
SMD duration	0.002 (-0.003 – 0.006)	0.466
	[-0.1; -0.3 – 0.1]	
Baseline SMD height*	0.125 (0.017 – 0.233)	**0.024**
	[-6.2; -11.7 – -0.9]	
Intercept	*0.105 (-1.111 – 1.320)*	*0.866*

Overall model significance: Wald $\chi^2(17)$:154.99, $p < 0.001$. Joint test of all visit # pattern interaction terms: Wald $\chi^2(5)$:5.47, p:0.361.

SMD: serous macular detachment; DROL: disorganization of retinal outer layers; NRT: neurosensory retinal thickness; ELM: external limiting membrane, EZ: ellipsoid zone, coeff: coefficient; CI: confidence interval.

*: Continuous covariates are per natural log-transformed (ln)-unit, with ELM/EZ alteration widths log-transformed after adding a +1 μm constant and then mean-centered for interaction terms. †: β coefficients are shown in logMAR units, with ETDRS letter equivalents in brackets. Bold p-values indicate statistical significance.

Table 3: Univariate and multivariate* ordinal regression analyses for the association of post-treatment external limiting membrane and ellipsoid zone status with outer retinal layer deterioration patterns.

Variable		ELM status				EZ status			
		Univariate		Multivariate*		Univariate		Multivariate*	
		OR (95% CI)	*p*	MP Mean ± SD	95% CrI	OR (95% CI)	*p*	MP Mean ± SD	95% CrI
DIFFUSE									
	Intact vs. Distruption+Loss	*1.00 (omitted)*	–			*1.00 (omitted)*	–		
				3.31 ± 0.95	**1.543 – 5.272**[a]			(Not included)	
	Intact+Distruption vs. Loss	25.045 (4.940 – 126.965)	**<0.001**			*1.00 (omitted)*	–		
PATCH									
	Intact vs. Distruption+Loss	4.223 (1.353 – 13.183)	**0.013**			*1.00 (omitted)*	–		
				0.59 ± 0.60	-0.611 – 1.704			0.96 ± 0.51	-0.066 – 2.058
	Intact+Distruption vs. Loss	0.995 (0.308 – 3.219)	0.994			3.629 (1.410 – 9.340)	**0.008**		
WEDGE									
	Intact vs. Distruption+Loss	0.147 (0.070 – 0.311)	**<0.001**			0.220 (0.072 – 0.672)	**0.008**		
				-1.65 ± 0.55	**-2.736– -0.573**[b]			**-1.92 ± 0.48**	**-2.843 – -0.951**[b]
	Intact+Distruption vs. Loss	0.049 (0.006 – 0.375)	**<0.001**			0.115 (0.045 – 0.294)	**<0.001**		

FISTULA									
	Intact vs. Distruption+Loss	1.443 (0.662 – 3.144)	0.357	–	–	0.921 (0.277 – 3.060)	0.893	(Not included)	
	Intact+Distruption vs. Loss	1.466 (0.578 – 3.717)	0.420			1.171 (0.538 – 2.547)	0.691		
SMD-DROL									
	Intact vs. Distruption+Loss	2.286 (1.092 – 4.783)	**0.028**	0.06 ± 0.49	-1.009 – 0.986	7.759 (0.993 – 60.630)	0.051	-0.42 ± 0.42	-1.235 – 0.548
	Intact+Distruption vs. Loss	0.920 (0.370 – 2.287)	0.857			1.129 (0.552 – 2.312)	0.739		

* Multivariate analyses were performed with Bayesian ordinal logistic regression, adjusted for log- transformed baseline neurosensory retinal thickness and foveal volume. MP means and (95% CrI) for log-transformed baseline neurosensory retinal thickness and foveal volume were 0.377 (-0.459 to 1.256) and 0.110 (-1.075 – 1.192), respectively, for ELM; and 0.003 (-0.955 – 0.889) and 1.017 (-0.524 – 2.554), respectively, for EZ.

[a]: Significant positive association

[b]: Significant negative association

ELM: external limiting membrane, EZ: ellipsoid zone, DROL: disorganization of retinal outer layers, OR: odds ratio, CI: confidence interval, MP: multivariate posterior, CrI: credible interval. Bold values indicate statistical significance.

Table 4: Age- and sex-adjusted multivariate regression models for the association of outer retinal layer deterioration patterns with log-transformed foveal neurosensory retinal thickness and foveal volume at baseline and post-serous macular detachment, adjusted for age and sex.

	Baseline NRT		**Post-SMD NRT**		**Baseline Foveal Volume**		**Post-SMD Foveal Volume**	
Variable	β coefficient (95% CI)	*p*	β coefficient (95% CI)	*p*	β coefficient (95% CI)	*p*	β coefficient (95% CI)	*p*
DIFFUSE	-0.332 (-0.761 − 0.098)	0.129	-0.205 (-0.588 − 0.178)	0.291	0.051 (-0.181 − 0.283)	0.664	-0.055 (-0.290 − 0.181)	0.647
PATCH	-0.248 (-0.516 − 0.021)	0.070	0.096 (-0.128 − 0.319)	0.398	-0.008 (-0.138 − 0.122)	0.903	0.026 (-0.122 − 0.175)	0.726
WEDGE	0.015 (-0.208 − 0.238)	0.896	0.189 (-0.026 − 0.404)	0.085	-0.004 (-0.113 − 0.105)	0.942	0.013 (-0.127 − 0.153)	0.853
FISTULA	0.002 (-0.207 − 0.211)	0.984	0.253 (0.038 − 0.469)	**0.021**	0.101 (-0.010 − 0.213)	0.074	0.092 (-0.051 − 0.234)	0.207
SMD-DROL	0.171 (-0.039 − 0.381)	0.109	-0.039 (-0.251 − 0.172)	0.715	0.162 (0.061 − 0.262)	**0.002**	-0.108 (-0.246 − 0.030)	0.123

Global pattern effect (MANOVA results): Wilks' λ:0.651, **p<0.001**.

Pattern-specific results (MANOVA results): Wilks' λ: 0.914, **p:0.021** for DIFFUSE; Wilks' λ: 0.929, p:0.051 for PATCH; Wilks' λ: 0.955, p:0.204 for WEDGE; Wilks' λ: 0.922, **p:0.033** for FISTULA; Wilks' λ: 0.933, p:0.063 for SMD-DROL.

Overall pattern effect (Wald F-statistic results): F(5,168):3.25, **p:0.008** for baseline NRT; F(5, 148):3.15, **p:0.010** for post- SMD NRT; F(5, 168):3.69, **p:0.004** for baseline foveal volume; F(5, 148):2.07, p:0.074 for post- SMD foveal volume.

SMD: serous macular detachment, NRT: neurosensory retinal thickness, DROL: disorganization of retinal outer layers, CI: confidence interval. Bold p-values indicate statistical significance.

Table 5: Frequencies of intraretinal cystic features coexisting with outer retinal layer deterioration patterns

	DIFFUSE (n:10)		PATCH (n:25)		WEDGE (n:60)		FISTULA (n:40)		DROL (n:54)	
Intraretinal cyst extended to the ELM, yes/no (%)	2 (20.0)	8 (80.0)	17 (64.0)	8 (36.0)	60 (100.0)	–	40 (100.0)	–	35 (64.8)	19 (35.2)
Intracystic hyperreflective material, yes/no (%)[a]	1 (50.0)	1 (50.0)	16 (94.1)	1 (5.9)	16 (26.7)	44 (73.3)	33 (82.5)	7 (17.5)	21 (60.0)	14 (40.0)

DROL: disorganization of retinal outer layers, ELM: external limiting membrane

[a]: Intracystic hyperreflective material was assessed only in eyes with intraretinal cysts extending to ELM.