Original Article

Subretinal hyperreflective material in central serous chorioretinopathy

Niroj K Sahoo, Vishal Govindhari, Rumneek Bedi[1], Abhilash Goud, Rishi Singh[1], Lihteh Wu[2], Jay Chhablani

Purpose: To describe the the appearance and behavior of subretinal hyperreflective material (SHRM) in eyes with central serous chorioretinopathy (CSCR). **Methods:** This retrospective study included 20 eyes of 20 patients with CSCR presenting with SHRM, defined as sub-retinal deposits that appear hyper-reflective on OCT The eyes underwent either laser (15 eyes) or observation (5 eyes). Optical coherence tomography and fundus fluorescein angiography (FFA) characteristics were analyzed at baseline and resolution of neurosensory detachment, which were then co-related with the visual acuity at resolution. **Results:** Improvement in vision was seen in 16 eyes. Ellipsoid zone damage ($P = 0.03$) and external limiting membrane (ELM) damage ($P = 0.000$) at resolution; diffuse retinal pigment epithelium (RPE) abnormalities on FFA ($P = 0.04$), and the presence of scar ($P = 0.000$), were associated with poor visual outcome in univariate analysis. ELM damage at resolution was statistically significant ($P = 0.001$) in multivariate analysis. **Conclusion:** CSCR with SHRM have a good visual prognosis. ELM damage at resolution corelates with a poor visual acuity at resolution.

Key words: Central serous chorioretinopathy, CSCR, subretinal hyperreflective material, SHRM, fibrin

Access this article online
Website: www.ijo.in
DOI: 10.4103/ijo.IJO_265_19
Quick Response Code:

Central Serous Chorioretinopathy (CSCR) is characterized by neurosensory detachment of the posterior pole with or without retinal pigment epithelium detachment due to collection of sub-retinal fluid (SRF). The role of choroidal vessels in the pathogenesis of CSCR is well known.[1-4] However, the exact mechanism of formation of the SRF and its composition is poorly understood. Although CSCR classically presents with a clear SRF on optical coherence tomography (OCT), patients do present with sub-retinal deposits that appear hyper-reflective on OCT, called as sub-retinal hyper-reflective material (SHRM).[5-7] These deposits in CSCR have been classically described with long standing steroid use[8,9] and in pregnancy.[8] However, it can also occur as a severe form of CSCR in patients without the above mentioned predisposing factors.

SHRM on OCT has recently been described in cases with neovascular age-related macular degeneration (AMD). It is believed to be composed of various elements like fibrin, hemorrhage, vitelliform deposits, or neovascular complex.[10,11] SHRM in AMD has a prognostic significance, as persistence of these materials are associated with sub-retinal fibrosis and a poor visual outcome even with treatment.[12] However, there is paucity of data supporting the description of this entity and its outcome in CSCR. Schatz *et al.* reported six cases of CSCR with sub-retinal deposits that progressed to fibrosis on follow-up.[13] However, Ie *et al*. reported spontaneous resolution of these deposits.[7] A study by Maruko *et al*. suggested that these deposits could be derived from shed photoreceptors.[6] Numerous studies have tried to describe these deposits on OCT.[5,14,15] However, there is less evidence regarding the behavior and outcome of these eyes.

The purpose of this study is to describe the characteristics of SHRMs in CSCR and factors determining the final visual acuity and structural outcomes.

Methods

We performed a retrospective study of 20 eyes of 20 patients presenting with CSCR with SHRMs. Prior approval from the Institutional Review Board of the institute was taken, and informed consent was obtained from each subject. Patients with presence of choroidal neovascularization were excluded. Cases with an established diagnosis of intraocular inflammation, age-related macular degeneration, polypoidal choroidal vasculopathy, diabetic retinopathy, or retinal vascular occlusive disease were excluded. SHRM was defined as yellowish white sub-retinal deposits seen ophthalmoscopically or hyper-reflective material seen in the sub-retinal space on optical coherence tomography (OCT). The time of diagnosis of CSCR was taken as the baseline. Baseline patient characteristics, duration of symptoms, best-corrected visual acuity (BCVA), and OCT parameters were recorded. The patients were either managed by observation or received micropulse or conventional laser. The choice of laser depended upon the site of leak. Perifoveal leak points were treated micropulse laser, while extrafoveal leak points were

Smt. Kanuri Santhamma Centre for Vitreo-Retinal Diseases , L V Prasad Eye Institute, Hyderabad, India, [1]Department of Ophthalmology, Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio, [2]Department of Ophthalmology, Instituto de Cirugia Ocular, San Jose, Costa Rica

Correspondence to: Dr. Jay Chhablani, Smt. Kanuri Santhamma Centre for Vitreo-Retinal Diseases, L V Prasad Eye Institute, Banjara Hills, Hyderabad - 500 034, Telangana, India. Email: jay.chhablani@gmail.com

Received: 04-Feb-2019 Revision: 08-Jul-2019
Accepted: 01-Aug-2019 Published: 19-Dec-2019

Cite this article as: Sahoo NK, Govindhari V, Bedi R, Goud A, Singh R, Wu L, *et al*. Subretinal hyperreflective material in central serous chorioretinopathy. Indian J Ophthalmol 2020;68:126-9.

treated with conventional laser. The patients were followed up until resolution of neurosensory detachment. Only those patients who had complete documentations of OCT, fundus fluorescein angiography (FFA), both at baseline and at resolution were included. FFA was performed using Heidelberg HRA (Heidelberg Engineering, Inc, Vista, CA) and OCT was performed using swept source DRI OCT-plus (Triton, Topcon, Tokyo, Japan). BCVA and OCT parameters were collected at each follow up until resolution and morphological or functional changes were assessed.

OCT features were analyzed qualitatively and quantitatively for changes at baseline and at resolution. Parameters analyzed were height of the neurosensory retinal detachment, percentage of EZ (Ellipsoid zone) and external limiting membrane (ELM) damage at the foveal 1000 microns, subfoveal choroidal thickness and central macular thickness (CMT). The percentage of EZ and ELM damage at the subfoveal 1000 microns was calculated as per previously reported method.[16] Choroidal thickness was manually measured by using an in-built caliper tool by drawing a perpendicular vector from the outer edge of the hyper-reflective RPE to the inner sclera (choroid–sclera junction) within 500 μ of the fovea. All parameters were recorded both at the baseline and at recurrence. The location of SHRM was divided into 3 categories i.e., involving center of fovea, within 1 mm^2 of fovea and outside 1 mm^2 area. The SHRMs were further classified as either dense (homogenous deposits of hyper-reflective material spanning the entire thickness of NSD) or minimal (localized collection of hyper-reflective material attached to the roof of NSD), which was then co-related with the final BCVA.

FFA images were analyzed for any specific pattern of leak in these cases. The eyes were divided as having either a localized leak (ink-blot/smoke-stack) or diffuse RPE changes. The pattern of leak was co-related with the appearance of scar and the BCVA at resolution.

Statistical analysis

Statistical analysis was done using SPSS v20.0. Continuous variables were expressed using mean ± standard deviation. The baseline patient characteristics and OCT parameters were co-related with the final BCVA using linear regression analysis. All *P* values of less than 0.05 were taken as significant.

Results

The study included 20 eyes of 20 (15 males and five females) patients with CSCR with SHRMs. The mean age of the patients was 43.8 ± 8.7 years (34-65 years). None of the patients were on any form of steroid or were pregnant at the initial presentation. Fifteen eyes underwent laser treatment (5 conventional and 10 micropulse) while the remaining five were observed. The mean time to resolution was 4.7 ± 3 months since presentation.

The SHRMs involved the center of fovea in 13 eyes (65%), was within 1000 μ in six eyes (30%) and outside 1000 μ in one eye (5%). Six eyes had dense SHRM (described as clumps of homogenous hyper-reflective material on OCT) in the subretinal space [Figs. 1 and 2], rest had minimal SHRM (described as dispersed hyper-reflective material on OCT). Four out of the six eyes had a vacuolation seen within the area of fibrin which corresponded with the site of leak on FFA [Fig. 2]. Thirteen eyes (11 ink-blot and 2 smokestack) had a localized leak in FFA, while five eyes had a diffuse RPE abnormalities. A fundus autofluorescence image (FAF) was available in six eyes out of which three had hyper-autofluorescence while three had hypo-autofluorescence.

Study eyes had a mean BCVA of 0.55 ± 0.36 logMAR (20/80 Snellen equivalent) at baseline. At resolution, improvement in vision was seen in all the patients with a mean of 0.18 ± 0.3 logMAR (Snellen equivalent of 20/30) with a mean improvement of 0.38 ± 0.29 logMAR (approximately 4 lines improvement). There was no statistically significant difference in the final visual acuity between the observation and the laser groups. The location of SHRM was not significantly (P = 0.2) related to the final visual acuity.

The EZ and ELM details were indistinct at baseline due to elongation of the photoreceptor outer segments. At resolution, 12 eyes were seen to have residual EZ damage (mean of 68.7 ± 34.5%), whereas only four eyes had ELM damage (mean of 62.5 ± 31.7%) [Fig. 2]. EZ damage (P = 0.03) and ELM damage (P = 0.00) at resolution was found to be significantly associated with a poorer BCVA at resolution in univariate analysis. The mean final BCVA in eyes with EZ damage was 0.23 ± 0.29 log MAR (Snellen equivalent of 20/30p) whereas it was 0.19 ± 0.43 logMAR (Snellen equivalent of 20/30) in eyes without EZ damage. Similarly, the final BCVA was 0.49 ± 0.35 logMAR (Snellen equivalent of 20/60) in eyes with ELM damage compared to 0.07 ± 0.12 logMAR (Snellen equivalent of 20/20p) in eyes without ELM damage. Diffuse RPE abnormalities on FFA (P = 0.04) and the presence of scar (P = 0.00) were also significantly associated with a poorer BCVA at resolution in univariate analysis. Other parameters like duration of symptoms and time taken to recurrence did not have any significant co-relation.

The mean time to resolution was 4.7 ± 3 months. Three eyes developed a subretinal scarring [Fig. 2] secondary to SHRM not involving the fovea. However, vision was affected in all the three eyes which corresponded with the amount of ELM damage at resolution (20/100, 20/30 and 20/200, respectively).

The mean CMT, NSD height, choroidal thickness at baseline was 432.1 ± 160.8 μ, 261 ± 190 μ, 502 ± 104 μ, respectively. At resolution of SRF, a statistically significant decrease was seen in the mean CMT by 197 ± 164.2 μ (P = 0.00) and CT value by 28.5 ± 84.2 μ (P = 0.019).

Although there was no statistically significant co-relation between the FFA pattern and scar development, all the three eyes that developed scar on follow-up, had a diffuse RPE abnormality.

Although ELM and EZ damage at resolution, FFA pattern and the presence of scar were the variables found to be significantly associated with a poor BCVA at resolution in univariate analysis, multivariate analysis [Table 1] showed only ELM damage at resolution to be statistically significant (P = 0.001) None of the other OCT or baseline parameters were found to be significantly co-related with the final BCVA in multivariate analysis.

Table 1: Results of the multivariate analysis of the associations between final BCVA as dependent variable and optical coherence tomography and fundus fluorescein angiography parameters as independent variables

Variables	B	*P*-value	95.0% Confidence Interval for B	
			Lower Bound	Upper Bound
IS/OS* damage at resolution	.001	.333	-.001	.003
ELM* damage at resolution	.005	.001	.003	.008
FFA* pattern	.024	.807	-.183	.231
Scar (Present/Absent)	-.245	.078	-.522	.031

*IS/OS: Inner segment/ Outer segment; ELM: External limiting membrane; FFA: Fundus fluorescein angiography

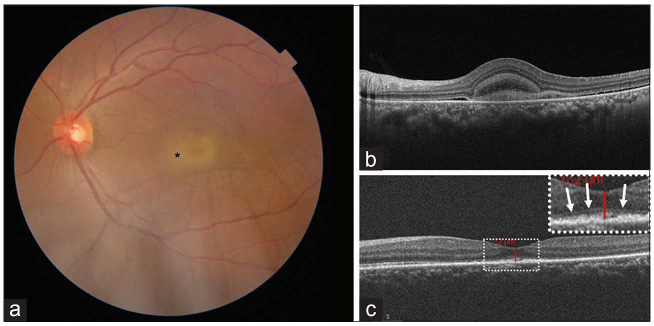

Figure 1: A 41-year-old male presented with neurosensory detachment with sub-retinal yellowish deposits involving the fovea and a visual acuity of 20/60 (a). Optical coherence tomography showed the presence of dense sub-retinal hyper-reflective material (SHRM) (b). The patient was treated with micropulse laser. A complete disappearance of the SHRM was seen at resolution (c). Visual acuity improved to 20/30 with an intact (*arrows*) external limiting membrane (*inset*)

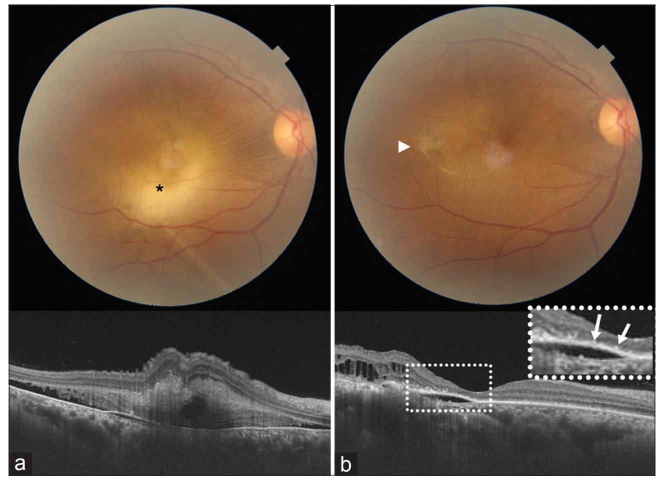

Figure 2: A 37-year-old male presented with neurosensory detachment with sub-retinal hyper-reflective material (SHRM) (*asterisk*) involving the fovea and a visual acuity of 20/400 (a). The patient was treated with conventional laser. Disappearance of the SHRM, along with an area of extrafoveal scarring (*arrowhead*) was seen at resolution (b). Visual acuity improved to 20/100 with 50% loss (*arrows*) of external limiting membrane (*inset*)

Discussion

In eyes with CSCR having SHRM, we found an overall good visual outcome. All eyes either maintained or had an improvement in visual acuity from baseline. ELM damage at resolution was found to be associated with poorer visual outcome. Also, although not statistically significant, diffuse RPE abnormality at baseline was associated with scar formation during follow-up.

The SHRMs that were seen in our study ranged in severity from being either very minimal to a dense collection. The dense collections had both well-defined and blurred margins, while the minimal deposits were fuzzy and strand like. Also, the deposits appeared to be continuous with the outer retina. On the other hand, we could make out a clear line of separation between the deposits and the RPE in most cases. The composition of the SHRM is poorly understood. There may be several explanations to the formation of the deposits. First, it could be a mere deposition of the products from leaking fluid over the photoreceptors. Classically, it has been described to be composed of fibrin in various studies.[7,13] However, the definitive composition of the sub-retinal fluid is yet to be elucidated. Maruko *et al*. reported similar findings when analyzing the deposits in CSCR.[6] The authors suggested that these deposits may have been derived from the photoreceptors and that they tend to hyperfluoresce only after the shed photoreceptor products have been metabolized by macrophages and RPE into active fluorophores. These fluorophores have been reported to cause damage to both the retinal outer segments and the RPE and thus could be a factor dictating the final visual outcome.[17] This led us to believe that these deposits could be derived from the shed photoreceptor outer segments rather than fibrin. Although not available in all patients, we tried to analyze the fundus auto-fluorescence images in the eyes in our study and found homogeneously increased auto-fluorescence in three retrieved scans which supports the latter explanation.

We tried to analyze the characteristics of these deposits that could possibly affect the final visual outcome. The location or the density of the SHRMs did not affect the final BCVA significantly in our study. Thus, it could have been the composition of the SHRMs, rather than the location, that seems to cause the structural damage. The component of SHRMs has still not been elucidated. Kowlczuk *et al*. did a proteomic analysis of the SRF in a pilot study and found up-regulation and down-regulation of various proteins and enzymes.[18] However, the effects of these proteins on the outer retina remain an enigma. All the eyes in our study had an elongated and indistinct photoreceptor outer segment (PROS) that was localized only to the areas of SHRM and did not involve the rest of the retina under the NSD. Also, it was seen that at resolution, EZ damage was seen at the same areas as the areas of PROS elongation. Nonetheless, the components of the SHRMs could be having localized toxic effects on the PROS, leading to damage to the EZ junction. However, it did not co-relate significantly with the final visual acuity. On the other hand, we noticed that the integrity of ELM was a better indicator of the final visual acuity in these eyes [Figs. 1 and 2]. This finding has been consistently been used in the prognosis of CSCR in the past and holds true even in our case series as well.[19] Thus, SHRMs appear to be capable of causing damage to the outer retina, but it doesn't affect vision unless the ELM is also affected. Thus, the integrity of ELM could be said to have a better prognostic significance than EZ loss in these cases.

Although we found the presence of a fibrotic band in three patients, it did not involve the fovea. The statistically significant low visual acuity at resolution could have been due to the associated ELM damage as detected by multivariate analysis. On comparing the FFA findings with the presence of scar, a diffuse RPE abnormality was seen at the baseline in all the three cases. However, no statistically significant co-relation was observed ($P = 0.9$). This could indicate a possible mechanism for the formation of scar. Presence of RPE damage could result in persistence and organization of these materials and formation of scar. Also, long standing exposure of ELM to these toxic substances could result in poor vision as seen in all the three eyes in our study.

The limitations of the study were mostly related to the small sample size and the lesser follow up time. Longer follow up would have helped in understanding the long-term effects of these SHRMs. Not having autofluorescence images for all eyes is one of the major drawbacks of the study. This makes the interpretation regarding the characteristics of SHRM unreliable. The decision on the type of laser (conventional/micropulse) was based on the location of leak and not the density of SHRMs. Similarly, most of the severe forms of SHRM were treated with laser, while the five cases in the observation arm had minimal deposits at baseline. This resulted in improper matching of the groups and prevented us from analyzing any beneficial effects of laser in our study.

Conclusion

Eyes with SHRMs in CSCR have a good visual prognosis, unless the ELM is involved. The deposits disappear completely in most cases and treatment should be planned according to the severity of collections. Diffuse RPE damage at baseline may lead to persistence of SHRM, and eventually predisposes to scar formation in these eyes. Future studies with longer follow-up and larger sample size are required to provide a better insight into the natural course of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Prünte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 1996;121:26-34.
2. Giovannini A, Scassellati-Sforzolini B, D'altobrando E, Mariotti C, Rutili T, Tittarelli R. Choroidal findings in the course of idiopathic serous pigment epithelium detachment detected by indocyanine green videoangiography. Retina (Philadelphia, Pa) 1997;17:286-293.
3. Spitznas M. Pathogenesis of central serous retinopathy: A new working hypothesis. Graefes Arch Clin Exp Ophthalmol 1986;224:321-4.
4. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina 2009;29:1469-73.
5. Landa G, Barnett JA, Garcia PMT, Tai KW, Rosen RB. Quantitative and qualitative spectral domain optical coherence tomography analysis of subretinal deposits in patients with acute central serous retinopathy. Ophthalmologica 2013;230:62-8.
6. Maruko I, Iida T, Ojima A, Sekiryu T. Subretinal dot-like precipitates and yellow material in central serous chorioretinopathy. Retina 2011;31:759-65.
7. Ie D, Yannuzzi LA, Spaide RF, Rabb MF, Blair NP, Daily MJ. Subretinal exudative deposits in central serous chorioretinopathy. Br J Ophthalmol 1993;77:349-53.
8. Reese M, Singerman M. Central serous chorioretinopathy and white subretinal exudation during pregnancy. Arch Ophthalmol 1991;109:677-81.
9. Bouzas EA, Karadimas P, Pournaras CJ. Central serous chorioretinopathy and glucocorticoids. Surv Ophthalmol 2002;47:431-48.
10. Keane PA, Patel PJ, Liakopoulos S, Heussen FM, Sadda SR, Tufail A. Evaluation of age-related macular degeneration with optical coherence tomography. Surv Ophthalmol 2012;57:389-414.
11. Shah VP, Shah SA, Mrejen S, Freund KB. Subretinal hyperreflective exudation associated with neovascular age-related macular degeneration. Retina 2014;34:1281-8.
12. Pokroy R, Mimouni M, Barayev E, Segev F, Geffen N, Nemet AY, *et al.* Prognostic value of subretinal hyperreflective material in neovascular age-related macular degeneration treated with bevacizumab. Retina 2018;38:1485-91.
13. Schatz H, McDonald HR, Johnson RN, Chan CK, Irvine AR, Berger AR, *et al.* Subretinal fibrosis in central serous chorioretinopathy. Ophthalmology 1995;102:1077-88.
14. Fujimoto H, Gomi F, Wakabayashi T, Sawa M, Tsujikawa M, Tano Y. Morphologic changes in acute central serous chorioretinopathy evaluated by fourier-domain optical coherence tomography. Ophthalmology 2008;115:1494-500.e2.
15. Wang M, Sander B, La Cour M, Larsen M. Clinical characteristics of subretinal deposits in central serous chorioretinopathy. Acta Ophthalmol (Copenh) 2005;83:691-6.
16. Chhablani JK, Kim JS, Cheng L, Kozak I, Freeman W. External limiting membrane as a predictor of visual improvement in diabetic macular edema after pars plana vitrectomy. Graefes Arch Clin Exp Ophthalmol 2012;250:1415-20.
17. Kim SR, Nakanishi K, Itagaki Y, Sparrow JR. Photooxidation of A2-PE, a photoreceptor outer segment fluorophore, and protection by lutein and zeaxanthin. Exp Eye Res 2006;82:828-39.
18. Kowalczuk L, Matet A, Dor M, Bararpour N, Daruich A, Dirani A, *et al.* Proteome and metabolome of subretinal fluid in central serous chorioretinopathy and rhegmatogenous retinal detachment: A pilot case study. Transl Vis Sci Technol 2018;7:3.
19. Yalcinbayir O, Gelisken O, Akova-Budak B, Ozkaya G, Cevik SG, Yucel AA. Correlation of spectral domain optical coherence tomography findings and visual acuity in central serous chorioretinopathy. Retina 2014;34:705-12.