

Predictors of Visual outcome in Post Fever Retinitis: A Retrospective Analysis

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Abstract

Purpose: To identify the predictors of final visual outcome in cases with post fever retinitis (PFR).

Methods : This is a retrospective study of cases with diagnosis of post fever retinitis. Color fundus photograph and optical coherence tomography (OCT) parameters at presentation and final visit were analysed. Various factors at presentation [age, systemic illness, best corrected visual acuity (BCVA), area of retinitis and hard exudates, OCT parameters], at final visit (optic disc pallor, OCT parameters) and the treatment modalities used were correlated with BCVA at final visit.

Results : Twenty four eyes of 16 patients with PFR were included in the study. Median BCVA at presentation was 6/60 and at final visit was 6/9. By multiple linear regression after adjusting for other variables, for every 1 unit increase in height of SRF at fovea at presentation, the value of final BCVA decreased by 0.001 unit. For every 1 unit increase in extent of EZ loss and subfoveal deposit height, the value of final BCVA decreased by 0.0001unit and 0.004 unit respectively.

Conclusion: Height of SRF at presentation, extent of EZ loss and subfoveal deposit height at final visit were associated with poor final BCVA in PFR.

Introduction

Post fever retinitis (PFR) is a term used to describe the posterior segment manifestations following a febrile illness.^{1,2} It is a relatively newer entity, described in literature by various names like epidemic retinitis, post febrile retinitis, acute multifocal retinitis and post febrile uveitis.^{1,2,3} Patients with PFR typically develop unilateral or bilateral retinitis after 2-4 weeks of febrile illness.⁴ It is characterized by the presence of unifocal or multifocal retinitis, predominantly involving the posterior pole and peripapillary region. It is associated with macular edema, neurosensory detachment and minimal vitritis. Vascular involvement is characterised by the presence of perivascular hemorrhages and perivascular yellow plaques.³ These manifestations are hypothesised to be either immune mediated or due to the direct invasion of causative agent.³ The treatment protocol is not established. The natural course of disease is believed to be self limiting. However, few prefer to treat with systemic steroids and antibiotics.^{1,3} The manifestations and course of post fever retinitis are described in the literature, but no data is available regarding the factors predicting the final visual outcome. In this retrospective study, the factors predicting the visual outcome in post fever retinitis were analysed.

Materials And Methods

This was a retrospective study conducted in a tertiary eye care centre in south India. The study was approved by the Institute ethics committee, Sankara eye hospital, Shimoga on December 4, 2020. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Patients diagnosed with post fever retinitis between August 2018 and May 2020 were included. The diagnosis of post fever retinitis was considered in patients presenting with acute onset unifocal or multifocal retinitis with or without vascular involvement following an episode of febrile illness within the last 6 weeks. Age, systemic illness, the interval between the onset of visual symptoms and febrile illness were recorded from the medical records. Best corrected visual acuity (BCVA) at presentation and final visit measured with Snellen's chart were recorded. Fundus photograph and optical coherence tomography (OCT) images captured with Topcon 3D OCT 2000 (Topcon medical systems, Japan) at presentation and at complete resolution were reviewed. '3D macula' and '6mm radial 16 mm overlap' OCT protocols were used for imaging. Patients with regular follow up with good quality color fundus photograph (45 degree) and OCT images centred on fovea at each visit up to complete resolution of retinitis were included. 'Resolution' was defined as absence of retinal whitening, intraretinal fluid and subretinal fluid. Patients lost to follow up and those with poor quality fundus or OCT images were excluded from the study. Details related to the treatment during the course of retinitis were recorded.

Color fundus photograph at presentation was analysed for the area of retinitis and area of hard exudates within the macula by Image J. Area of retinitis (retinal whitening) was marked on color photograph by the inbuilt marker of image J software and was calculated. Area of the circular 45 degree color photograph was measured with Image J. As the image resolution can affect the measurements in Image J, the area was recorded as ratio of retinitis to the area of color photograph to maintain uniformity (figure 1). Similarly the area of hard exudates was measured as ratio. Presence or absence of perivascular plaque was documented. Color fundus photograph at final visit was analysed for optic disc pallor. Optic disc pallor was graded as grade1: no pallor, grade 2: pallor in 1 temporal quadrant (either supero-temporal or infero-temporal quadrant), grade 3: pallor in temporal half of disc, grade 4: pallor involving the entire optic disc.

OCT parameters at presentation were analysed using both 3D macula and 6mm radial 16 mm overlap scan centred on fovea. The OCT parameters recorded at presentation and final visit are described in table 1 and table 2 respectively. Figure 2 and 3 depicts the measurement of OCT parameters. All the factors including age, systemic illness, interval between fever and retinitis, BCVA at presentation, area of retinitis and hard exudates at presentation, the OCT parameters at presentation and final visit, optic disc pallor at final visit and the mode of treatment were correlated with BCVA at final visit using univariate and multiple linear regression.

Results

The medical records revealed 28 patients with post fever retinitis during the study duration. Twenty four eyes of 16 patients satisfied the inclusion criteria and were included in the study. Nine (56.25%) patients were men. The mean age at presentation was 44.38 ± 17.28 years (range: 19 to 74 years). Mean interval between fever and onset of symptoms was 4.13 ± 2.13 weeks. Eight (50%) patients had bilateral involvement. Two patients had systemic hypertension and 2 patients had both systemic hypertension and diabetes mellitus. The etiology of fever was evaluated during the febrile illness in 9 patients. Two

patients were diagnosed with dengue fever, one with typhoid fever and etiology of fever was not established in rest of the cases. Considering the less number of patients with established etiology, statistical analysis of its significance on outcome was not possible.

At presentation, the median best corrected visual acuity (BCVA) was 6/60 (range: 1/60 to 6/6, mean: 0.29 ± 0.35 in decimal notation). BCVA was $\leq 6/60$ in 13 eyes (54.16%). On fundus photograph, the mean area of retinitis within the macula was 0.20 ± 0.19 (range: 0 to 0.63) and that of hard exudates was 0.015 ± 0.02 (range: 0 to 0.10). Perivascular plaques were seen in 6 (25%) eyes.

Eight patients were treated with oral steroids alone (prednisolone 1gm/kg/day tapered over 6-8 weeks), 8 were treated with intravenous methyl prednisolone 1 gm for 3 days in addition to oral steroid therapy. One eye of a patient with bilateral PFR was treated with intravitreal triamcinolone in view of poor response to oral and intravenous steroids.

The median follow up duration was 17 weeks (range: 4 to 220 weeks). Fourteen eyes (58.3%) showed progressive resolution of retinitis with treatment. Initial progression of retinitis for 1-2 week followed by resolution was noted in 8 (33.3%) eyes and recurrence of retinitis after completion of steroid therapy was seen in 2 (8.3%) eyes. The median final BCVA was 6/9 (range: 1/60 to 6/6, mean: 0.59 ± 0.40 in decimal notation). BCVA was $\leq 6/60$ in 6 (25%) eyes and better than 6/12 in 16 (66.6%) eyes. Optic disc pallor was seen in 12 (50%) eyes.

There was no statistically significant correlation between age, gender, systemic illness, interval between fever and retinitis, area of retinitis, area of hard exudates, initial worsening of retinitis, different treatment modalities and final BCVA. The OCT parameters at presentation and its correlation with final BCVA are summarised in table 3. The OCT parameters at final visit and its correlation with final BCVA are summarised in table 4.

By univariate linear regression, presence of inner retinal hyperreflectivity (IRH) within 500 microns of centre of fovea, central macular thickness (CMT), height of subretinal fluid (SRF) at fovea, disorganisation of retinal inner layers (DRIL) within 1000 microns of centre of fovea, hyperreflectivity of papillomacular bundle (PMB), hyperreflectivity of SRF at presentation had a statistically significant effect on final BCVA. Unadjusted coefficients with p value of univariate linear regression is reported in Table 3. By multiple linear regression, height of SRF at fovea had a statistically significant effect on final BCVA. After adjusting for other variables, for every 1 unit increase in height of SRF at fovea, the value of final BCVA decreased by 0.001 unit.

By univariate linear regression, DRIL within 1000 micron of centre of fovea, presence of subfoveal deposit, height and length of subfoveal deposit, extent of ellipsoid zone (EZ) loss at fovea, presence of vitreoretinal (VR) interface abnormality and presence of disc pallor at final visit had a statistically significant effect on final BCVA. Unadjusted coefficients with p value of univariate linear regression is reported in Table 4. By multiple linear regression, subfoveal deposit height and extent of EZ loss at fovea had a statistically significant effect on final BCVA. After adjusting for other variables, for every 1 unit

increase in extent of EZ loss, the value of final BCVA decreased by 0.0001unit. After adjusting for other variables, for every 1 unit increase in subfoveal deposit height, the value of final BCVA decreased by 0.004 unit.

Figure 4 and 5 depicts two cases of PFR.

Discussion

Post fever retinitis predominantly involves the inner retina. But significant subretinal fluid is also seen due to vascular involvement and break down of inner blood retinal barrier (iBRB). So the retinal damage in post fever retinitis might be due to neuro-retinal loss secondary to retinitis and loss of photoreceptors due to subretinal fluid. In this study, the parameters which assess the severity of retinitis and exudation were analysed. Studies on diabetic retinopathy have noted that the accumulation of SRF and hard exudates are due to vascular leak with protein and lipid exudation secondary to breakdown of iBRB.⁵ So OCT parameters such as altered foveal contour, CMT, intraretinal cystic spaces, hyperreflective foci secondary to hard exudates, height of subretinal fluid and its reflectivity at presentation are indicators of breakdown of iBRB. Parameters such as area of retinitis, IRH within 500 and 1000 micron from centre of fovea, PMB hyper reflectivity, DRIL within 1000 microns from centre of fovea at presentation are indicators of the severity of retinitis.

In this study, multiple linear regression showed that the increase in SRF height was associated with decrease in final BCVA. This can be explained by disruption or damage of photoreceptors due to accumulation of SRF, as it deprives them of metabolic support. Few studies on experimental models and human tissue have shown that photoreceptor cell death occurs as early as 12 hours and peaks at around 2-3 days after retinal detachment (RD).^{6,7,8} Hyperreflectivity of SRF at presentation was associated with poor visual outcome. The hyperreflectivity of SRF would indicate the presence of protein and lipid which can lead to development of subretinal deposits at resolution (discussed later). IRH within 500 microns of fovea and papillomacular bundle had statistically significant effect on final visual acuity. But the area of retinitis had a weak correlation with final BCVA. This would imply that retinitis closer to the fovea and papillomacular bundle has more detrimental effect than the overall extent of retinitis.

The parameters which assess the severity of neuro-retinal and photoreceptor damage at resolution were also analysed. Parameters such as DRIL within 1000 microns of centre of fovea and papillomacular bundle, optic disc pallor at resolution are indicators of the severity of neuro-retinal damage. Parameters such as presence of subfoveal deposits, its height and length, extent of EZ loss at fovea are indicators of severity of photoreceptor loss. This study showed that these parameters had statistically significant effect on final BCVA.

Multiple linear regression showed that final BCVA is poor in cases with higher subfoveal deposit height at resolution. On resolution of SRF, the protein and lipid may condense to form sub foveal deposits. In a study by Otani et al, the poor visual acuity in diabetic macular edema (DME) on resolution was due to the

subfoveal hyperreflective deposits, which is consistent with the results of the present study.⁹ They hypothesised that hindrance of interaction between the neurosensory retina and retinal pigment epithelium (RPE) due to presence of the subfoveal deposits resulted in poor visual outcome. It is also possible that the subretinal deposits may have toxic effect on the photoreceptors. In DME, the subretinal deposits are predominantly due to hard exudates, whereas in PFR, in addition to hard exudates inflammatory debris may contribute to subretinal deposits. In central serous chorioretinopathy (CSC), after the resolution of SRF, subfoveal deposits are formed and is composed of lipids and macrophages with outer segments of photoreceptors. It is hypothesised that loss of the contact between RPE and photoreceptors prevents phagocytosis of the metabolic products of photoreceptors by RPE. If this continues to persist despite resolution of SRF, the subfoveal deposits become permanent leading to poor visual outcome.¹⁰ Similar mechanisms may be involved in PFR.

Increase in length of subfoveal EZ loss showed poorer final visual acuity. Ellipsoid zone integrity reflects the presence of healthy photoreceptors. Shen et al, reported that the EZ integrity is more strongly correlated with BCVA.¹¹ Presence of intact EZ is a positive predictive factor for visual acuity in other retinal disorders like DME, vein occlusion and CSC.¹² The disruption of EZ is considered to represent the cellular damage of photoreceptors.

Progression of retinitis is considered to be a part of natural course of disease and can occur despite initiation of steroid therapy.³ Initial progression was seen in about one third of cases in the present study, but it did not correlate with final BCVA. This could be due to small sample size. Route of steroid administration did not have an effect on final BCVA.

This study gives a better understanding of the various factors predicting visual outcomes in post fever retinitis. Height of subretinal fluid and its reflectivity, inner retinal hyper reflectivity, papillomacular bundle hyper reflectivity, DRIL close to fovea at initial presentation had poor visual outcome. DRIL close to fovea, presence of subfoveal deposits, its height and length, extent of EZ loss, presence of VR interface abnormality and presence of disc pallor at resolution had poor visual outcome. The limitations of this study are that it is a retrospective study with small sample size and the follow up duration was variable. The etiology of fever was not established in all the cases and the effect of etiology on the final outcome could not be established. Macular ischemia can be one of the predictors of poor visual outcome, but it was not evaluated in the study.

Declarations

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Competing interest:

None

Funding:

None

Data availability:

Data protection, confidentiality and privacy was maintained

Conflict of interest:

None

Ethics approval:

Approval was obtained from the institute ethics committee, Sankara eye hospital, Shimoga on December 4, 2020. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Animal research:

Study does not involve

Consent to participate:

Not applicable as this is a retrospective study

Consent for publication:

Not applicable as this is a retrospective study

Author contribution:

1. Suchitra Biswal: Conceptualized the study. Involved in collection of data, analysis of data and manuscript preparation
2. Ankush Gondchawar: Conceptualized the study. Involved in collection of data
3. Ravishankar HN: Conceptualized the study. Involved in manuscript preparation

4. Pradeep Sagar: Conceptualized the study. Involved in collection of data, analysis of data and manuscript preparation
5. P Mahesh Shanmugam: Involved in critical analysis of results and manuscript preparation
6. Aanal Shah: Involved in collection of data
7. Pradeep Tekade: Involved in collection of data
8. Vidya Mooss: Involved in manuscript preparation

All authors critically revised the paper

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Tables

Table 1

OCT parameters recorded at presentation

OCT parameters	Description of the methods used to record the parameter
Foveal contour	Presence of foveal pit was considered as normal.
Intra retinal cystoid spaces within 1000 microns from centre of fovea (IRC-1000)	12 radial scans were screened for the presence or absence of intra retinal hyporeflective spaces within 1000 microns from centre of fovea.
Inner retinal layer hyperreflectivity (IRH) within 500 microns and 1000 microns from centre of fovea	12 radial scans were screened for presence of IRH. The distance between IRH and centre of fovea was measured in the scan in which the IRH was nearest to fovea.
Hyper reflective dots secondary to hard exudates (HRD) within 500 microns and 1000 microns from centre of fovea	12 radial scans were screened for presence of hyper reflective dots correlating with hard exudates on fundus image. The distance between hyper reflective dots and centre of fovea was measured in the scan in which it was nearest to fovea.
Central macular thickness (CMT-I)	Measured from retinal pigment epithelium (RPE) to internal limiting membrane (ILM) in a single well centered scan of the 12 radial scans.
Subretinal fluid (SRF) 1. Maximum height 2. Height at the fovea 3. Mean horizontal extent 4. Reflectivity	After analysing all the radial scans 1. Maximum SRF height was measured from under surface of detached retina at its highest point to RPE. 2. Height of SRF at the fovea was measured (if SRF was present at fovea). 3. Horizontal extent of SRF was measured in all the 12 radial scans and the mean value was recorded. If the extent of SRF was beyond the scan length, it was considered as 6000 micron 4. Reflectivity of SRF was graded as Grade 1: Iso-reflective to outer nuclear layer (ONL) Grade 2: Iso-reflective to outer plexiform layer (OPL) Grade 3: Iso-reflective to nerve fibre layer (NFL)
Disorganisation of retinal inner layers (DRIL) within 1000 microns from centre of fovea	12 scans were analysed to assess whether individual retinal layers were distinct on either side of fovea within 1000 microns. If the layers were indistinct on one side of fovea in one scan it was assigned a score of 1. Each eye was scored from minimum score of 0 to a maximum of 24.
Papillomacular bundle hyper reflectivity	The horizontal scan centred on fovea was assessed for presence or absence of hyper reflectivity of papillomacular bundle.

Table 2
OCT parameters recorded at final visit

OCT parameters	Description of the methods used to record the parameter
Central macular thickness (CMT-F)	Measured from retinal pigment epithelium (RPE) to internal limiting membrane (ILM) in a single well centered scan of the 12 radial scans.
Disorganisation of retinal inner layers within 1000 microns from centre of fovea (DRIL-1000).	12 scans were analysed to assess whether disorganisation of inner retinal layers were seen on either side of fovea within 1000 microns. If the layers were disorganised on one side of fovea in one scan it was assigned a score of 1. Each eye was scored from minimum score of 0 to a maximum of 24.
Horizontal extent and height of sub foveal deposits	Subfoveal deposits were identified as hyperreflective material between neurosensory layer and RPE. Horizontal extent and height of sub foveal deposits was measured in a single well centred radial scan.
Extent of ellipsoid zone (EZ) loss.	Extent of EZ loss was measured in a single well centred scan.
Disorganisation of papillomacular bundle	Presence or absence of disorganisation was noted in nasal half of horizontal scan.
Vitreomacular interface	Vitreomacular interface was assessed for absence of posterior vitreous detachment, presence of vitreomacular adhesion and vitreomacular traction.

Table 3
Correlation between OCT parameters at presentation and final BCVA

Parameters		Results	β coefficient	P value
Foveal contour	Altered	66.7%	Not significant	
	Maintained	33.3%		
IR cystic space within 1000 micron from centre	Yes	37.5%	Not significant	
	No	62.5%		
IRH within 1000 micron from centre	Yes	58.3%	Not significant	
	No	41.7%		
IRH within 500 micron from centre (Reference: No)	Yes	29.2%	-0.35	0.046*
	No	70.8%		
HRD-HE within 1000 micron from centre	Yes	79.2%	Not significant	
	No	20.8%		
HRD-HE within 1000 micron from centre	Yes	66.7%	Not significant	
	No	33.3%		
PMB hyperreflectivity (Reference: No)	Yes	58.3%	-0.33	0.03*
	No	41.7%		
Reflectivity of SRF (Reference: No SRF)	No SRF	16.7%	-0.80	0.014*
	ONL	58.3%		
	OPL	16.7%		
	NFL	8.3%		
Mean distance of IRH from centre		391 \pm 303	Not significant	
Mean foveal thickness		521 \pm 292	-0.001	0.009*
Mean SRF height at fovea		325 \pm 308	-0.001	0.002*
Mean extent of SRF		2284 \pm 2244	Not significant	
DRIL within 1000 micron from centre		6 \pm 6	-0.03	0.016*

Parameters	Results	β coefficient	P value
OCT: Optical coherence tomography; IR: Intraretinal; IRH: Intraretinal hyperreflectivity; HRD-HE: Hyperreflective dots due to hard exudates; PMB: Papillomacular bundle; SRF: Subretinal fluid; ONL: Outer nuclear layer; OPL: Outer plexiform layer; NFL: Nerve fibre layer; DRIL: Disorganisation of retinal inner layers.			

Table 4
Correlation between final fundus, OCT parameters and final BCVA

Parameters	Results	β coefficient	P value	
Subfoveal deposits (Reference: No)	Yes	45.8%	-0.55	0.001*
	No	54.2%		
Subfoveal EZ loss (Reference: No)	Yes	70.8%	-0.49	0.002*
	No	29.2%		
Disorganization of PMB	No	45.8%	Not significant	
	Yes	54.2%		
VR interface (Reference: Normal)	Normal	41.7%	-0.53	0.021*
	VMA	41.7%		
	VMT	16.7%		
Disc pallor	No	50.0%	-0.51	0.007*
	1 quadrant	12.5%		
	Temporal	25.0%		
	Global	12.5%		
CMT		190 ± 68	Not significant	
DRIL within 1000 microns from centre of fovea (score)		11 ± 7	-0.035	0.001*
Mean subfoveal deposit height (microns)		34 ± 41	-0.007	0.001*
Mean subfoveal deposit length (microns)		393 ± 518	-0.005	0.001*
Mean extent of EZ loss (microns)		1989 ± 2333	-0.00014	0.0018*
OCT: Optical coherence tomography; BCVA: Best corrected visual acuity; EZ: Ellipsoid zone; PMB: Papillomacular bundle; VMA: Vitreomacular adhesion; VMT: Vitreomacular traction; CMT: Central macular thickness; DRIL: Disorganisation of retinal inner layers.				

Figures



Figure 1

1a: Measurement of area of retinitis from color photo using image J marked with yellow outline 1b: Measurement of area of color photograph using image J marked with yellow outline

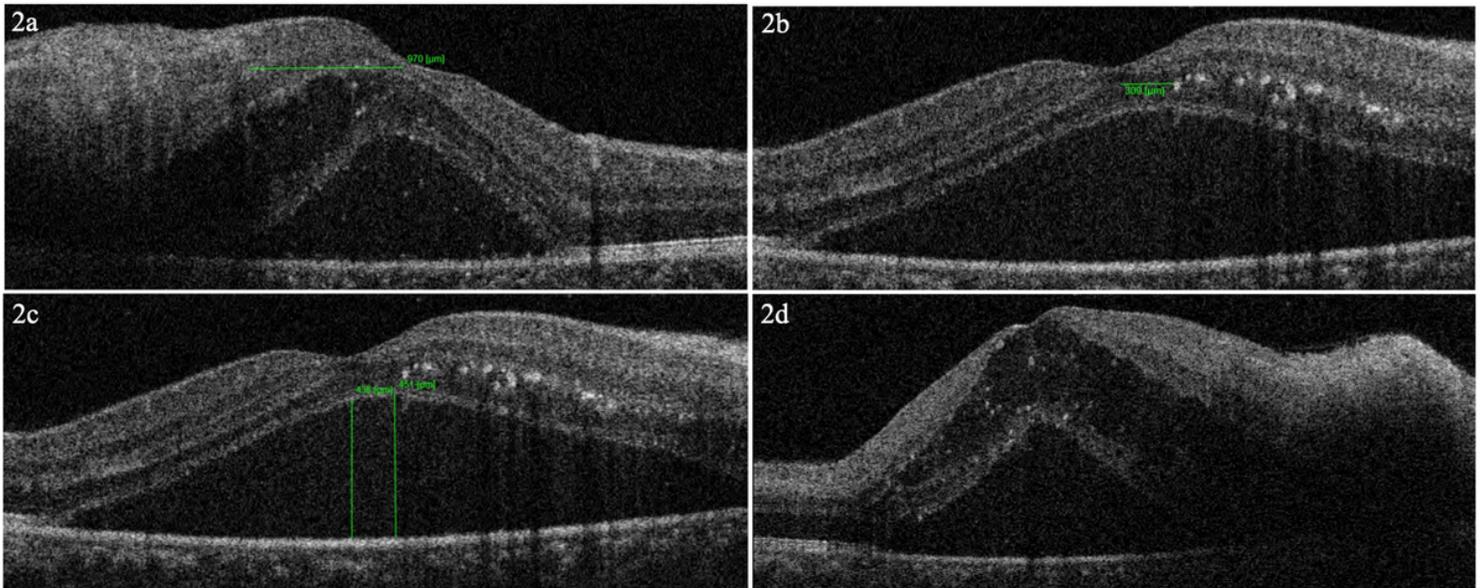


Figure 2

Optical coherence tomography parameters at presentation 2a: Optical coherence tomography (OCT) image showing distance of inner retinal hyperreflectivity from centre of fovea 2b: OCT image showing distance of hyperreflective dots secondary to hard exudates from centre of fovea 2c: OCT image showing the height of sub retinal fluid at the fovea and maximum height of sub retinal fluid 2d: OCT image showing hyperreflectivity of papillomacular bundle

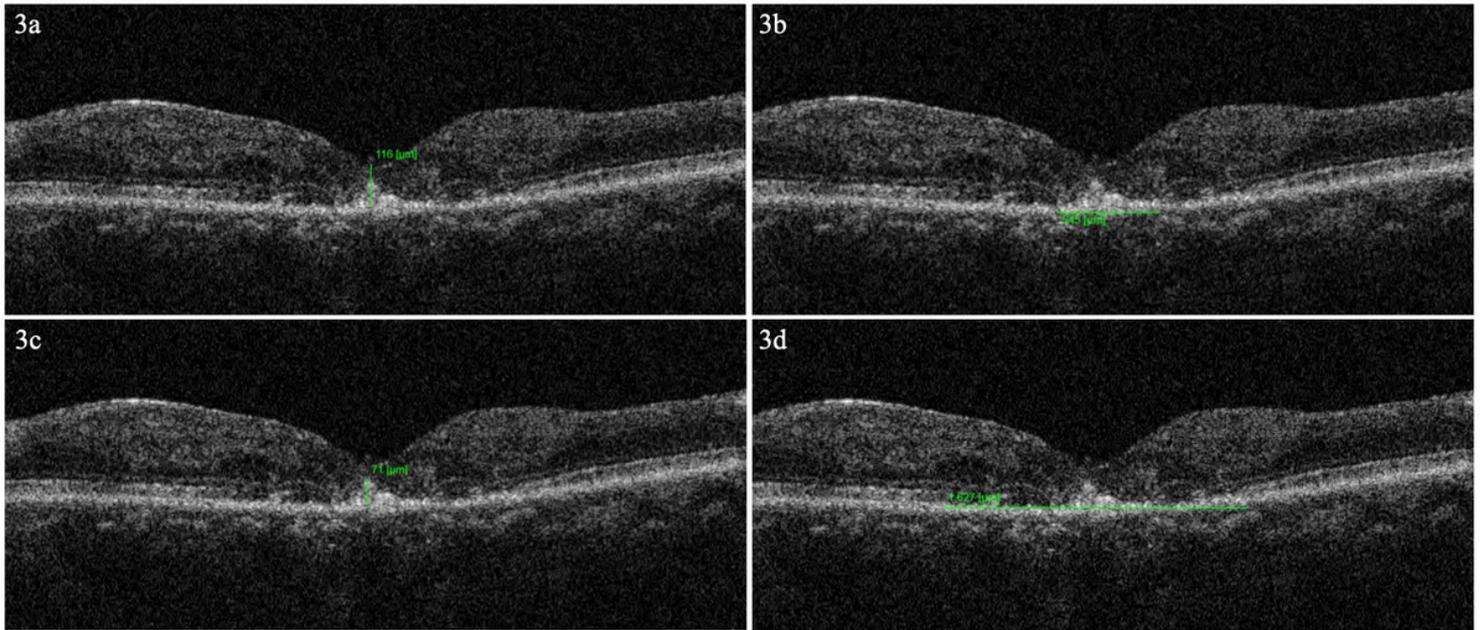


Figure 3

Optical coherence tomography parameters at final visit 3a: OCT image showing the measurement of central macular thickness 3b: OCT image showing the measurement of extent of sub foveal deposit 3c: OCT image showing the measurement of height of subfoveal deposit 3d: OCT image showing the extent of ellipsoid zone loss

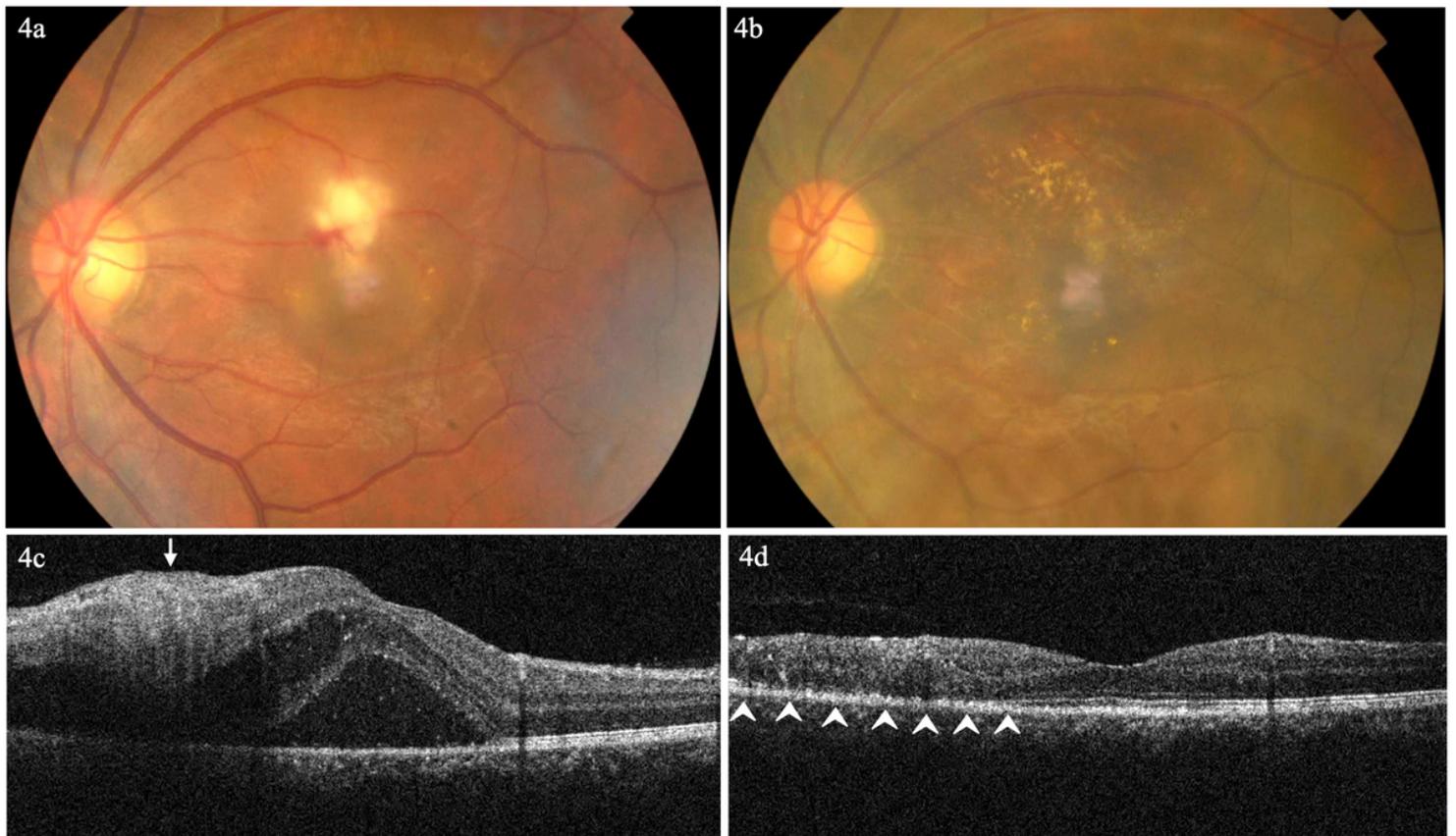


Figure 4

Case of a 32 year old gentleman with post fever retinitis with presenting BCVA of 6/18. He was treated with oral steroids. At final visit, BCVA was 6/6. 4a: Color photo showing area of retinitis, superficial haemorrhage with subretinal fluid at fovea 4b: Color photo showing resolved retinitis with hard exudates superior to fovea 4c: OCT image of figure 2A centered on fovea showing inner retinal hyperreflectivity (white arrow) outside 500 microns from centre of fovea 4d: OCT image of figure 2B showing ellipsoid zone loss (arrow head) away from the centre of fovea

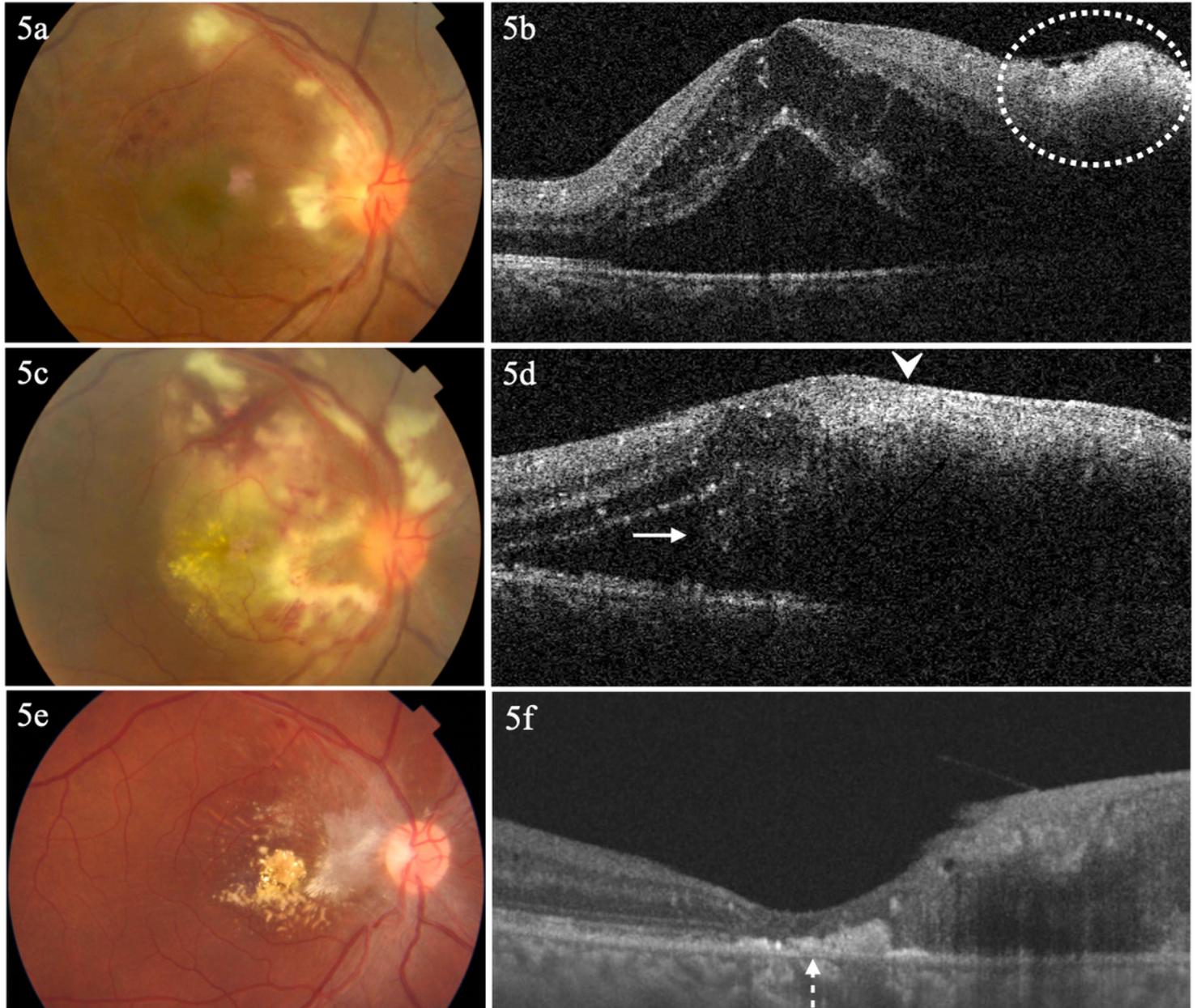


Figure 5

Case of a 19 year old gentleman with post fever retinitis with presenting BCVA of 1/60. He was treated with oral steroids initially. But as the retinitis continued to progress, he was treated with intravenous methylprednisolone for 3 days and oral steroids were continued. At final visit, BCVA was 1/60. 5a: Color photo at presentation showing retinitis involving papillomacular bundle (PMB) 5b: OCT image at presentation showing hyperreflectivity of PMB (dotted circle) and subfoveal fluid 5c: Color photo showing

progression of retinitis with involvement of nasal half of macula with retinal hemorrhages and hard exudates 5d: OCT image of figure 3C showing inner retinal hyperreflectivity close to fovea (arrow head). Subretinal fluid is iso reflective (arrow) to outer plexiform layer 5e: Color photo at resolution showing hard exudate clump at fovea and epiretinal membrane over PMB 5f: OCT image of figure 3E showing presence of subfoveal deposits (dotted arrow), loss of subfoveal ellipsoid zone and foveal thinning