Clinical and imaging characteristics of outer retinal folds in eyes with retinitis

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Purpose: To describe clinical and imaging characteristics of the outer retinal folds (ORF) in cases of retinitis, retinochoroiditis, and chorioretinitis. Methods: Retrospective review of retinitis cases with presence of ORFs either at presentation or during follow up. Results: ORFs were seen adjacent to retinitis lesions in 16 eyes of 14 cases (retinitis post-febrile illness n = 10, toxoplasma retinochoroiditis n = 2, fungal chorioretinitis n = 2) either at presentation (n = 2) or during follow up (n = 14). Optical coherence tomography (OCT) appearance was outer retinal vertical stout lesions involving ellipsoid, external limiting membrane, and outer nuclear layer. All the cases had a presence of past or concurrent subretinal fluid and/or subretinal hyperreflective material when ORF was seen. ORF resolved with variable outer retinal atrophy over a mean period of 2.86 months. Conclusion: ORF is observed in cases of retinitis with subretinal fluid either at presentation or during resolution. It is not specific to any etiological disease. Differentiation of this sign from vertical outer retinal stripes in viral retinitis on OCT is important to avoid misinterpretation.

Key words: Chorioretinitis, optical coherence tomography, outer retinal folds, retinitis, retinochoroiditis

Optical coherence tomography (OCT) has been widely used in cases of posterior uveitis. OCT at presentation helps in differential diagnosis while on follow-ups it is useful to monitor disease activity and/or predict disease outcome.¹ Optical coherence tomography is also useful in the diagnosis and monitoring of complications in posterior uveitis like macular edema, choroidal neovascular membrane and/or epiretinal membrane. Retinitis is a common form of posterior uveitis which could either be infectious or non-infectious.³⁻⁵

Outer retinal folds (ORFs) have been widely described in cases of retinal detachment following vitrectomy or scleral buckle surgery.⁶⁻⁷ OCT features of these folds is described as outer retinal hyperreflective linear lines over the retinal pigment epithelium (RPE) and encroaching into the outer nuclear layer (ONL).⁸⁻¹⁰ ORF is a rarely described clinical sign in association with retinitis, retinochoroiditis, or chorioretinitis. While evaluating an OCT in retinitis, the presence of ORF can confound the understanding or interpretation of the disease entity. It is also important to differentiate these lesions from hyperreflective vertical stripes within the ONL which have been described as an OCT biomarker for viral retinitis.⁹

In this retrospective case series, we describe 16 eyes of 14 cases with active retinitis, with ORF on OCT either at presentation or during resolution of retinitis.

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Methods

We retrospectively reviewed electronic medical records of patients diagnosed with retinitis, retinochoroiditis or chorioretinitis during the study period between January 2017 to December 2020. The study was approved by the institutional review board (IRB) and adhered to the guidelines of the Declaration of Helsinki.

Cases of retinitis, retinochoroiditis, or chorioretinitis with a complete comprehensive ocular examination including best-corrected visual acuity (BCVA), slit-lamp examination, intraocular pressures (IOPs), fundus photography and OCT were recruited in the study. Fundus fluorescence angiography (FFA), autofluorescence (AF) imaging, red-blue-green reflectance imaging, if available, were documented and analyzed. Cases with inadequate documentation and investigations were excluded.

We define an ORF on OCT as a vertical or oblique outer retinal hyperreflective lesion over the retinal pigment epithelium with no evidence of the fold involving the inner retina. However, changes in the inner retina due to retinitis, distortion of inner retinal layers or elevation of the inner retina were included in the study. The definition of ORF is based on publications and reference images by Dell’Omo R et al.,⁹⁻¹⁰ Wong R,¹¹ and Gupta RR et al.¹² We define an incomplete ORF as an inverted V-shaped indentation of outer retinal layers with or without associated subretinal fluid.¹³

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We analyzed our retinitis cases retrospectively based on the number of folds, type (complete/incomplete), pattern (concentric/radial/irregular), and the location from retinitis. Baseline features, subretinal fluid (SRF) and involvement of retinal layers on OCT were analyzed. Fate and sequelae of ORF in subsequent visits were documented. Of the cases recruited in the study according to the inclusion criteria, we included only those cases which had the presence of ORFs either at presentation or during follow-up for further analysis and interpretation.

Statistical analysis: Snellen visual acuity was converted to LogMAR for statistical analysis. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. The data was entered on Microsoft Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

**Results**

We retrieved the data of 182 cases of retinitis, retinochoroiditis, or chorioretinitis with OCT and fundus photo documentation.

**Etiological diagnosis of retinitis with or without choroiditis**

The etiological diagnosis of these cases included toxoplasma retinochoroiditis ($n = 49$), syphilitic chorioretinitis ($n = 11$), viral retinitis ($n = 8$), retinitis post-febrile illness ($n = 41$), fungal chorioretinitis ($n = 3$), retinitis in Behcet’s disease ($n = 2$), tubercular chorioretinitis ($n = 68$).

Of the 182 cases studied for the presence of ORF, we could observe ORF on OCT in 14 cases (16 eyes) only. The etiological diagnosis of these 14 cases (16 eyes) with ORF seen either at baseline or during follow-up was retinitis post-febrile illness ($n = 10$), toxoplasma retinochoroiditis ($n = 2$), and fungal chorioretinitis ($n = 2$). Two cases with bilateral presence of ORF had retinitis post-febrile illness. Seventy-five percent of recruited eyes had the diagnosis of retinitis post-febrile illness.

Toxoplasma retinochoroiditis cases ($n = 2$) had macular focal necrotizing retinochoroiditis lesions. Both cases received trimethoprim (160 mg) with sulfamethoxazole (800 mg) twice a day for six weeks; along with tapering oral steroids for one month. In both cases, the retinochoroiditis healed with pigmented scarring within 3–4 months after presentation. Both the cases of fungal chorioretinitis with subretinal abscess were treated with oral antifungals, intravitreal amphotericin B with voriconazole (weekly injections for three weeks). Retinitis post-febrile illness ($n = 10$ cases) was seen after typhoid fever ($n = 2$), chickenpox ($n = 1$), culture-negative urinary tract infection ($n = 1$), and undifferentiated fever ($n = 6$). Retinitis post-febrile illness was treated with tapering oral steroids ($n = 4$) or intravitreal triamcinolone acetonide ($n = 6$).

**Demographic data and visual acuity**

The mean age at presentation in our series was 39.78 years (±11.55) with male preponderance (male = 10; females = 4). The mean duration of symptoms before presentation was 3.07 weeks (±1.94). The mean total duration of follow up for enrolled cases was 9 months (±7.77). The mean baseline best-corrected LogMAR visual acuity (BCVA) was 1.14 (±0.34) which significantly ($P=0.03$) improved at the final visit to BCVA 0.75 (±0.74).

**Figure 1**: Case of fungal chorioretinitis post SARS-CoV-2 infection; (a) left eye fundus photo showing whitish chorioretinitis lesions at presentation with SRF and subretinal hyperreflective material; (b) follow up at 3 days showing appearance of ORF (arrowhead); (c) appearance of multiple ORFs around the retinitis at 1 month; (d) well-delineated ORFs at 6 weeks; (e and f) gradual resolution of ORFs at 4 and 7 months, respectively. Complete resolution was seen at 9 months.
**Outer retinal folds**

ORF was seen in a concentric pattern around the retinitis lesion as single or multiple yellowish-white, bright lines [Fig. 1]. OCT showed the presence of ORF at the edge of retinitis as a hyperreflective, vertical or oblique stout lesion overlying RPE and restricted in the extent to the outer nuclear layer in all cases [Figs. 2–4]. Variable convexity of the outer plexiform layer overlying the ORF was seen [Fig. 4d, 4e, 4f]. The ellipsoid layer at the edges of ORF had a dipping down appearance with narrowing [Fig. 2b].

The unilateral presence of ORF (n = 12) was more common than bilateral (n = 2). All the eyes at baseline had the presence of subretinal fluid (SRF) (n = 16) clinically. On OCT, SRF was seen in 15 eyes while subretinal hyperreflective material was in one eye [Fig. 2a, 2b]. The mean time interval between the presentation of retinitis and the appearance of ORF was 2.86 weeks (±2.26). The latest presentation of ORF after retinitis was at 9 weeks. ORF was seen at baseline in two eyes (12.5%). The appearance of ORF was associated with resolution of SRF in 62.5% of eyes (n = 10 eyes) while 37.5% of eyes (n = 6) had persistent SRF when ORF was first seen.

**Incomplete ORF**

The incomplete ORF was seen as an inverted V appearance in the outer retina either with (n = 4) or without the presence of SRF (n = 1). OCT conversion of incomplete to complete ORF was seen in all eyes. The earliest time interval of conversion was 3 weeks.

Incomplete ORF [Figs. 3b, 3c, 4a–c] was present in 5 eyes initially, of which 4 eyes had the presence of SRF around ORF. In all instances, an incomplete ORF progressed to complete ORF [Fig. 3c, 3f] with the resolution of SRF.

**The fate of ORF and SRF**

All cases had resolution of SRF before resolution of retinitis lesion, while the resolution of retinitis was seen before the resolution of ORF in all cases. One eye developed rhegmatogenous retinal detachment requiring vitreoretinal surgery. In another eye with retinitis post-febrile illness, resolution of retinitis but the persistence of ORF was seen at 2 months after which the case was lost to follow up. We excluded these two eyes from the analysis of time taken for clinical resolution of ORF. The mean time required for clinical resolution of ORF was 2.86 months (±2.5). After clinical resolution or disappearance of ORF, corresponding OCT feature of variable outer retinal atrophy and focal ellipsoid loss/distortion was seen [Fig. 4g, h].

**Discussion**

We have described 16 eyes of 14 cases with retinitis with or without accompanying choroiditis who developed ORF either at presentation or during resolution [Table 1]. In our retrospective review, we did not come across the presence of ORF in cases of tubercular posterior uveitis, syphilitic posterior uveitis, and viral retinitis during the study period.

Interestingly, all the eyes in this study had SRF at baseline. The appearance of ORF after rapid attachment of detached retina

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**Figure 2:** OCT montage scans corresponding to case in Figure 1; (a) Dome-shaped hyperreflective central chorioretinitis lesion with subretinal hyperreflective material (arrow); (b) Appearance of ORF at day 3 follow up; (c-f) show gradual resolution of ORF height, thickness along with focal ellipsoid distortion at months 1, 1.5, 4, and 7, respectively.
Figure 3: Case of retinitis post-febrile illness (a) at presentation. Vertical OCT scan marked on (a) at presentation (b) shows inverted V appearance (c) of incomplete ORF with SRF. At 6 weeks follow up, resolution of retinitis is seen along with formation of multiple ORFs (arrow) on red reflectance imaging as white lines (d) and hyperautofluorescent on autofluorescence imaging (e). OCT showed conversion of incomplete to complete ORF (f).

Figure 4: Various morphological patterns of ORF on OCT; (a-c) demonstrate incomplete ORFs with variable dome-shaped elevation of overlying OPL and presence of SRF; (d-f) demonstrate ORF at edge of retinitis with variable OPL curvatures ranging from semicircular (d), dome-shaped elevation (e) to shallow elevation (f); (g) shows presence of two ORFs resolving with focal ellipsoid loss in (h).
Table 1: Demographic and clinical characteristics of cases with retinitis associated outer retinal folds

| Study cohort (14 cases, 16 eyes) | Study cohort (14 cases, 16 eyes) |
|---------------------------------|---------------------------------|
| Mean age±SD (years)             | 39.78±11.55 years               |
| Gender (M: F)                   | 10:4                             |
| Mean baseline BCVA (LogMAR)     | 1.14 (±0.34)                     |
| Mean final visit BCVA (LogMAR)  | 0.75 (±0.74); P=0.03             |
| Mean duration of symptoms prior to presentation as retinitis (weeks) | 3.07 (±1.94)                     |
| Etiological diagnosis of retinitis with ORF |                     |
| Retinitis post-febrile illness (cases) | 10 (75%)                     |
| Toxoplasma retinochoroiditis     | 2                               |
| Fungal chorioretinitis          | 2                               |
| Subretinal fluid at baseline (eyes) | 16 (100%)                     |
| Mean time interval between retinitis and appearance of ORF (weeks) | 2.86 (±2.26)                     |
| Incomplete ORF at baseline (eyes) | 5                               |
| Mean time for resolution of ORF (months) | 2.86 (±2.5)                     |

BCVA=best corrected visual acuity, ORF=Outer retinal fold

is a known phenomenon. This is due to the differential elasticity of the inner and outer retina. The internal limiting membrane (ILM) and cortical vitreous attachment offer rigidity to the inner retina while also exerting a transverse vector force. In a detached retina, the outer retina often has corrugations or incomplete ORFs. These corrugations/incomplete ORFs on the resolution of subretinal fluid and attachment of retina lead to ORF. The presence of ORF can cause the vision to be subnormal with distortion or blurring. The fate of ORFs is fading and/or complete resolution with variable grades of outer retinal atrophy. The retinal “memory” of photoreceptor layer alignment with the underlying RPE and outer retinal elasticity is hypothesized to be the cause of retinal straightening and resolution of ORF over a few months.

In our case series, we observed these folds at the edge of the retinitis lesion in a concentric pattern during resolution of retinitis and re-absorption of SRF. ORF at the macula, in our opinion, is a risk factor for subnormal vision in addition to the visual loss due to sequel and/or complications of retinitis itself.

Another concern regarding ORF is to differentiate it from hyperreflective vertical stripes seen in viral retinitis. The appearance of ORF on OCT in the association of retinitis can simulate and be misinterpreted as hyperreflective vertical stripes. We had briefly entertained the diagnosis of viral retinitis in a case of retinitis post-febrile illness on observation of ORF on a subsequent visit [Fig. 2]. We observed that ORF is stouter in appearance, limited till ONL, has convexity of overlying OPL, is associated with simultaneous or past SRF, and is not specific to any particular retinitis. In contrast, hyperreflective vertical stripes according to the original description are associated with viral retinitis, can be accompanied by intra-retinal fluid, seen within ONL as slender or thin strips when compared to ORF. A common feature of both of these signs, however, is the location at the margin of retinitis. There is paucity of literature regarding the presence of outer retinal folds in association with posterior uveitis and its impact on diagnosis and outcome. Our study attempts to describe this rare sign in the presence of retinitis, though it does have limitations of being retrospective in nature and non-randomized. Further prospective studies are needed to establish the correlation of ORFs with various treatment modalities, their preponderance to certain forms of retinitis, and their multimodal imaging characteristics.

Conclusion

In conclusion, ORF is a sign which is observed in cases of retinitis with subretinal fluid either at presentation or during resolution. It is not specific to any etiological cause of retinitis. ORFs often have delayed and slow resolution up to nine months. Differentiation of this sign from vertical outer retinal stripes in viral retinitis is important to avoid misinterpretation.

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Conflicts of interest

There are no conflicts of interest.

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