Novel features of degenerative retinoschisis identified using ultra-widefield multicolor channels: A review of 139 eyes

Samantha Orr1,2 | Amin Hatamnejad2,3 | Simrat Sodhi2,4 | John Golding1,2 | Niveditha Pattathil1,2 | Netan Choudhry1,2,5

1Vitreous Retina Macula Specialists of Toronto, Toronto, Ontario, Canada
2Octane Imaging Lab, Toronto, Ontario, Canada
3McMaster University, Hamilton, Ontario, Canada
4University of Cambridge, Cambridge, UK
5Department of Ophthalmology & Visual Sciences, University of Toronto, Toronto, Ontario, Canada

Correspondence
Netan Choudhry, Vitreous Retina Macula Specialists of Toronto, Toronto, ON, Canada.
Email: netan.choudhry@vrmto.com

Abstract
Background/Objective: To utilize ultra-widefield multimodal imaging (Optos PLC) to describe novel findings in degenerative retinoschisis.

Methods: This retrospective, non-comparative case series of degenerative retinoschisis received a waiver of consent from Advarra IRB, Protocol 00066379. Initial ultra-widefield pseudocolour, colour-separated, autofluorescence, and peripheral OCT imaging were analysed for characterizing features.

Results: In total, 139 eyes were included. A hyporeflective reticular pattern associated with retinoschisis was seen on pseudocolour images in 39% of cases, but visible in 53% on green-separated images. Fine hyper-reflective foci were observed in 49%. In 27%, retinoschisis was confirmed with OCT.

Conclusions: Ultra-widefield pseudocolour and green-separated images are valuable for the diagnosis and characterization of degenerative retinoschisis. The findings described may prompt the evaluation of subtle retinoschisis with peripheral OCT.

KEYWORDS
multi-modal imaging, ophthalmic imaging, retinoschisis, widefield imaging

INTRODUCTION

Degenerative, senile or acquired retinoschisis was first described in 1933 by M. Bartels (Ness et al., 2022). The prevalence of this common condition is similar in males and females and increases with age (Ness et al., 2022). In patients over age 40, prevalence ranges from 7% to 22% (Ness et al., 2022). Although most cases remain asymptomatic, monitoring for progression or retinoschisis-related retinal detachments (RSRD) is recommended (Ness et al., 2022). Degenerative retinoschisis can be diagnostically challenging as it may appear quite subtle or similar to retinal detachment (RD) on examination. Given differences in their management, the distinction between these pathologies is of great clinical importance (Ness et al., 2022). Advances in imaging of the retinal periphery have contributed to the accuracy of distinguishing retinoschisis from RD or RSRD, but additional insights can be gained through further characterization and study (Banda et al., 2019; Eibenberger et al., 2017; Ho et al., 2016; Nadelmann et al., 2019; Navaratnam et al., 2021; Stehouwer et al., 2014; Yeoh et al., 2012).

Degenerative retinoschisis is characterized by splitting of the retinal layers, often at the outer plexiform layer (OPL) and adjacent nuclear layer (Agarwal et al., 2016). Septae may be observed connecting split layers, typically composed of remnants of glial cells, axons and dendrites (Yanoff & Fine, 2002). On examination, glistening yellow-white dots are thought to represent glial cell remnants damaged by retinal splitting (Rachitskaya et al., 2017). According to histological descriptions, a beaten metal appearance may represent glial cell remnants adhered to the inner layer of the schisis cavity (Rachitskaya et al., 2017; Yanoff & Fine, 2002). Degenerative retinoschisis is distinct from other schisis pathologies, such as inherited x-linked retinoschisis and myopic foveoschisis (Gohil et al., 2015; Rao et al., 2018).

Recent literature has discussed the role of ultra-widefield retinal imaging in characterizing retinoschisis. On autofluorescence imaging, retinoschisis usually appears isoautofluorescent, whereas retinal detachments...
are often hypoaurofluorescent (Francone et al., 2020; Huang et al., 2020; Nadelmann et al., 2019; Navaratnam et al., 2021). Peripheral OCT beyond the posterior pole has also proven useful, allowing for diagnostic confirmation and detection of retinal holes or RSRD (Eibenberger et al., 2017; Rachitskaya et al., 2017; Stehouwer et al., 2014; Yeoh et al., 2012).

Optos pseudocolour scanning laser ophthalmoscopy, which uses red and green lasers to generate a colour image of the retina, can be reviewed as a combined pseudocolour image or as monochromatic red-colour image of the retina, can be reviewed as a composite image, which uses red and green lasers to generate a detailed visual representation of neurosensory retina down to retinal pigment epithelium (RPE), while the red-separated image shows a focused view from the RPE down to the choroid (Park et al., 2022). This extra dimension of information vastly increases the clinical utility of these images. Colour-separated images have provided insight into pathologies including Vogt-Koyanagi-Harada disease and choroidal lesions (Park et al., 2022). To the best of our knowledge, the utility of colour-separated images has not yet been investigated to improve understanding of pathophysiology and detection of degenerative retinoschisis. Given the location of retinoschisis within the neurosensory retina, we anticipate additional information from the green-separated image. Here, we present 139 cases of degenerative retinoschisis from a single vitreoretinal practice, aiming to illustrate previously discovered and novel findings on Optos imaging. Multimodal imaging will be evaluated, including pseudocolour, colour-separated, autofluorescence and OCT images.

2 METHODS

2.1 Study design

This is a single-centre, retrospective, non-comparative case series conducted at the Vitreous Retina Macula Specialists of Toronto (VRMTO). The research adhered to the tenets of the Declaration of Helsinki. A waiver of consent was obtained for this study from Advarra IRB, (Protocol 00066379). Patients consented to use of their de-identified medical information and images at the time of intake. Consecutive cases of degenerative retinoschisis from 2013 to 2022 were collected. Baseline demographic information was collected, including age, gender and ocular comorbidities. Dilated fundus examination was carried out for each patient.

2.2 Inclusion and exclusion criteria

Key inclusion criteria were: (1) diagnosis of degenerative retinoschisis between 2013 and 2022, (2) ultra-widefield pseudocolour and autofluorescence imaging, with or without peripheral OCT, completed using Optos machine—imaging protocols described below. Exclusion criteria included: (1) poor image quality for analysis, (2) incomplete imaging, (3) diagnosis or suspicion of X-linked retinoschisis.

2.3 Image acquisition

Pseudocolour and autofluorescence images were acquired bilaterally in dilated eyes (Mydfrin, Mydriacyl) using the Optos California or Silverstone device (Optos PLC Edinburgh). Images were captured in primary gaze, with additional eye-steered images in the temporal, nasal, superior and inferior gazes. Peripheral swept source OCT (SS-OCT) in the area of schisis was acquired when the Silverstone device was used (at technician's discretion) using a line scan (6, 14 or 23 mm), volume scan (3.5 mm × 6 mm, 121 scans) or both.

2.4 Analysis

Optos pseudocolour images, colour-separated images, autofluorescence images and any available OCT of retinoschisis were analysed for imaging characteristics and patterns. In unilateral cases, contralateral images were evaluated for any subtle retinoschisis. A list of imaging findings was generated, and images were independently reviewed by two authors (S.O., A.H.). Conflicts were resolved by a third author (N.C.) and documented for review. No statistical analysis was done.

3 RESULTS

3.1 Patient demographics and baseline characteristics

In this cohort, 40% of patients were female with a mean age of 56 (±14.8) years (Table 1). Baseline visual acuity was 0.14 (±0.23) LogMAR (approximately 20/25 Snellen) (Table 1). Two patients were excluded from analysis due to lack of imaging, and two eyes were excluded due to poor image quality. Approximately 70% of patients were managed with observation. The remaining patients underwent prophylactic laser retinopexy, most commonly due to inner retinal holes.

3.2 Imaging findings

Ninety-one patients with degenerative retinoschisis were included. Diagnosis was made based on fundus examination and multimodal ultra-widefield imaging whenever available. Of these, 32 had bilateral retinoschisis, and 59 presented with unilateral retinoschisis (123 eyes) (Table 1). Analysis of contralateral eye images in unilateral retinoschisis led to detection of 16 additional cases, resulting in a total of 139 eyes.
Twenty-seven percent of cases (37 eyes) had OCT imaging confirming retinoschisis. Retinoschisis was observed inferotemporally in 80% of eyes, superotemporally in 60% of eyes and nasally in 7% of eyes. Of 16 documented cases with inner retinal holes, 7 were visible on imaging (Figures 1 and 2). On imaging, 5 additional retinal holes were detected; however, these eyes had previously documented or treated retinal holes and the retinoschisis was at a different location. It did not appear to be related to the previous treatments of holes. RSRD was seen in 7 eyes (Figures 1 and 2).

A hyporeflective reticular pattern of variable size was associated with areas of schisis (Figures 3 and 4). This pattern was observed in pseudocolour images in 39% of eyes (54 eyes), but was visible in 53% (73 eyes) on the green-separated images (Figure 1). Fine hyperreflective foci were noted over the area of schisis or at its anterior edge in 49% (68 eyes) of cases on pseudocolour and green-separated image (Figures 1, 4 and 5). These foci were typically less obvious on red-separated images, and in 41% of 68 eyes, they were not visible on red-separated images. Peripheral OCT imaging of the reticular pattern correlated with schisis cavities. Hyper-reflective foci correlated on OCT with scattered hyperreflectivities between the inner and outer retina (Figures 3 and 5, Figure S1).

### TABLE 1  Patient demographics and baseline information.

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of participants</td>
<td>91</td>
</tr>
<tr>
<td>Number of males (Proportion)</td>
<td>55 (0.60)</td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>56.0 (14.8)</td>
</tr>
<tr>
<td>Right eye presentation</td>
<td>28</td>
</tr>
<tr>
<td>Left eye at presentation</td>
<td>31</td>
</tr>
<tr>
<td>Both eyes at presentation</td>
<td>32</td>
</tr>
<tr>
<td>Baseline BCVA LogMAR (mean±SD)</td>
<td>0.13 (0.22)</td>
</tr>
<tr>
<td>Refraction: Spherical equivalent (mean±SD)</td>
<td>0.184 (3.5)</td>
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In the area of schisis, 113 eyes (81%) exhibited iso-autofluorescence, 14 eyes (10%) showed hypoautofluorescence and 3 eyes (2%) showed hyperautofluorescence (Figure 1). The posterior border of schisis was iso-autofluorescent in 66 eyes (47%), hypoautofluorescent in 49 eyes (35%) and hyper-autofluorescent in 17 eyes (12%) (Figure 1). Remaining eyes displayed mixed autofluorescence patterns. Overall, 59 eyes (42%) presented with isoautofluorescence at both the area of schisis and its posterior border and 43 eyes (31%) presented with a hypoautofluorescent posterior border and isoautofluorescence in the area of schisis (Figure 6). Previous literature has examined clinical utility of autofluorescence pattern in differentiating between retinoschisis and retinal detachments related to retinal layer separations and metabolic changes, however, no specific prognostic factors have been associated with different patterns observed in area of schisis.

### DISCUSSION

Similar patterns of hyporeflective reticular pattern and the fine hyper-reflective foci were first explained by Straatsma and Foss in 1973 using histological analysis in a non-clinical setting. Previous studies have provided insight into multimodal imaging of degenerative retinoschisis (Ness et al., 2022; Palma-Carvajal et al., 2019; Thanos et al., 2019). Our study is the first to employ a more comprehensive multimodal approach using ultra-widefield pseudocolour, colour-separated, autofluorescence and OCT imaging in 139 eyes with degenerative retinoschisis.

In alignment with the literature, most retinoschisis cases (80%) were inferotemporal (Ness et al., 2022). Many eyes had schisis in multiple quadrants: 60% of eyes had superotemporal retinoschisis, higher than previous studies reporting 28% (Ness et al., 2022). In this cohort, there...
**FIGURE 2** Inferior degenerative retinoschisis with schisis-related retinal detachment and retinal hole in the right eye. (a) Pseudocolour image with inferior retinal hole with magnified inset of hole. (b) Green-separated image with inferior retinal hole with magnified inset of hole. (d) Autofluorescence image showing mainly isoautofluorescence with some discrete areas of hyperautofluorescence. (c) OCT B-Scan showing retinoschisis-related retinal detachment, location indicated by green line.

**FIGURE 3** Inferotemporal degenerative retinoschisis in the right eye. (a) Pseudocolour image illustrating retinoschisis with one larger schisis cavity (white arrow). Notably, the reticular pattern indicated by the green arrow in the green-separated image is expected to be observed in this pseudocolour representation, correlating with the superficial splitting of the retina and the resultant thick and excavated outer layer as confirmed by OCT. (c) Green-separated image at higher magnification of the schisis area, displaying the larger schisis cavity (white arrow) alongside the reticular pattern (green arrow), which suggests the depth of retinal splitting and the extent of outer layer excavation. (b) Peripheral OCT B-scan across the white line on the green-separated image, revealing the schisis cavity. (d) Peripheral OCT B-scan across the green line on the green-separated image, delineating a localized detachment of the outer layer at the edge of the outer layer break, which is a critical observation for understanding the morphology and progression of the retinoschisis (Silverstone, Optos PLC, Edinburgh).
ORR et al. were fewer bilateral cases than have been previously reported: 50% compared to 77% (Ness et al., 2022). The higher incidence of unilateral cases may be due to this practice's comprehensive imaging protocols, which may detect subtle signs of degenerative retinoschisis earlier. Our study specifically evaluated images at time of diagnosis; if additional time-points were analysed, the incidence of bilateral cases may have increased over time.

4.1 | Diagnostic methods for degenerative retinoschisis

The distinction between RD and retinoschisis has long presented a diagnostic challenge (Agarwal et al., 2016; Banda et al., 2019; Eibenberger et al., 2017; Ho et al., 2016; Huang et al., 2020; Ip et al., 1999; Kylstra & Holdren, 1995; Lincoff et al., 2003; Nadelmann et al., 2019; Navaratnam et al., 2021; Stehouwer et al., 2014; Yeoh et al., 2012). In 1995, Kylstra et al. used indirect ophthalmoscope perimetry to test the visual field anterior to the equator (Kylstra & Holdren, 1995). A shadow was projected onto the elevated retina using scleral depression. If the shadow was seen by the patient, retinoschisis was ruled out, since retinoschisis produces an absolute scotoma (Kylstra & Holdren, 1995). In 2003, Lincoff described the modified green argon laser test to distinguish retinoschisis from RD (Lincoff et al., 2003). Non-elevated retina has a grey response to the laser whereas laser signal is attenuated by a detached retina. In retinoschisis, the laser can pass through inner retinal layers to cause a grey response, thus ruling out RD (Lincoff et al., 2003). Both of these exam techniques must be done by the physician, are time consuming and can still provide equivocal results.

Ophthalmic imaging provides many advantages over these techniques, including detailed documentation of pathology and reproducible images. On high-resolution ultrasound B-scan, three hyper-reflective layers are visible: the RNFL interface, OPL interface and RPE (Agarwal et al., 2016). Agarwal et al. used this technology in 2016 to distinguish cases of retinoschisis and RD. In retinoschisis, one hyper-reflective layer was detached (RNFL interface) while the OPL interface and RPE were both attached (Agarwal et al., 2016). In RD, 2 hyper-reflective layers were detached (RNFL and OPL interface) (Agarwal et al., 2016). On infrared imaging, retinoschisis has been described as light, isoreflective and translucent with prominent vasculature (Banda et al., 2019; Ho et al., 2016). By contrast, RD appeared dark, hyporeflective and opaque and hyper-reflective where RPE was exposed by a retinal tear (Banda et al., 2019; Ho et al., 2016). RSRD showed mixed reflectivity with blurred vasculature (Banda et al., 2019; Ho et al., 2016).

FIGURE 4 Superotemporal degenerative retinoschisis in the right eye. (a) Pseudocolour image shows smooth dome-shaped retinal elevation with well-defined and darker vasculature. Reticular pattern is visible in the anterior half of the area of retinoschisis and there are hyper-reflective foci present at the anterior border of the area of retinoschisis. (b) Green-separated image showing reticular pattern and hyper-reflective foci corresponding to the distribution on the pseudocolour image. (c) Autofluorescence imaging showing a hypoautofluorescent posterior border and isoautofluorescence over the area of schisis. (d) and (e) are peripheral OCT B-scans corresponding to the white and green lines on the pseudocolour image, respectively.
4.2 | Autofluorescence imaging findings

Although literature describes autofluorescence findings in degenerative retinoschisis, it is not entirely consistent. Retinoschisis is most commonly characterized by isoautofluorescence in 68%–100% of cases, with or without a hypoautofluorescent posterior border (Francone et al., 2020; Nadelmann et al., 2019; Navaratnam et al., 2021). In this cohort, approximately 80% of cases were isoautofluorescent over the area of schisis (Francone et al., 2020; Nadelmann et al., 2019; Navaratnam et al., 2021). A hypoautofluorescent posterior border of retinoschisis was found in 35% of eyes, similar to previously reported rates of 30%–33% (Francone et al., 2020; Nadelmann et al., 2019; Navaratnam et al., 2021). By contrast, Huang et al. in 2020 reported some degree of hypoautofluorescence in all cases of retinoschisis (Huang et al., 2020). Typically, hypoautofluorescence is seen due to the subretinal fluid in RD (Francone et al., 2020; Huang et al., 2020; Nadelmann et al., 2019; Navaratnam et al., 2021). It is worth noting that according to our observations, autofluorescence findings sometimes differed between eye-steered images. We believe that this is due to the vignetting effect. The schisis is by nature non-aligned and not uniform. The schisis bubble is curved and orientation to the light path would be variable with steered or centre fixation. When steering the optical pathway to the peripheral retina, the light is going through the centre of the lens and cornea. When using centre fixation, the pathway to the peripheral retina is more vignetted by the lens and cornea. The light in peripheral OCT is going through a thicker and more optically dense cornea and the same is true for the lens. The centre of the retina will have greater signal than the light that comes back from the far periphery.

4.3 | OCT imaging findings

OCT has been recognized as the most reliable single modality in the diagnosis of retinoschisis. OCT can detect splitting of the neurosensory retina, a finding with histological correlation. Previous literature has examined clinical utility of autofluorescence pattern in differentiating between retinoschisis and retinal detachments related to retinal layer separations and metabolic changes, however, no specific prognostic factors have been associated with different patterns observed in area of schisis (Eibenberger et al., 2017; Ip et al., 1999; Yeoh et al., 2012). Traditionally, there have been challenges in acquiring OCT of the peripheral retina where retinoschisis is typically located. As early as 1999, OCT was used to differentiate retinoschisis from RD, work furthered by Yeoh et al. in 2012 (Ip et al., 1999; Yeoh et al., 2012). Rachitskaya et al. in 2017 documented the ability of OCT to detect outer retinal holes, and suggested that schisis detachments may be underdiagnosed on clinical exam (Rachitskaya et al., 2017). In this cohort, OCT was primarily used
to confirm presence of retinoschisis and to assess for RSRD. The OCT scans of the far peripheral retina using Silverstone can visualize the anatomic differences and contribute significantly to diagnosis of retinoschisis. Previously some studies have been able to capture the peripheral retina on the Heidelberg Spectralis and the Topcon Triton and through using 3-mirror contact lens as well as Goldmann lens in conjunction with intraoperative OCT. These techniques would be useful to capture the OCT of the peripheral retina in the absence of Silverstone device.

4.4 | Pseudocolour imaging findings

On widefield pseudocolour imaging, retinoschisis has been described as a smooth, dome-shaped elevation without folds or undulations (Ness et al., 2022; Thanos et al., 2019). Vessels may appear dark over the area of schisis, likely an imaging artefact due to retinal elevation (Ness et al., 2022; Thanos et al., 2019). Our study expands on pseudocolour image findings by describing a novel reticular pattern and bright hyper-reflective foci that have not been previously discussed. We propose that this reticular pattern is likely representative of schisis cavities in the neurosensory retina. Since the green-separated image can provide more detail of the neurosensory retina, we analysed these images and found that this pattern became more prominent. In some cases, this pattern was not visible on pseudocolour imaging, but was revealed upon analysis of the green-separated image: of 73 eyes in which this pattern was visible on the green-separated image, it was detected in 74% (54 eyes) on pseudocolour imaging. In some cases, OCT line or volume scans were acquired over the area where this pattern was visible and confirmed the presence of schisis. Previous studies have described a pitted or honey-combed appearance in areas of retinoschisis, attributed to outer layer irregularity or breaks (Eibenberger et al., 2017; Yeoh et al., 2012). A honey-combed appearance on pseudocolour imaging has recently been described in the setting of X-linked retinoschisis, similar in appearance to the pattern described here (Ma et al., 2023). Of note, the pattern described in X-linked retinoschisis by Ma and colleagues was well visualized on the red-separated image, which was not the case for the pattern described in this study (Ma et al., 2023).

The yellowish-green foci described may represent glial dots, seen in histologic samples as remnants of glial cells adhering to the internal limiting membrane, which have been described as glistening dots or a beaten-metal appearance. Given the hyper-reflective foci's prominent appearance on the green-separated image and subtle or absent appearance on the red-separated image, we would expect the pathology to be

![Figure 6](image-url)

**Figure 6** Superotemporal and inferotemporal degenerative retinoschisis in the left eye. (a) Pseudocolour image shows reticular pattern at superotemporal area of schisis (white arrow) and subtle reticular pattern inferotemporally (black arrow). Subtle area of inferotemporal schisis (blue arrow) shows some blurring of vasculature, but no reticular pattern. (c) Green-separated image demonstrates more prominent reticular pattern (white and black arrows), and highlights presence of more subtle area of schisis (blue arrow). (b) Magnified autofluorescence image of superotemporal schisis with hypoautofluorescent posterior border and isoautofluorescence over the area of schisis. (d) Magnified autofluorescence image of inferotemporal schisis with isoautofluorescence over the area of schisis and the posterior border (blue arrow) and hyperautofluorescence (black arrow).
located within the neurosensory retina. This observation aligns with the hypothesis that these foci represent glial cell remnants.

4.5 Limitations

The retrospective nature of the study design does present a limitation as image acquisition, although standardized, was performed according to technicians’ discretion, and relied on available technology. We also analysed images from the initial visit or from the earliest images available after diagnosis. Subsequent images may have shown other findings or improved image quality. However, we did not analyse these images since not all patients received follow-up imaging which would have led to smaller sample size. Furthermore, OCT scans aimed to simply confirm retinoschisis, and thus findings of interest were not always captured. Some retinal holes documented on clinical exam were not seen on imaging, highlighting the continued importance of a thorough clinical exam. Finally, our study population had no presence of high myopia which is associated with peripheral retinal changes such as degenerations, retinal holes, tears and detachments.

Interpretive conflicts between authors were present, particularly in autofluorescence findings (25%). This is unsurprising considering variability in the literature and previously discussed differences between eye-steered views. In nearly 10% of conflicts, the reticular pattern on pseudocolour imaging was in question. This occurred in cases where the pattern was quite subtle, but present upon closer examination with increased magnification. The presence of hyper-reflective foci was rarely in question as they are typically a prominent finding.

In conclusion, we describe the first study to utilize ultra-widefield imaging in conjunction with peripheral SS-OCT and colour-separated images in the diagnosis and characterization of degenerative retinoschisis. We have discussed findings on pseudocolour and green-separated images, including the reticular pattern and hyper-reflective foci. These findings may denote the presence of otherwise subtle retinoschisis, aid in differentiation from RD and inform management decisions. With continued evaluation using ultra-widefield-OCT, these findings can be further corroborated.

**SUPPORTING INFORMATION**
Additional supporting information can be found online in the Supporting Information section at the end of this article.