Original Article

Spectral domain optical coherence tomography evaluation of macular changes in Eales disease

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Purpose: The purpose of the study was to describe macular changes in treatment-naïve eyes with Eales disease using spectral domain optical coherence tomography (SD-OCT). **Methods:** A cross-sectional study was done on 79 eyes of 66 patients with Eales disease. Best-corrected visual acuity (BCVA), slit-lamp biomicroscopy (SLB), indirect ophthalmoscopy, fundus fluorescein angiography (FFA), and quantitative (central macular thickness [CMT]) and qualitative analysis on SD-OCT were performed. **Results:** Forty-six (58.2%) eyes had macular involvement as assessed with SD-OCT, while in 33 (41.8%) eyes, macula was not affected. Macular edema was the most common feature when macula was affected followed by epiretinal membrane. Mean CMT was higher (315.3 ± 102.3 μm) in eyes with macular involvement than those without it (243.8 ± 19.3 μm). Eyes with active vasculitis involving larger vessels and neovascularization had greater chance of macular involvement. SLB and FFA alone missed 28.3% and 50% eyes with macular abnormalities on SD-OCT, respectively. **Conclusion:** While the clinical description of Eales disease points mainly to a peripheral location, macular involvement can be commonly picked up when SD-OCT is used. Macular involvement when present is associated with a poorer BCVA.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_845_17

Quick Response Code:

Key words: Eales disease, epiretinal membrane, macula, macular edema, retinal vasculitis, spectral domain optical coherence tomography

Eales disease is an idiopathic vasoproliferative disorder of the retina characterized by inflammation of the peripheral small retinal veins, resulting in peripheral retinal ischemia, neovascularization (NV), and recurrent vitreous hemorrhages.[1,2] It is a diagnosis of exclusion, and as opposed to the rest of the world, it is particularly common in the Indian subcontinent, with an estimated incidence of 1 in 200–250 ophthalmic patients.[3] Eales disease primarily affects the peripheral retina, and macular involvement is considered uncommon.[1,2]

Data on macular involvement in Eales disease are scant and limited to retrospective studies that have reported rates ranging from 28.1% to 35.4% using slit-lamp biomicroscopy (SLB) and fluorescein angiography.[4-6] Optical coherence tomography (OCT) has revolutionized the diagnosis and management of macular disorders in the past two decades. It is a sensitive and specific noninvasive tool for the assessment of the macula and is more sensitive than using clinical examination alone. Spectral domain OCT (SD-OCT) has an axial resolution of 3–5 μ and provides high-resolution images of the macula.[7] The purpose of this study is to prospectively evaluate macular changes in Eales disease using SD-OCT, which has not been reported previously.

Methods

This was a prospective cross-sectional study on patients with Eales disease, recruited from a tertiary referral eye center. This study was performed in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients at the outset. Inclusion criteria included treatment-naïve eyes with Eales disease (active or healed retinal periphlebitis) with clear media, to enable good quality SD-OCT scans. Patients with peripheral retinal periphlebitis and/or peripheral retinal nonperfusion and/or peripheral retinal NV on fundus fluorescein angiography (FFA) were diagnosed as Eales disease after exclusion of other causes of retinal vasculitis.[1,2] Appropriate clinical evaluation and relevant laboratory tests were done to rule out diseases such as tuberculosis, sarcoidosis, syphilis, diabetes mellitus, blood dyscrasias, and immunological disorders (complete blood counts, peripheral smear, erythrocyte sedimentation rate, chest X-ray, Mantoux, serum calcium and angiotensin-converting enzyme levels, venereal disease research laboratory, and blood sugar). The presence of tuberculin sensitivity (Mantoux test) alone was not considered diagnostic of tuberculosis in the absence of any systemic foci of disease. Eyes with retinal

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Manuscript received: 10.09.17; Revision accepted: 12.12.17

Cite this article as: Goel N, Kumar V, Arora S, Jain P, Ghosh B. Spectral domain optical coherence tomography evaluation of macular changes in Eales disease. Indian J Ophthalmol 2018;66:433-8.

detachment or dense vitreous hemorrhage were excluded from the study.

Detailed demographic data including age, gender, and laterality were noted. All patients underwent complete ophthalmological examination including measurement of best-corrected Snellen visual acuity (BCVA) and slit-lamp examination including biomicroscopy and indirect ophthalmoscopy. Patients with vascular sheathing, perivenous exudates, and superficial retinal hemorrhages were classified as active vasculitis, while those with sclerosed vessels were labeled as healed vasculitis.

FFA was performed in all patients using VISUPAC and FF450^{plus}, Carl Zeiss Meditec, Inc., Dublin, California, USA. The presence of capillary nonperfusion, collaterals, NV, and the status of the macula was recorded. The macula was assessed with SD-OCT (Optovue, Inc., Fremont, CA, USA). Quantitative evaluation was carried out by measuring the macular thickness in the central 1 mm subfield of macular thickness cube (6 mm × 6 mm), and this was denoted as the central macular thickness (CMT). Qualitative evaluation of the macular anatomy was studied using the six radial line scans, each 6 mm long, oriented at intervals of 30° and centered on the patient's fixation point.

Outcome measures included SD-OCT features of the macula in patients with Eales disease including quantitative (CMT) and qualitative analysis. Macular involvement was defined as an increase in the CMT compared to age- and sex-matched controls and/or any abnormality on qualitative analysis.

Statistical analysis was performed using Statistical Package for the Social Sciences Software version 10.1.0 (SPSS Inc., Chicago, Illinois, USA). The data are presented as a mean ± standard deviation. Quantitative variables were compared between eyes with and without macular involvement using the nonparametric Mann–Whitney test. $P < 0.05$ was considered statistically significant.

Results

This study enrolled 79 eyes of 66 consecutive patients, 62 males (93.9%) and 4 females (6.1%), diagnosed with Eales disease. All patients were of Indian origin. The ages of the patients ranged from 16 to 54 years, with a mean of 27.97 ± 8.98 years. Forty-one patients had bilateral involvement (62%), while 25 patients had evidence of unilateral disease (38%). Out of 132 eyes, 53 eyes were excluded from the study. The various causes for exclusion included 25 normal eyes (without any evidence of Eales disease), 19 eyes with dense vitreous hemorrhage, 7 eyes with retinal detachment (rhegmatogenous and tractional), and 2 eyes that had undergone laser photocoagulation. Thus, a total of 79 eyes with Eales disease qualified for the study. Forty-six eyes (58.2%) had macular involvement, while 33 eyes (41.8%) had no macular involvement.

Table 1 depicts the various abnormalities seen on qualitative analysis of the SD-OCT scans in patients with macular involvement. Macular edema was the most common feature followed by epiretinal membrane (ERM) and macular thinning. Mean CMT was higher (315.3 ± 102.3 μm) in eyes with macular involvement than those without it (243.8 ± 19.3 μm) which corroborated well with macular edema being the most common finding on qualitative analysis.

Mean BCVA of the study eyes was 0.63 (0.17) ± 0.38. Eyes with affected macula had a lower mean BCVA (0.42 [0.39] ± 0.34) than eyes without it (0.78 [0.09] ± 0.31), and this difference was statistically significant ($P = 0.00001$). Among eyes with macular involvement, the eyes with premacular hemorrhage had the poorest mean BCVA (0.016 [1.79]), followed by eyes with macular edema and serous retinal detachment (SRD) (0.11 [0.954]) and macular hole (0.1 [1]). When compared among eyes with involved macula, eyes with serous detachment had poorer visual acuity than eyes without serous detachment ($P = 0.002$, unpaired t-test).

SLB was performed in all eyes to assess the macular status as well. In eyes with affected macula, 13 eyes (28.3%) were noted to have a normal macula based on SLB while the remaining were labeled as having macular involvement. All 33 eyes without macular involvement were found to have a normal macula on SLB.

On indirect ophthalmoscopy and FFA, 41 out of 79 (51.9%) eyes had evidence of active vasculitis, while 38 (48.1%) had signs of healed vasculitis. Twenty-eight eyes of those with active vasculitis had macular involvement (68.3%), while 13 had no macular involvement (31.7%). Among the eyes with healed vasculitis, 18 had macular involvement (47.5%) and 20 had no macular involvement (52.5%).

FFA was performed in all patients, and in addition to the presence of NV, the macular status was studied in detail. In eyes with macular involvement, 50% of the eyes showed no macular abnormalities on FFA. The remaining half demonstrated vascular leakage at the macula in ten eyes, blocked fluorescence corresponding to hemorrhage in 9 eyes, CME in 2 eyes, and nonperfusion in 2 eyes. In eyes without macular involvement, all eyes had a normal macula on FFA.

As per the classification of Eales disease given by Saxena *et al.*,[4] all eyes were distributed in the various stages [Fig. 1]. In eyes with macular involvement, a maximum number of eyes belonged to Stage 1B and 2B, while in eyes without macular involvement, Stage 1A and healed disease were the most common. None of the eyes without macular involvement could be categorized as Stage 1B.

The patients with active vasculitis were treated with local or systemic steroids and those with NV underwent sectoral laser

Table 1: Details of macular involvement on spectral domain optical coherence tomography

Feature on SD-OCT	Number of eyes (%)
Macular edema	19 (24)
Macular edema with neurosensory detachment	9 (11.4)
Epiretinal membrane	9 (11.4)
Macular thinning	9 (11.4)
Hard exudates	5 (6.3)
Hemorrhages	4 (5)
Inner retinal or inner limiting membrane folds	3 (3.8)
Premacular hemorrhages	2 (2.5)
Macular hole	1 (1.2)

SD-OCT: Spectral domain optical coherence tomography

photocoagulation. The patients with healed vasculitis without any signs of NV were advised regular follow-up.

Discussion

Eales disease occurs as an idiopathic condition in young healthy males, which maybe bilateral in 50%–90% of cases.[1,2] The etiopathogenesis is not well understood, but it is presumed to be an immunological reaction triggered by the exposure of an exogenous agent.[8,9] The clinical manifestations are due to three pathologic changes – inflammation (manifesting as peripheral retinal perivasculitis), ischemia (evidenced as peripheral retinal capillary nonperfusion), and neovascularization of the disc and/or retina, which may lead to vitreous hemorrhage.[2] Our study demonstrated a strong male preponderance, clustering of cases in the third and fourth decades of life, and propensity for bilaterality. This is accordance with previous reports.[1,2]

Characteristically, the vision in patients with Eales disease is affected by recurrent vitreous hemorrhage and its sequelae.[1,2] The macula is usually not involved primarily despite extensive peripheral nonperfusion; this preserves the central vision.[2,10] Data on macular involvement in Eales disease are scant. A retrospective study on patients with Eales disease presenting between 1989 and 1997 found that one or more macular lesions were found in 28.1% of eyes. SLB and FFA were used to assess the macular status in this study.[5] The same authors reported macular involvement in 32% of eyes with Eales disease in a retrospective analysis undertaken to evaluate the visual outcome in Eales disease.[4] The method of macular assessment was not elaborated and is presumed to be clinical examination alone. More recently, a retrospective analysis of retinal vasculitis in Eastern India from 2007 to 2009 found macular abnormalities in 35.4% of eyes using SLB.[6] However, they included all types of retinal vasculitis and not just Eales disease. To the best of our knowledge, this is the first prospective study undertaken to ascertain macular involvement in Eales disease using SD-OCT.

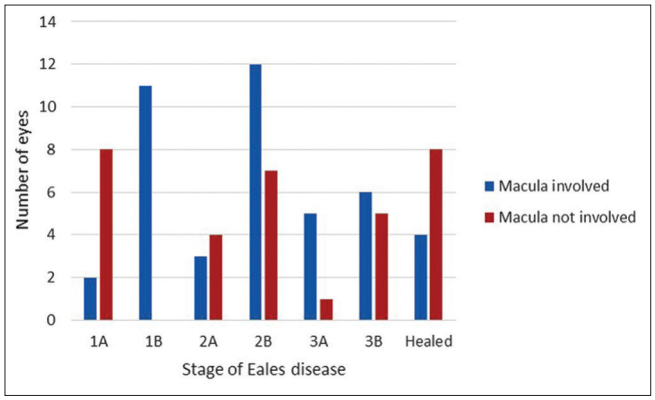

Figure 1: Distribution of eyes with and without macular involvement according to the stage of Eales disease given by Saxena *et al*.:[4] Stage 1 – periphlebitis of small (1A) and large (1B) caliber vessels, Stage 2A – capillary nonperfusion, 2B – neovascularization elsewhere/of the disc, Stage 3A – fibrovascular proliferation, 3B – vitreous hemorrhage

OCT is a cross-sectional imaging modality that allows evaluation of the macula in a manner that maybe unrecognizable by SLB and FFA. In addition to quantitative analysis of retinal thickness, it provides important qualitative information with regard to the vitreomacular interface and intraretinal abnormalities.[7] SD-OCT better delineates structural changes and fine lesions in the retinal layers as compared to time-domain OCT, owing to advances in signal detection technique. It has improved retinal coverage by the scan protocols (6 mm × 6 mm), high-speed scanning ability, and increased resolution of scans.[11] As a result of the greater precision of SD-OCT in detection of macular abnormalities, our study found macular involvement in 58.2% of eyes with Eales disease. This is much higher than the previous rates of 28.1%–35.4% reported in studies that did not use OCT.[4-6] In addition, our study demonstrated that, of the eyes having macular involvement on SD-OCT, 28.3% were observed to have a normal macula on SLB and 50% were interpreted as having no macular abnormalities on FFA [Fig. 2a-h]. None of the eyes with a normal SD-OCT displayed abnormalities on FFA. These observations confirm the utility of SD-OCT for assessing the macular status in Eales disease.

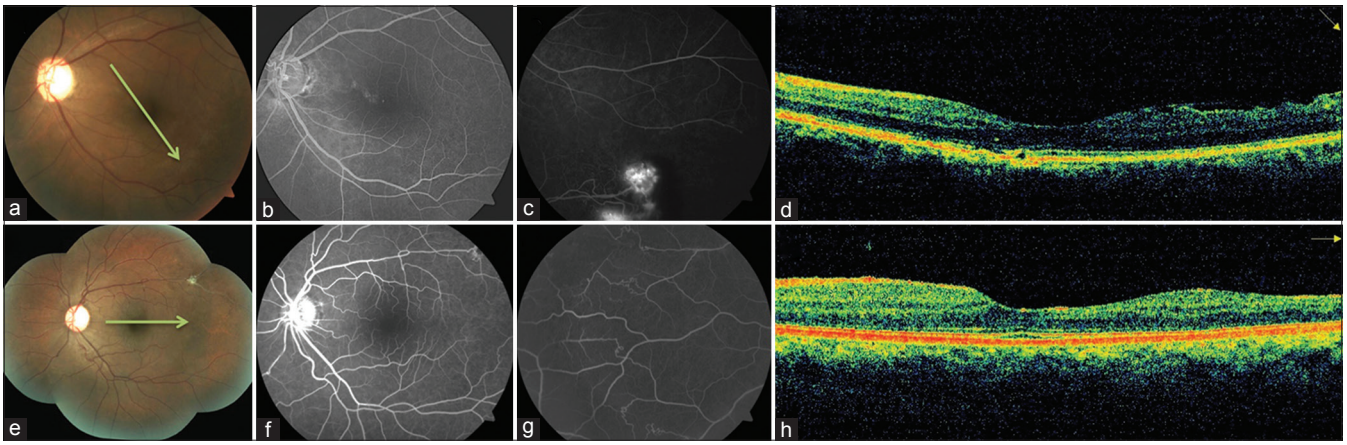

Figure 2: (a) Fundus photograph and (b and c) fluorescein angiogram of a 28 years male with Eales disease Stage 3B and best-corrected visual acuity 0.67 showing peripheral neovascularization, capillary nonperfusion, and a normal macula (d) spectral domain optical coherence tomography revealed epiretinal membrane inferiorly, in addition (e) fundus photograph and (f and g) fluorescein angiogram of a 30-year-old male with best-corrected visual acuity 0.05 showing superotemporal healed vasculitis, peripheral collaterals, and a normal macula (h) spectral domain optical coherence tomography showed temporal macular thinning not visible clinically or on fluorescein angiogram

SD-OCT quantifies macular thickness in an automated and reproducible manner. In patients with Eales disease and macular involvement, the CMT was found to be significantly higher than those without macular involvement. Macular edema was the most common feature among those with involvement of the macula and this may be accompanied by SRD [Fig. 3a-f]. This was followed by ERM [Fig. 3g-j] and macular thinning [Fig. 4a-d and Table 1]. Other studies utilizing FFA[5] or SLB[4,6] have also found macular edema to be the most common macular abnormality in Eales disease. However, they described ERM to be less common than observed in our study and did not report macular thinning as a feature of Eales disease, as they did not use OCT in macular evaluation. Histopathological features of ERM in 18 patients with Eales disease, of which 13 involved the macula, have been elaborated; however, preoperative or postoperative OCT was not carried out in them.[12] Vitreopapillary and vitreomacular traction has been described on SD-OCT in a single case of proliferative Eales disease.[13]

Macular involvement led to a significantly poorer BCVA in patients with Eales disease. This suggests that macular changes in Eales disease are visually significant and must be looked for actively. Two patients had a premacular hemorrhage and presented with profound visual loss. This feature has been reported very rarely in Eales disease.[14,15] Fig. 5 illustrates the fundus photograph of one of those two patients showing a premacular hemorrhage centered at the macula, around 2 disc

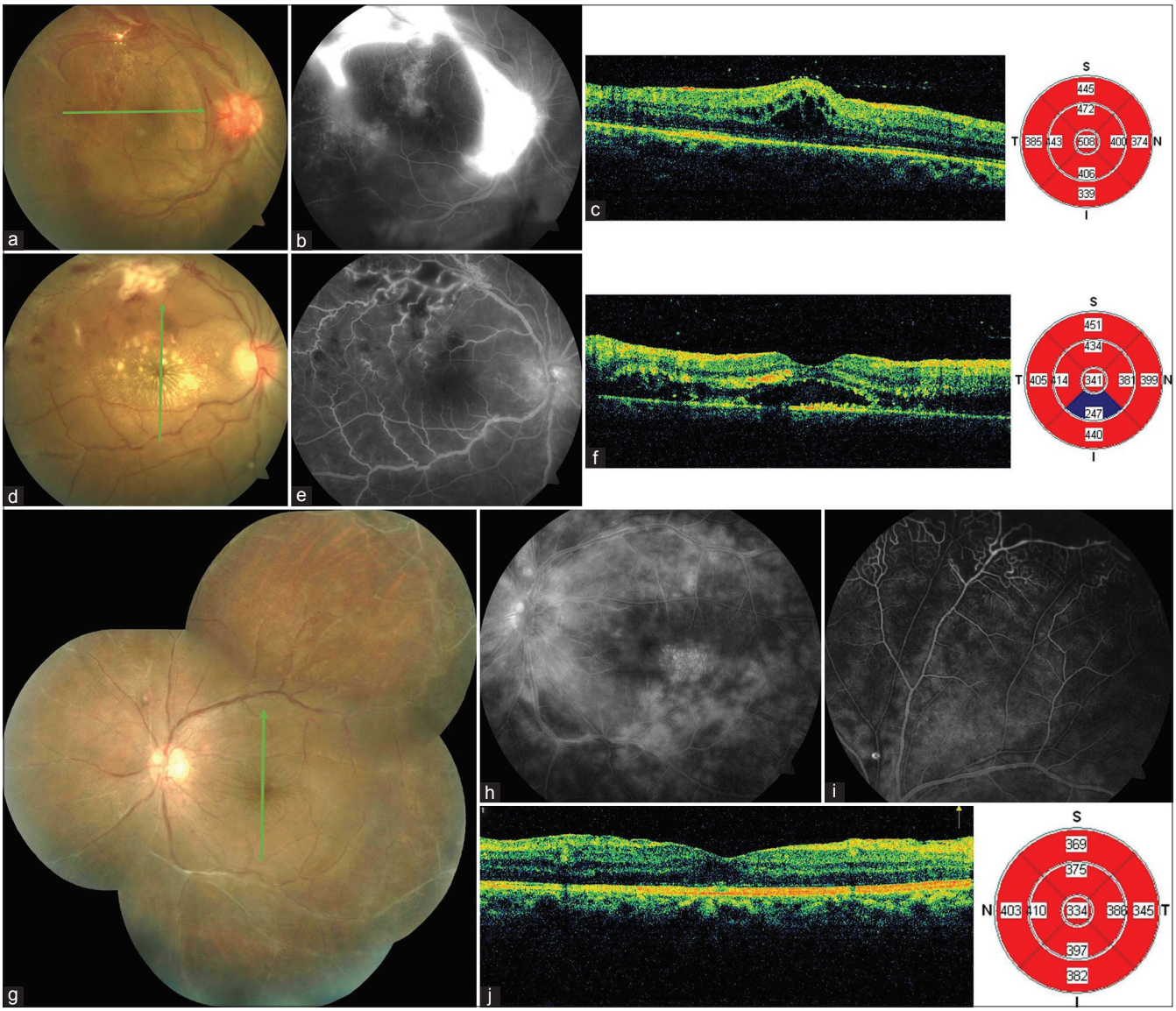

Figure 3: (a) Fundus photograph and (b) fluorescein angiogram of a 22-year-old male with Eales disease Stage 3A and best-corrected visual acuity 0.1 showing fibrovascular proliferation at the disc (c) spectral domain optical coherence tomography showed cystoid macular edema (d) fundus photograph and (e) fluorescein angiogram of a 25-year-old male with best-corrected visual acuity 0.05 showing superotemporal periphlebitis and macular hard exudates (Eales disease Stage 1B) (f) spectral domain optical coherence tomography showed macular edema and subfoveal neurosensory detachment (g) fundus photograph of a 30-year-old male showing active vasculitis in all quadrants (Eales disease Stage 2B). Best-corrected visual acuity was 0.167. Fluorescein angiogram showed diffuse vascular leakage (h), and superior collaterals (i), (j) spectral domain optical coherence tomography showed epiretinal membrane and macular edema

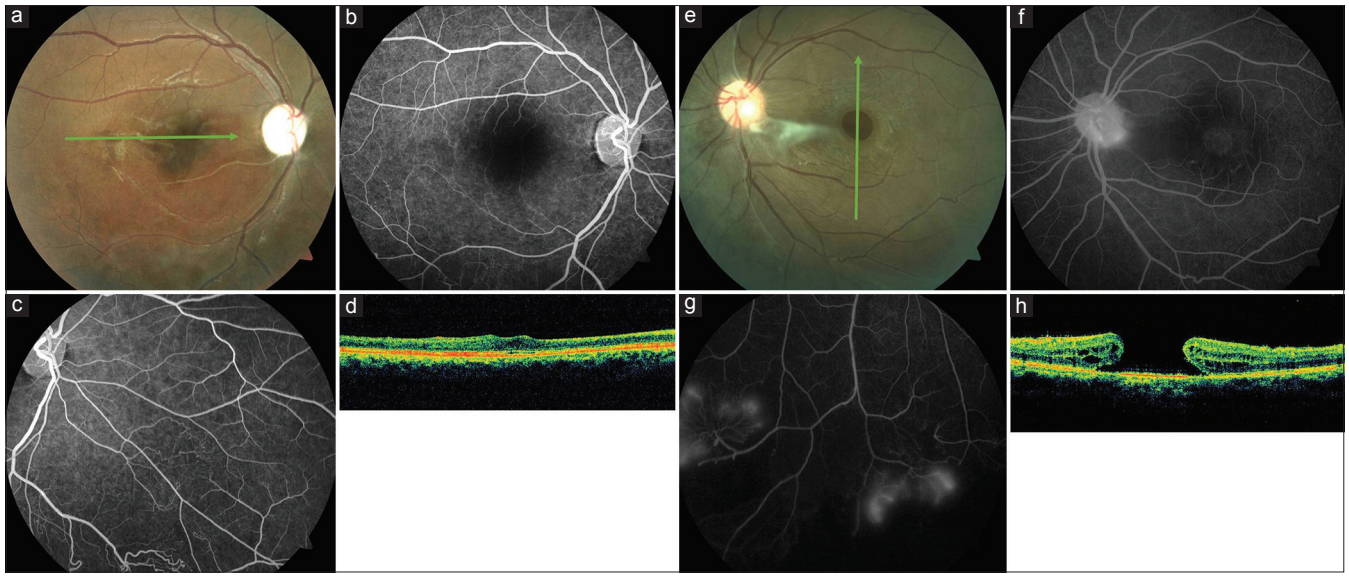

Figure 4: (a) Fundus photograph of a 17-year-old male showing an inferior sclerosed vessel with an altered foveal reflex. Best-corrected visual acuity was 0.67. Fluorescein angiogram showed inferior macular nonperfusion (b) with inferonasal collaterals (c). This was Stage 2A of Eales disease (d) spectral domain optical coherence tomography demonstrated gross macular thinning. (e) Fundus photograph of a 37-year-old male with Eales disease Stage 2B and best-corrected visual acuity 0.1 showing fibrous proliferation at the disc and a macular hole. Fluorescein angiogram showed staining at the disc and window defects corresponding to the macular hole (f) with neovascularization inferiorly (g), (h) spectral domain optical coherence tomography confirmed a full-thickness macular hole

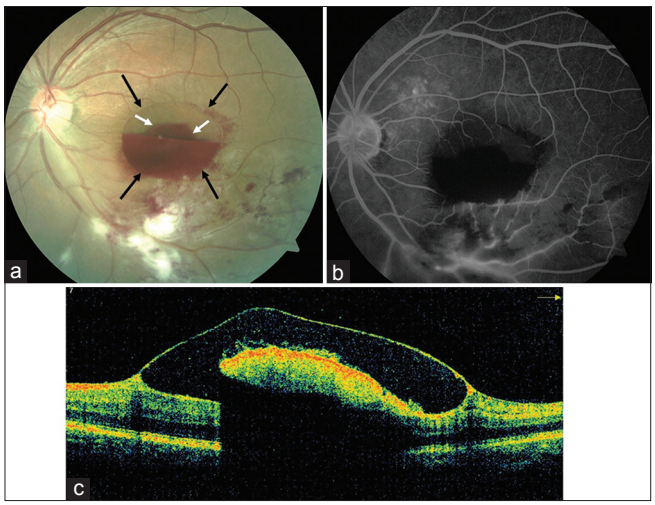

Figure 5: A 39-year-old male presented with sudden loss of vision in his left eye for 2 days. Best-corrected visual acuity was 0.016. (a) Fundus showed a premacular hemorrhage giving the appearance of a "double ring" (outer black and inner white arrows) with periphlebitis of the inferotemporal vein. (b) Fluorescein angiogram showed blocked fluorescence in the area of the hemorrhage with inferior active vasculitis. (c) Spectral domain optical coherence tomography demonstrated that the outer ring was that of a subinternal limiting membrane hemorrhage and the inner ring was composed of hyperreflective deposits below the internal limiting membrane causing shadowing of the remaining retinal layers

diameters in size, surrounded by glistening striae, giving the clinical appearance of a "double ring." A SD-OCT scan revealed that the outer ring (black arrows) was that of a subinternal limiting membrane (ILM) hemorrhage, while the inner ring (white arrows) was formed by hyperreflective deposits below the ILM that caused shadowing of the underlying retinal layers.

The macular "double ring sign" has been described in Terson's syndrome,[16] Valsalva retinopathy,[17] and anemia.[18] This is the first report of the entity in Eales disease. Another rare finding in Eales disease is a full-thickness macular hole which was observed in a single patient and also led to severe impairment of visual acuity [Fig. 4e-h].

SRD in association with macular edema was picked up in 11.4% of patients with macular involvement and was found to account for poorer BCVA in this study. SRD is a feature readily and exclusively detected by OCT and has been observed in 15%–20% of uveitis patients with macular edema.[19] A variety of mechanisms have been postulated to underlie its pathogenesis including hemodynamic overload from loss of integrity of the blood–retinal barrier associated with decreased function of the retinal pigment epithelium pump.[20] There is conflicting literature pertaining to the correlation between the presence of SRD and decreased visual acuity.[19,20]

Saxena *et al*. have classified Eales disease based on ophthalmoscopic and fluorescein angiographic variables and shown that patients presenting with an earlier stage of the disease would have a better final visual outcome after treatment.[4] However, they did not study macular abnormalities according to the stage. Our study is the first report of evaluation of macular involvement according to the stage of Eales disease. We found that, in patients with active vasculitis, a greater number of eyes (68.3%) showed macular involvement as compared to those with healed vasculitis (47.5%). Overall, a maximum number of eyes belonged to Stage 2B (24%), that is, neovascularization of the disc and/or elsewhere. In eyes with macular involvement, Stage 2B and 1B (periphlebitis of large caliber vessels) were the most common, while in eyes without macular involvement, Stage 1A (periphlebitis of small caliber vessels) and healed disease were the most common. Thus, macular involvement was more common when the posterior,

larger vessels were involved in the inflammatory process and in the stage of neovascularization. Previous studies have hypothesized that the macula is involved more commonly in the advanced stage of the disease; however, they have not divided the eyes with macular abnormalities according to stage to confirm this.[4,21]

Conclusion

Our observations are contrary to the clinical description of peripheral location of the disease in Eales disease and show that macular involvement is common, especially in eyes with active vasculitis, central disease, and neovascularization. SD-OCT is an indispensable ancillary test in the evaluation of the macula and picks up subtle changes that can be missed on SLB and/or FFA. Macular edema is the most common macular abnormality in Eales disease, followed by ERM and macular thinning. Presence of SRD in addition to macular edema is associated with a poorer visual acuity. Since the involvement of the macula leads to a decreased visual acuity, it must be actively looked for, and SD-OCT of the macula is recommended in all patients with Eales 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.

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