Purpose: (1) The purpose of this study was to describe significance and prevalence of the newly reported pearl necklace spectral domain optical coherence tomography (SDOCT) sign, in diabetic macular edema (DMO), (2) to track the course of this sign over a period of at least 10 months. Materials and Methods: The pearl necklace SDOCT sign refers to hyperreflective dots in a contiguous ring around the inner wall of cystoid spaces in the retina, recently described for the first time in 21 eyes with chronic exudative maculopathy. A retrospective analysis was performed of SDOCT images of all patients presenting to the DMO referral clinic of a tertiary eye care center, over a period of 24 months. Images of patients displaying this sign were sequentially analyzed for at least 10 months to track the course of the sign. Results: Thirty-five eyes of 267 patients (13.1%) were found to display the pearl necklace sign. Twenty-eight eyes responded to intravitreal ranibizumab treatment with resolution of edema. In 21 eyes, the dots coalesced to form a clump, visible in the infrared fundus photograph as hard exudates; in seven eyes, dots disappeared without leaving visible exudates. In three eyes, the sign was seen in subfoveal cystoid spaces, with subsequent development of hard exudates, and drop in visual acuity of 20 letters or more. Conclusion: Pearl necklace SDOCT sign is not infrequent in DMO. This sign is a precursor to hard exudates in the majority of cases. If this sign is seen subfoveally, drop in visual acuity can be expected, despite treatment.

Key words: Diabetic macular edema, hard exudates precursor, pearl necklace sign

Hyperreflective dots on macular optical coherence tomography (OCT) scan of eyes with diabetic macular edema (DMO) have been observed across all retinal layers and within the walls of intraretinal microaneurysms.[1,2] In existing literature, there has been a debate about the nature and origin of these dots. Some authors have attributed these dots to subthreshold hard exudates.[3-4]

Gelman et al.[3] reported a series of 21 eyes with chronic exudative maculopathy where these hyperreflective dots were arranged as a contiguous ring along the inner wall of cystoid spaces in the retina (pearl necklace sign). They speculated that this sign indicated the presence of lipoproteins or lipid-laden macrophages in patients with exudative maculopathy and chronic cystoid macular edema.[3]

We conducted this study to estimate the prevalence of this “pearl necklace” sign seen on spectral domain OCT (SDOCT) in eyes with DMO and study the evolution of this sign following intravitreal therapy with ranibizumab. This would help confirm or refute the speculation of these dots being subthreshold hard exudates and could throw light on the visual prognosis in such eyes.

Materials and Methods

This study was conducted at a tertiary eye care center, catering to a population of approximately a million. All patients on the diabetes mellitus register held at general practices in the catchment population were screened by a national diabetic eye screening program, and all patients with referable diabetic retinopathy (DR) were seen in dedicated DR clinics. In these clinics, all patients underwent a comprehensive ophthalmic examination, including visual acuity evaluation, slit-lamp examination, and dilated fundus examination, along with SDOCT imaging and infrared fundus photography, and those patients who met the NICE guidelines for intravitreal treatment with ranibizumab were referred to a dedicated DMO clinic. All patients received intravitreal treatment in a “one-stop” setting as per the treatment protocol.

We retrospectively reviewed SDOCT images of all eyes that were initiated on intravitreal ranibizumab treatment for DMO with central subfield thickness (CST) more than 400 µ, as per NICE guidelines,[6,7] between April 2013 and March 2015. Each OCT was carefully observed for the presence of hyperreflective dots in a contiguous ring around the inner wall of cystoid spaces (“pearl necklace” sign); the location of these cystoid spaces was noted for each case. Images of patients displaying this sign were singled out and these were sequentially followed up for a minimum of 10 months to track the course of this sign. SDOCT images were acquired at every clinic visit as part of the established standard of care.

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Cite this article as: Ajay K, Mason F, Gonglore B, Bhatnagar A. Pearl necklace sign in diabetic macular edema: Evaluation and significance. Indian J Ophthalmol 2016;64:829-34.
using the macula protocol for Heidelberg SDOCT (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). OCTs were performed with volume scans with at least 19 single sections. On each follow-up, same sections were performed to allow matching sections for evaluation. The OCT images of patients included for the study were matched with the infrared fundus photograph of the corresponding location. Clinical charts were retrospectively reviewed and patient characteristics of age, gender, Electronic Early Treatment for Diabetic Retinopathy Study visual acuity and response to treatment, were recorded and correlated with SDOCT imaging findings.

Results

Totally, 267 patients (age 24–91 years, 64 ± 14.8 years) were seen and initiated on intravitreal ranibizumab therapy in the DMO clinic between April 2013 and March 2015. All eyes were treatment naïve. 35 eyes of 35 patients (23 males, 12 females) were found to display the pearl necklace sign, giving a prevalence of 13.1% in our cohort of patients [Table 1]. This sign was seen in cystoid spaces located in the outer nuclear/outer plexiform layer of the retina in 30 eyes [Fig. 1] and lining the inner wall of a neurosensory detachment in 5 eyes [Fig. 2]. The follow-up period ranged between 10 and 24 months (16 ± 4 months).

In the 35 eyes showing the pearl necklace sign, the mean best-corrected visual acuity (BCVA) letter score at the start of treatment was 46.7 ± 12.9 letters; at the final follow-up, the mean BCVA was 53.5 ± 14.1 letters. Of the 35 eyes, 15 (42.8%) improved by 10 letters or more; 3 eyes lost 10 or more letters over the follow-up period. The mean CST was 524 ± 82 µ at baseline and 365 ± 62.3 µ at final follow-up.

Table 1: Details of patients displaying pearl necklace sign

| Serial number | Age (years) | Sex | Affected eye | Date pearl necklace first seen | Course of pearl necklace sign |
|---------------|-------------|-----|--------------|--------------------------------|------------------------------|
| 1             | 57          | Male| Left         | October 31, 2014               | Disappears; absent at 3-month follow-up |
| 2             | 56          | Male| Left         | April 15, 2013                 | Clumps; coalescence at 6-month follow-up |
| 3             | 91          | Male| Right        | March 06, 2015                 | Disappears                   |
| 4             | 54          | Male| Left         | December 12, 2014              | Retinal detachment at 2-month follow-up. No pearl necklace seen at 6-month follow-up |
| 5             | 83          | Male| Left         | January 03, 2014               | Clumps at 3-month follow-up   |
| 6             | 67          | Male| Right        | December 02, 2014              | Clump seen at 3-month and 6-month follow-up |
| 7             | 58          | Male| Left         | December 03, 2014              | Persists                     |
| 8             | 62          | Male| Left         | February 06, 2013              | Clumps; small residual clump seen |
| 9             | 56          | Male| Left         | April 02, 2013                 | Clumps; coalescence at 5-month follow-up |
| 10            | 85          | Male| Right        | May 23, 2014                   | Clumps; coalescence at 5th month follow-up |
| 11            | 70          | Male| Left         | February 20, 2015              | Clumps; coalescence at 3rd month follow-up |
| 12            | 75          | Female| Right     | October 24, 2014               | Clumps in 6 months           |
| 13            | 73          | Female| Right     | April 16, 2013                 | Persists                     |
| 14            | 81          | Female| Right     | September 22, 2014             | Disappears; absent at 6-month follow-up |
| 15            | 43          | Male| Right        | March 19, 2014                 | Persists                     |
| 16            | 53          | Male| Right        | September 21, 2013             | Clumps; at 11-month follow-up |
| 17            | 56          | Male| Right        | October 22, 2014               | Clumps in 6 months           |
| 18            | 61          | Female| Left       | January 17, 2014               | Clumps; at 6 months          |
| 19            | 68          | Male| Left         | December 05, 2014              | Disappears; absent at 4-month follow-up |
| 20            | 67          | Female| Left       | May 02, 2013                   | Clumps in 6 months           |
| 21            | 52          | Female| Right     | July 30, 2013                  | Persists                     |
| 22            | 62          | Female| Right     | January 07, 2015               | Clumps; by 4 months          |
| 23            | 62          | Male| Right        | November 14, 2014              | Clumps; by 4 months          |
| 24            | 68          | Male| Left         | December 03, 2014              | Clumps; seen within 15 days   |
| 25            | 51          | Female| Right     | January 13, 2015               | Disappears                   |
| 26            | 24          | Female| Right     | December 31, 2014              | Persists                     |
| 27            | 85          | Male| Left         | September 17, 2014             | Clumps in 6 months           |
| 28            | 77          | Male| Right        | July 16, 2014                  | Clumps by 6 months           |
| 29            | 49          | Male| Right        | May 31, 2013                   | Clumps by 4 months           |
| 30            | 63          | Female| Right     | June 13, 2014                  | Persists; retinal detachment present |
| 31            | 75          | Male| Right        | March 20, 2015                 | Clumps; coalescence in 3 months |
| 32            | 71          | Female| Left       | March 07, 2014                 | Clumps; coalesce in 4 months  |
| 33            | 74          | Female| Right     | November 11, 2014              | Persists                     |
| 34            | 30          | Male| Right        | February 25, 2015              | Clumps; coalescence in 2 months |
| 35            | 81          | Male| Left         | January 30, 2015               | Disappears; no necklace seen at 5th month follow-up |
Figure 1: Pearl necklace sign in outer plexiform layer

Figure 2: The sign in subretinal space

Figure 3: (a) Optical coherence tomography of the eye in Fig. 1 at month 3; fluid resolved and hard exudate clump at exactly the same spot. (b) Color fundus photograph of the eye in Fig. 3a; clinically visible hard exudate in the area of pearl necklace
Qualitative assessment of the pearl necklace sign over the follow-up period showed that of the 35 eyes, 28 showed a significant reduction in macular edema, and in 21 eyes the hyperreflective dots forming the pearl necklace coalesced to form a clump. This appeared as a visible clump of hard exudates in infrared fundus photographs [Fig. 3a], which were also visible clinically [Fig. 3b]. The location of these hard exudate clumps was closely associated with the location of the intraretinal/subretinal cysts seen on OCT [Fig. 4a–c] and correlated with the color fundus photograph [Fig. 5a–c]. In seven eyes, as the edema resolved, the pearl necklace sign disappeared completely, without leaving visible hard exudates. Macular edema and the pearl necklace sign persisted, despite treatment in seven eyes.

In three eyes, the pearl necklace sign was seen in cystoid spaces located subfoveally [Fig. 6a]. With intravitreal therapy, although there was resolution of macular edema, large clumps of hard exudates appeared subfoveally [Fig. 6b]. This was associated with a drop in the vision of 20 letters or more in these three eyes.

Discussion

Multiple studies published previously have described “hyperreflective foci” (HF), detectable by SDOCT techniques, in various retinal pathologies, including exudative age-related macular degeneration and retinal vein occlusion. In age-related macular degeneration, it has been reported that after a loading dose of three intravitreal ranibizumab injections, the number of HFs reduced; the number of such HF at baseline was suggested as a predictive factor for the outcome of treatment.

The presence of similar HF on SDOCT, across all retinal layers, has also been reported in DMO. Gelman et al. described a novel “pearl necklace sign” of the contiguous ring of hyperreflective dots along the inner wall of cystoid spaces in the retina in 21 eyes with exudative macular diseases. Five of these eyes had DMO.

We found that this sign is not uncommon in DMO and was seen in 13.1% eyes in our series of patients. 75% of eyes where the DMO resolved with treatment developed clinically visible hard exudates in exactly the same location as the pearl necklace sign. This confirms the previously held belief that intraretinal HF represent precursors of hard exudates. The characteristic arrangement along the wall of the cystoid spaces may indicate a relatively large amount of lipoproteins/lipid-laden macrophages that tend to precipitate and leave behind clinically observable hard exudates once the edema resolves following intravitreal therapy.

We did not find that the presence of this either predicts or adversely affects the outcome of treatment. Our results of a mean letter gain of 6.8 letters with 42.8% eyes improving by 10 letters or more and mean reduction in CST of 159 µ are comparable to those achieved in RESTORE and DRCRnet studies.

Figure 4: (a) Intraretinal pearl necklace extrafoveally. (b) Four injections later showing partial resolution of edema and HE in the same location as a pearl necklace. (c) 12 months and 10 injections later; HE++
Figure 5: (a) Pearl necklace sign before treatment. (b) Optical coherence tomography scan at month 3 posttreatment showing HE. (c) Color fundus photograph of the eye in Fig. 5b showing new clump of HE in the location of pearl necklace.

Figure 6: (a) Subfoveal pearl necklace sign. (b) Three injections later HE++ subfoveally.
However, of note is the fact that three eyes that had a dramatic loss of vision (20 letters or more) had subfoveal “pearl necklace sign” and a large clump of hard exudates appeared subfoveally as the edema resolved in these three eyes. We infer that the presence of this sign in a subfoveal location may result in accumulation of this particulate entity subfoveally (clinically visible hard exudates), causing irreversible damage to photoreceptors in that area, thereby limiting the long-term visual outcome.

**Conclusions**

Hyperreflective dots arranged as a contiguous ring along the inner wall of cystoid spaces on the macular OCT scan, termed as the pearl necklace sign, are commonly seen in DMO patients who require intravitreal treatment. With a resolution of edema, hard exudates frequently appear in the same location on the retina, implying that the pearl necklace sign is a precursor to hard exudates, in the majority of cases. The presence of this sign does not affect visual prognosis or the response to intravitreal treatment, except where this sign is located subfoveally.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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