

Reticular drusen in a Chinese population

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Abstract

Aims: To determine the association of reticular drusen with macular diseases in a Hong Kong Chinese population.

Methods: This was a cross-sectional study of patients with reticular drusen recruited from 1 January 2013 to 30 June 2013. Optical coherence tomography was performed in all patients to confirm the presence of subretinal drusenoid deposits. Near-infrared photography, red-free photography, fundus fluorescein angiography, indocyanine green angiography, and fundus autofluorescence were performed on selected patients. Diagnosis of reticular drusen was made by an experienced retinal specialist, after which data were collected and analyzed.

Results: A total of 105 patients were identified and included for analysis. The mean age was 73.8 (standard deviation, 3.7) years. Overall, 21.9% of the patients were found to have non-exudative age-related macular degeneration, 17.1% had exudative age-related macular degeneration, and 3.8% had polypoidal choroidal vasculopathy. No other macular pathology apart from reticular drusen was detected in the remaining 57.1%.

Conclusions: The spectrum of macular diseases associated with reticular drusen was noted to differ between Chinese and other ethnic groups, with a lower proportion of patients with wet age-related macular

degeneration in the Chinese population. Despite a higher prevalence of polypoidal choroidal vasculopathy in the Chinese population, the proportion of polypoidal choroidal vasculopathy in the current cohort was still low, possibly due to different layers being involved in pathogenesis.

Key words: Genetic predisposition to disease; Macular degeneration; Retinal drusen; Retinal pigment epithelium

Introduction

Reticular drusen were first described in 1990 by Mimoun et al¹ as “les pseudo-drusen visibles en lumière bleue”, translated as “pseudo-drusen that is better visualized with blue light”. Reticular drusen are yellowish lesions resembling drusen that are arranged in a network and therefore termed ‘reticular’.^{2,3} It is more prevalent in females and its incidence increases with age.^{3,4} In addition to funduscopy, reticular drusen can be seen on near-infrared (IR) photographs taken with a scanning laser ophthalmoscope. Bindewald et al⁵ described reticular drusen as one of the recognized abnormal autofluorescence patterns in early age-related macular degeneration (AMD). Under fundus autofluorescence (FAF), reticular drusen show up as regions with reduced autofluorescence and brighter lines in-between. In contrast, these lesions cannot be detected (neither hyperfluorescent nor hypofluorescent) with the more commonly used fundus fluorescein angiography (FFA). Reticular drusen, however,

are hypofluorescent on indocyanine green angiography (ICG).⁶ In addition to the central macula, reticular drusen are typically found in the superotemporal quadrant.^{3,5}

Reticular drusen, also known as ‘pseudo-drusen’, can also be visualized with fundus biomicroscopy. They were not identified prior to the development of optical coherence tomography (OCT). Arnold et al⁷ attempted but were unable to locate these clinically observed ‘drusen-like lesions’ in the choroidal layer of their histological specimens. Since they could only correlate the presence of reticular drusen with significant choroidal thinning, they concluded that ‘pseudo-drusen’ (i.e. reticular drusen) were indeed a kind of choroidal ischemia and fibrosis. Interestingly, Arnold et al’s histological specimens did not include the neurosensory retina, thus the location of the pathologies in relation to the different retinal and subretinal layers could not be identified.⁷ The nature of reticular drusen was made less mysterious by the work of Rudolf et al⁸ and Zweifel et al.⁹ Rudolf et al⁸ described histological findings of subretinal drusenoid deposits in 3 eyes that shared characteristics of classical subretinal pigment epithelium (sub-RPE) soft drusen, but no clinical correlations were identified at that time. With the development of OCT, non-invasive, high-resolution imaging of the retinal and choroidal layers became easily available, and posterior segment pathologies could be identified and quantified with these cross-sectional scans.¹⁰⁻¹² Zweifel et al⁹ investigated patients with clinical reticular drusen using spectral domain OCT (sd-OCT). They compared these sd-OCT findings of reticular drusen with the findings from re-examination of a histological specimen previously reported by Rudolf et al.⁸ They concluded that reticular drusen are actually drusenoid deposits with many components of classical drusen found in AMD, and are located between the RPE and the photoreceptor inner segment/outer segment junction.⁹ The presence of reticular drusen has been proven by research teams worldwide to be a risk factor for late AMD, both in the diseased eye and in the fellow eye.^{3,9,12-18}

A number of studies have already demonstrated the association between reticular drusen and macular diseases in Caucasian patients.^{14,15,17,19} However, since the prevalence

and pattern of AMD in the Chinese population are very different to that of Caucasians, we attempted to evaluate the association of reticular drusen with AMD among the Chinese patients in Hong Kong.

Methods

This was a cross-sectional study that aimed to evaluate the correlation of the presence of reticular drusen with AMD in the local Chinese population in Hong Kong. Chinese patients referred to the retina clinic of the University of Hong Kong for AMD from 1 January 2013 to 30 June 2013 were screened for the presence of reticular drusen.

Reticular drusen were defined as multiple yellowish-white lesions in a reticular network pattern seen on fundus examination. In addition, these granular hyperreflective deposits are found between the RPE layer and the photoreceptor ellipsoid zone on sd-OCT scans (**Figure 1**). The OCT scans were obtained with the Heidelberg Spectralis HRA sd-OCT (Heidelberg Engineering, Heidelberg, Germany). Macular thickness protocol was used, and each section comprised up to 100 scans for the final averaged image to reduce image noise and improve image quality. Other imaging modalities including near-IR photography, color fundus photography (**Figure 2**), FAF (**Figure 3**), FFA, and ICG were performed where appropriate. Heidelberg software was used to view the scans and images where appropriate. In addition to fundal and sd-OCT findings, diagnosis was further supported by one or more of the following: (1) light lesions corresponding to subretinal yellowish lesions in a network pattern on red-free photography; (2) hypoautofluorescent lesions with brighter lines in-between on FAF images; (3) hyporeflectant lesions on a hyperreflectant background on near-IR photography; and (4) hypofluorescent lesions on mid- to late-phase of ICG.

Consecutive patients were examined by the same experienced retina specialist (I. Wong). Those who met the diagnostic criteria of reticular drusen stated above were recruited for analysis. Patients with macular conditions other

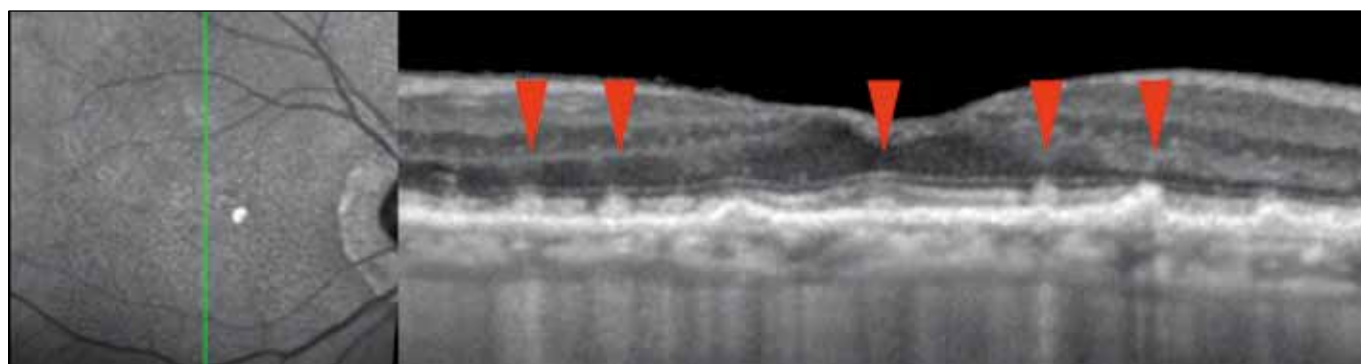


Figure 1. Optical coherence tomographic scans revealing subretinal hyperreflective reticular drusen above retinal pigment epithelium (arrows).



Figure 2. Color fundus photograph showing multiple yellowish reticular drusen arranged in a reticular network pattern; corresponding lesions are indicated (arrows).

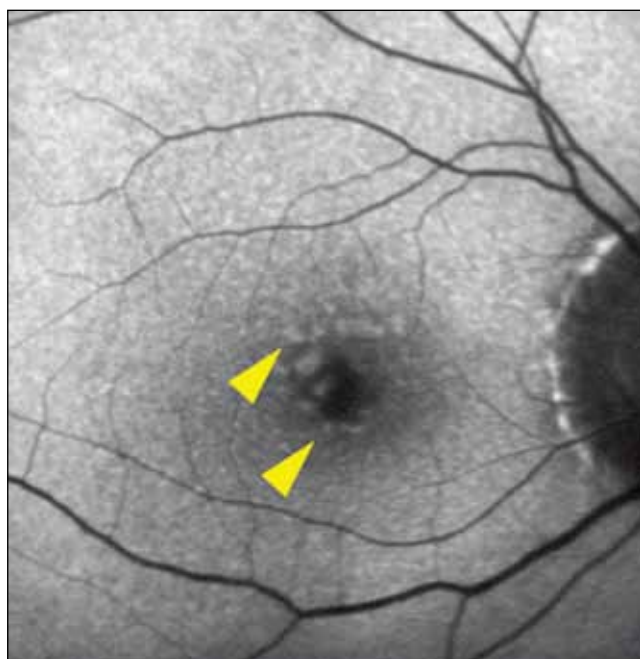


Figure 3. Fundus autofluorescence showing numerous hypofluorescent reticular drusen corresponding to regions of reticular drusen on color fundus photograph; corresponding lesions are indicated (arrows).

than AMD that would lead to atrophic macular changes, e.g. myopic maculopathy, were excluded. The macular diagnosis was made according to the findings of clinical examination and investigations. AMD was defined according to the International Classification and Grading System provided by

the International Age-related Maculopathy Epidemiological Study Group.²⁰ If AMD was present, patients were further classified as non-exudative AMD, exudative AMD, polypoidal choroidal vasculopathy (PCV), or retinal angiomatous proliferation (RAP), according to sd-OCT, FFA and ICG findings. The diagnosis was PCV when polyps with or without a branching vascular network were noted on ICG. In contrast, the diagnosis was RAP if retinal-retinal (R-R) anastomosis and/or retinal-choroidal (R-C) anastomosis was present. Cases with choroidal neovascularization (CNV)-like leakage on FFA without evidence of R-R or R-C anastomosis or polyps on ICG were regarded as AMD.

This study complied with the Declaration of Helsinki and had Institutional Review Board approval through the Hong Kong West Cluster Institutional Review Board.

Results

A total of 105 patients with reticular drusen were recruited. Bilateral reticular drusen were noted in 95 (90.5%) patients. Their mean (\pm standard deviation) age was 73.8 ± 3.7 years, with 27 males and 78 females (male-to-female [M:F] ratio = 1:2.9). Their mean logMAR visual acuity was 0.33 at presentation.

Of the 105 patients, AMD (all types) was noted in 45 (42.9%). In the remaining 60 patients (57.1%), no macular disease besides the presence of reticular drusen was identified. Non-exudative AMD type atrophic changes including geographic atrophy were identified in 23 (21.9%) of the 105 patients. Among our patients with presumed CNV, FFA, ICG and OCT were used to differentiate between exudative AMD, PCV and RAP. Of the patients, 18 (17.1%) were noted to have exudative AMD, and 4 (3.8%) PCV. None of our reticular drusen patients had RAP. Subgroup analysis of patients with and without AMD is shown in the **Table**.

Discussion

To our knowledge, there is no report on reticular drusen in a Chinese population in the literature. In this study, all patients were Chinese and the diagnosis of reticular drusen was made by clinical appearance, corresponding lesions on red-free photography and the appearance of subretinal hyperreflective deposits of the reticular drusen on sd-OCT scans (**Figure 1**).

In our patients with reticular drusen, the mean age was 73.8 years with a female predominance (M:F ratio of 1:2.9). These findings concur with other reports that old age and female gender are risk factors for the development of reticular drusen.^{3,15-17}

Most studies have shown that reticular drusen are bilateral only in 50% to 75% of patients^{2,9,21,22} — Cohen et al² reported bilaterality in 55.0% of their 100 French reticular drusen patients; Zweifel et al⁹ reported 75.8% bilaterality among their 33 American subjects; Smith et al²¹ detected bilaterality in 54.8% of the 42 American patients; and Ueda-

Table. Patient demographics and present VA with subgroup analysis*

	Overall (n = 105)	No macular disease otherwise (n = 60)	Non-exudative AMD (n = 23)	Exudative AMD (n = 18)	PCV (n = 4)
Age (years)	73.8 ± 3.7	72.2 ± 4.3	78.9 ± 5.2	74.2 ± 6.5	67.4 ± 2.9
Gender					
Male	27 (25.7)	11 (18.3)	3 (13.0)	11 (61.1)	2 (50.0)
Female	78 (74.3)	49 (81.7)	20 (87.0)	7 (38.9)	2 (50.0)
logMAR VA	0.33	0.17	0.66	0.85	0.52

Abbreviations: AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; VA = visual acuity.

* Data are shown as mean ± standard deviation, No. (%), or mean.

Arakawa et al²² diagnosed bilateral disease in 53.3% of their 216 Japanese patients. In contrast, a Korean study revealed 97.7% bilaterality in their patients with reticular drusen.²³ This is echoed by this study, in that 95 (90.5%) had bilateral drusen among our 105 patients. This high degree of bilaterality among Korean and Chinese compared with Caucasians cannot only be attributed to the ethnic closeness of these 2 Asian races compared with Caucasians, because only 53.3% of patients with bilateral reticular drusen were found in the Japanese population by Ueda-Arakawa et al.²² Since most identified risk factors of reticular drusen to date are systemic risk factors that do not show a preference for restricting the pathology to 1 eye, other underlying differences between ethnic groups must influence the development of reticular drusen and account for the discrepancy between races in the prevalence of bilateral disease.

Many Caucasian studies report a prevalence of exudative AMD at least double that of non-exudative AMD among their patients with reticular drusen.^{2,9,16,21} This is, however, not the case in Asian populations. In the study by Ueda-Arakawa et al,²² 50.0% of their Japanese reticular drusen patients had non-exudative AMD whereas only 9.0% had wet AMD. Contrary to this, Lee et al²³ reported a prevalence of 16.1% non-exudative and 10.6% exudative AMD among their Korean subjects. In the current cohort, 21.9% of our Chinese patients had non-exudative AMD and 17.1% had wet AMD. Apart from the prevalence of dry and wet AMD, other differences in the spectrum of AMD have been identified in reticular drusen patients of different races. PCV was not found in any reticular drusen patients in the literature except in Ueda-Arakawa's study wherein PCV was the diagnosis in 2% of their 216 Japanese patients.²² Of our 105 patients with reticular drusen, 4 (3.8%) had PCV. The differences in the proportion of dry AMD, wet AMD, PCV and RAP among different races may be due to the fact that Asian populations have relatively fewer AMD patients, but a higher proportion of PCV patients. The fact that PCV originates from choroidal vasculature underneath the RPE may explain the low prevalence of reticular drusen in PCV patients since the pathogenesis lies in different layers. Yoneyama et al²⁴ reported a higher prevalence of reticular drusen in RAP patients than in AMD or PCV patients, in whom reticular drusen were present in 38.2%, 13.6% and

0%, respectively. Interestingly we had no patients with RAP among the 105 recruited subjects in our study.

As there is no standardized grading system for reticular drusen, diagnosis is based on the experience of the clinician, and may be biased. In addition, imaging modalities used to detect reticular drusen vary among studies. Each imaging modality has its own sensitivity and specificity for reticular drusen, with sd-OCT and IR imaging reported as the better screening tools for the condition.^{21,25} Differences in the experience of clinicians and the utilization of different imaging modalities will therefore have affected the prevalence and incidence of reticular drusen reported by various research studies, thus rendering the results inaccurate and inconsistent. As awareness of knowledge about reticular drusen increases, it is thought that the presence of reticular drusen is even more important than the presence of soft drusen in the prognosis of AMD.^{3,17} In order to improve understanding of reticular drusen and develop more accurate documentation of the condition, a standardized grading system is warranted for future studies and reporting by researchers.

There are a number of limitations to our study. We may have omitted a proportion of patients with subtle reticular drusen where lesions could not be identified with fundus biomicroscopy. In addition, all our cases were seen in the retina clinic and there may have been selection bias. Furthermore, the small sample size and lack of control in this study may have impacted the measured outcomes.

Conclusions

Reticular drusen are an important risk factor for the development of advanced AMD. There may be ethnic differences in the prevalence of the condition and the macular pathologies associated with reticular drusen. A standardized grading system is needed to improve documentation of the condition.

Declaration

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