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Review Article

Reticular Pseudodrusen and Its Importance in AMD

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Abstract

This article aims to provide an insight into the pathophysiology and clinical features of the emerging entity called reticular pseudodrusen (RPD). The diagnosis of RPD requires multimodal imaging and it is important to distinguish them from other types of drusen. AMD can be a blinding disease with a huge impact of quality of life and the presence of RPD can further complicate the disease as RPD portend a faster progression of AMD to the wet form and are also known to be associated with geographic atrophy. Hence, it is important to diagnose this enitity and these patients require a closer follow up.

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Keywords: *Reticular pseudodrusen, ARMD, subretinal drusenoid deposits, geographic atrophy.*

Reticular pseudo drusen also known as Reticular Soft Drusen[1], reticular drusen or sub-retinal drusenoid deposits[2], is a terminology used to describe drusen-like deposits occurring in the subretinal space on OCT.

History of RPD

RPD were first described by Mimou and colleagues in 1990 as yellow interlacing structures seen in the outer macula with variable diameter of about 100 microns that did not fluoresce on FFA but demonstrated fluorescence on blue light filter.[1] Arnold J and colleagues further described these structures as first appearing in the superior macula and then spreading circumferentially. In 2013, Curcio and colleagues coined the term Subretinal drusenoid deposits as these appeared in the subretinal space on OCT[2].

Pathophysiology of Reticular Pseudo drusen:

The key feature causing the occurrence of RPD is para inflammation (Figure 1). Ageing leads to chronic insults to the retino choroidal tissue. This in turn activates the microglial cells and causes accumulation of macrophages in the subretinal space and activation of the compliment cascade. In a healthy individual maintaining a healthy immune system and a healthy lifestyle, these changes are reverted, and no damage ensues. However, in a dysregulated immune system there is retinal para-inflammation that will cause healing by forming a scar leading to age related macular degeneration (ARMD). Secondly a chronically inflamed retina at the molecular level leads to RPE and photoreceptor damage which will again contribute to the development of ARMD. Para inflammation results from the mal response of the RPE and retinal immune system to the age related chronic oxidative insults. Genetic predisposition (CFH, Cx3cr1), Environmental factors and epigenetic modifications are some of the factors responsible for the maladaptive retinal response to oxidative stress.

Burden and pathophysiology of ARMD:

ARMD is known to be the leading cause of irreversible blindness in the West. It is postulated to affect 14 million people worldwide.[3] 4 main processes are responsible for causing ARMD (Figure 2). Photoreceptor outer segments (POS) and Retinal pigment epithelium (RPE) undergo wear and tear and produce Lipofuscin. Accumulation of lipofuscin pigments result in drusen formation. Accumulation of drusen leads to complement activation and inflammation which results in the Dry form of ARMD. Inflammation at

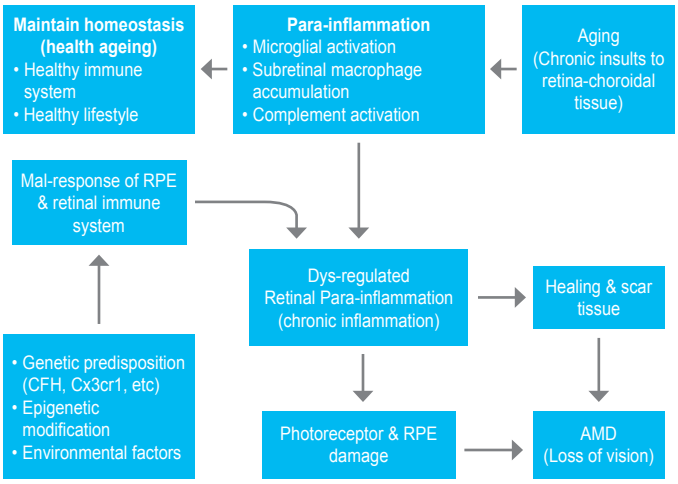

Figure 1: *Pathophysiology of Reticular pseudodrusen*

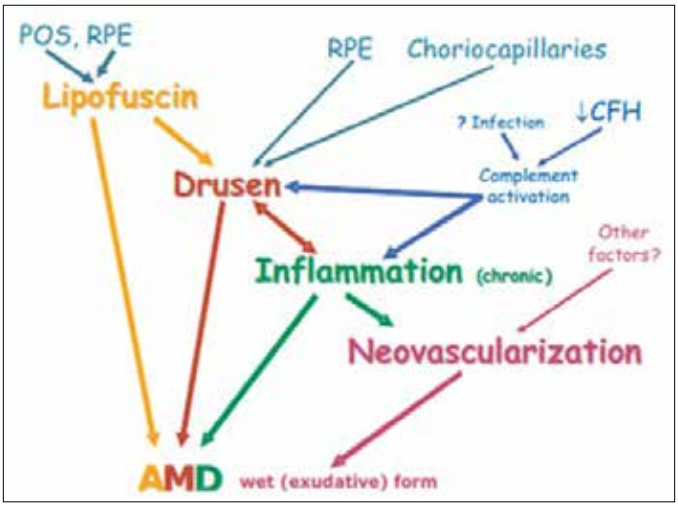

Figure 2: *Pathophysiology of ARMD*

times will lead to neovascularization which causes the Wet form of ARMD.

RPD and age-related macular degeneration (ARMD):
The Beaver Eye Dam study found that the Cumulative incidence of RPD was 3% over 15 years in the 43-86-year-old age group. Another landmark study, the Blue mountains study found that the 15-year cumulative incidence of RPD was 4% in patients >49 years of age. More disturbing is the fact that 36%-54% patients having neovascular AMD had associated RPD. 29-92.3% of patients having geographic atrophy had associated RPD. Innumerable studies quote some disturbing facts regarding RPD. Presence of RPD has a high correlation with Geographic atrophy. 30-50% eyes having RPD progress to develop late AMD. The 5-year progression to late AMD in eyes with RPD was found to be 6-fold higher than those with no RPD.

Imaging characteristics of RPD:
On a dilated fundus examination, RPD appear as yellow interlacing pattern which starts becoming more punctate as they approach the fovea (Figure 3). These pseudo drusen typically start appearing first in the superior macula and then spread circumferentially. Unlike drusen, these are first found in the extrafoveal areas and later on spread to the center. RPD have a predilection for the rods and are responsible to cause a delayed dark adaptation and impaired scotopic sensitivity.
Green wavelength or the red free image basically delineates pre RPE structures better due to its intermediate wavelength (Figure 4). It causes less scatter than Blue light. Red free image thereby delineates the RPD very clearly since these structures are pre RPE.
Short wavelength autofluorescence is also a good tool to image the RPD (Figure 5). On Short wavelength autofluorescence, these appear as hyper autoflourescent dots surrounded by hypoautoflourescence.
The hyperautoflourescence is thought to be due to the damaged photoreceptor outer segments and the subsequent window defects whereas the hypoautoflourescence is due to the normal blocking phenomenon of RPE.
Near infrared reflectance, though not an ideal tool to image RPD as infra-red is more useful to delineate choroidal structures, will give target like, ribbon like or dot like hyperreflective lesions (Figure 6).
Spectral domain OCT in RPD: SD-OCT typically shows the pseudo drusen to be present in the subretinal space.
RPD are also staged according to their SD-OCT characteristics (Figure 7).

Stage 1 (blue arrow): diffuse hyperreflective granular material between the RPE and Ellipsoid Zone (EZ)

Stage 2 (yellow arrow): mounds of accumulated material sufficient to alter the contour of EZ

Stage 3 (white arrow): Thicker material adopting a conical appearance and break through the EZ

Stage 4: material fades and migrates within the inner retinal layers with disruption of EZ

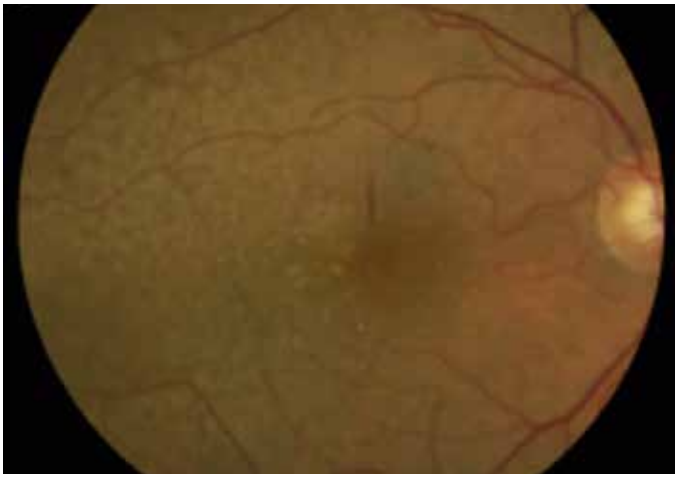

Figure 3: *Color photograph showing reticular pseudodrusen*

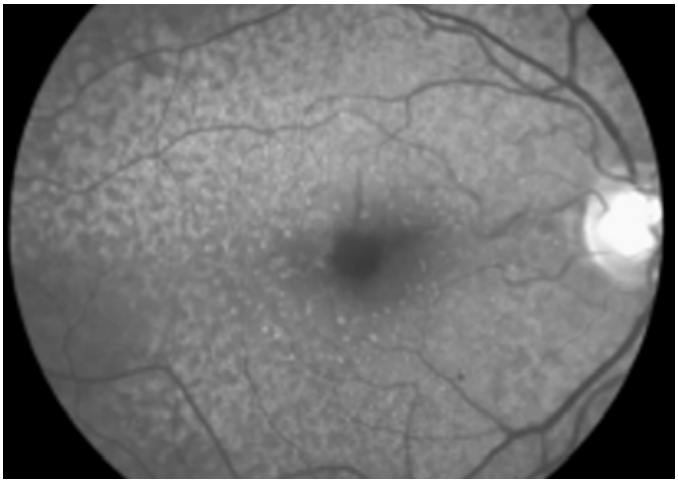

Figure 4: *Red free image showing reticular pseudodrusen*

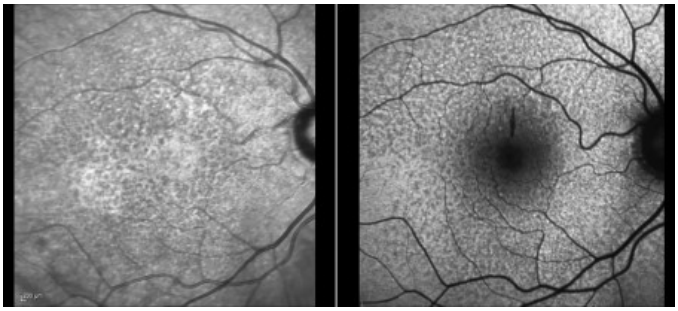

Figure 5: *Short wave autoflourescence depicting reticular pseudodrusen*

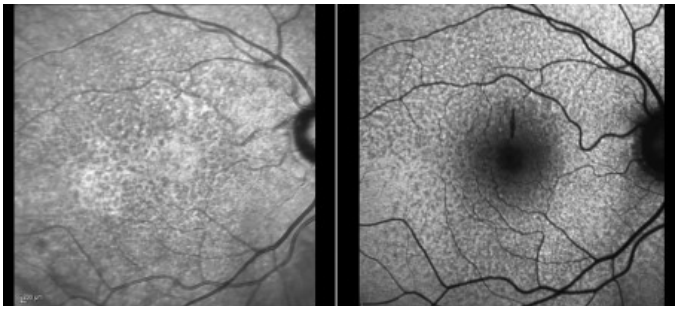

Figure 6: *Near infra-red reflectance showing reticular pseudodrusen*

A multimodality imaging is required to diagnose RPD, however various modalities have differing sensitivities. (Table 1) To further elaborate, Wu Z et al conducted a study on 300 subjects with bilateral large drusen and found that color fundus photograph has a low sensitivity to detect RPD but SD-OCT and NIR were very good tools to detect RPD.[4]
It is very important to distinguish and differentiate between true drusen and RPD (Table 2) since the presence of RPD will mandate a closer observation as their progression to GA, more severe Wet AMD is higher.
It is also important to know that many times, RPD and drusen may coexist and it is important to distinguish the two. (Figure 8 A and B)

Natural history and clinical implications of RPD:
RPD exhibit dynamism as they evolve and also resorb over time. Patients with RPD in an otherwise healthy macula confer a 2-fold higher risk of developing AMD during follow-up. Patients with RPD exhibit an increased risk of progressing to late AMD.[5] It is found that presence of RPD is linked to the development of multilobular geographic atrophy.[6] RPD is an independent risk factor for the development of bilateral disease and also an earlier onset of wet AMD.[7] RPD and type 3 CNV share a special bond as presence of RPD increases the chance of developing type 3 CNV and vice versa.[7] The relationship between RPD and Type 3 CNV is not just an association thereby the presence of RPD is a diagnostic sign distinguishing Type 3 CNV from other forms.[8] RPD have prognostic implications in treatment as well. Presence of RPD is linked with a higher chance of developing atrophy following intravitreal Anti VEGF.[9] In case of CNV development, RPD fade nearby the CNV itself, but they may still be observed more peripherally.[10] Disappearance of RPD is usually a gloomy situation since their disappearance occurs either when there is outer retinal atrophy or an onset of neovascular AMD.[11]
In conclusion, multimodal imaging can aid in detecting reticular pseudo drusen and the appearance and temporal evolution of reticular pseudo drusen can guide us in prognosticating patients with AMD and their presence mandates a close follow up.

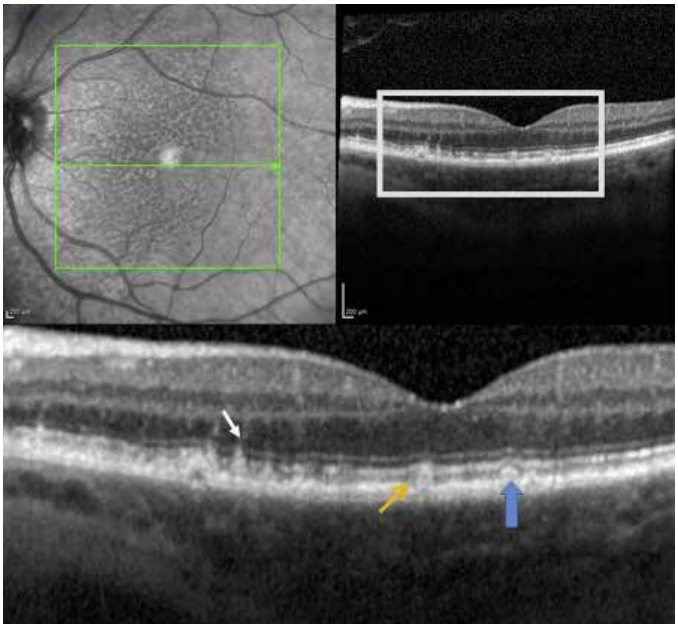

Figure 7: *SD-OCT characteristics of Reticular pseudodrusen*

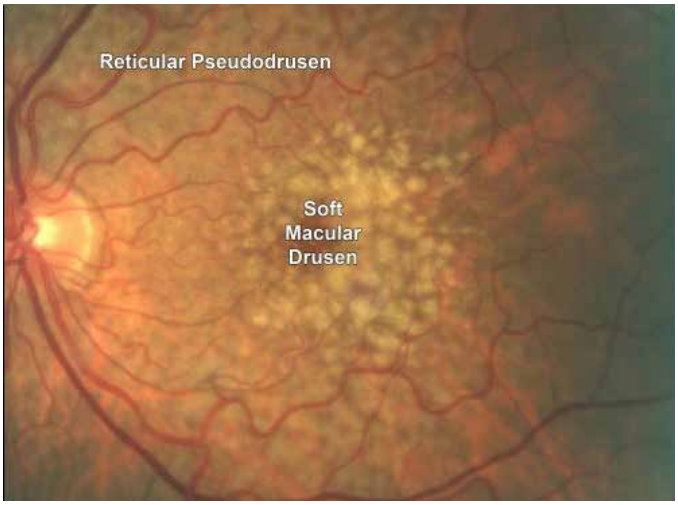

Figure 8: *Coexistence of drusen and reticular pseudodrusen on clinical photo and OCT*

Table 1: Sensitivities of various modalities to image reticular pseudodrusen

Image Type	Pattern Description	Sensitivity
Color Fundus	Yellow, interlacing networks ranging from 125-250 microns in width	88%
RF	Light, interlacing networks ranging from 125-250 microns in width	88%
AF	Groupings of ill-defined, hyporeflective lesions against a background of mildly elevated AF	86%
IR	Groupings of hyporeflective lesions against a background of mild hyperreflective with analogous characteristics	95%
FA	Defects in choriocapillaris filling in the early-phase images	17%
ICG angiography	Distinctive groupings of hypofluorescent dots present in the mid-to-late phases of the angiogram	100%

Table 2: Difference between drusen and reticular pseudodrusen

	Drusen	Reticula Pseudodrusen
Location	**Sub-RPE**	**Sub-retinal**
Classification	Cuticular, hard, soft, confluent	Dots, targets and reticular on IR reflectance
Biomarker positivity	Glial fibrillary acid proteins, RPE marker proteins, opsins present	Absent
Macular involvement	Cone rich central area	Rod rich parafoveal area
Appearance in blue light/filter	Yellow	Grey

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