Association between Choroidal Characteristics and Systemic Severity in Amyloidosis

Short title: Choroidal Characteristics in Amyloidosis

Fukutaro Mano MD[1,2], Angela Dispenzieri MD[3], Shunji Kusaka MD, PhD[2], Carlos Pavesio MD[4], Hagar Khalid MD[4], Pearse A. Keane MD[4], and Jose S. Pulido MD, MS, MBA, MPH[1,5,6]

Corresponding author:

Jose S. Pulido

[1] Mayo Clinic, Department of Ophthalmology, Rochester, Minnesota, USA

[2] Department of Ophthalmology, Kindai University Faculty of Medicine, Osakasayama, Osaka, Japan

[3] Department of Hematology, Mayo Clinic, Rochester, Minnesota, USA

[4] Moorfields Eye Hospital NHS Foundation Trust, London, UK

[5] Mayo Clinic, Department of Molecular Medicine, Rochester, Minnesota, USA

[6] Wills Eye Hospital, Department of Ophthalmology, Jefferson Kimmel Medical School, Philadelphia, PA, USA

1 Larry Donoso Endowed Chair in Translational Ophthalmology

2 Wills Eye Hospital, Philadelphia, PA

3 Professor Emeritus

4 Mayo Clinic, Departments of Ophthalmology and Molecular Medicine

5 200 1st St SW, Rochester, MN 55905

6 Phone number: 2625658206

7 Fax number: 5072844612

8 E-mail: pulido.jose@mayo.edu

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Key Words

Amyloidosis, Choroid, Indocyanine green angiography, Multimodal imaging, Optical coherence tomography

Summary Statement

We examined the choroidal manifestations of eleven patients with systemic amyloidosis using a multimodal imaging system with a combination of optical coherence tomography and indocyanine green angiography. We suggest a grading system that can be used to categorize choroidal features in relation to the systemic severity of amyloid involvement.

Abstract

Purpose: This study aimed to describe the choroidal features of ocular amyloidosis using multimodal imaging, to correlate these findings with systemic involvement, and thus to propose a choroidal grading system for this condition.

Methods: Eleven patients with systemic amyloidosis were reviewed retrospectively. Each case was assigned a grade according to the severity of choroidal findings as determined by both enhanced depth imaging optical coherence tomography (EDI-OCT) and indocyanine green angiography (ICGA). The severity of systemic amyloidosis was investigated and systemic score was evaluated in each case.

Results: On ICGA, all patients exhibited hyperfluorescent spots in the late stage and were classified according to pre-existing criteria. On EDI-OCT, hyperreflective foci were seen in the choriocapillaris and Sattler's layer in grade 1, partial loss of Sattler's layer was additionally seen in grade 2, and a dense hyperreflective Haller's layer was seen in grade 3. Choroidal grading scores were significantly correlated with systemic severity score ($p=0.0014$, Pearson's correlation co-efficient; $\rho=0.83$).

Conclusion: In patients with ocular amyloidosis, evaluation of choroidal characteristics using multimodal imaging may serve as a biomarker for systemic involvement in this condition.

Introduction

Amyloidosis is a group of diseases in which insoluble proteins aggregate in the extracellular space, causing dysfunction of the surrounding tissues. The most common forms of amyloidosis results from accumulation of insoluble immunoglobulin light-chain (AL) protein. Hereditary amyloidosis is caused by aggregation of transthyretin protein, and secondary amyloidosis arises from chronic inflammatory conditions that stimulate the hepatic secretion of serum amyloid A protein.[1-4] Wild-type transthyretin amyloidosis (Wild-type ATTR) is categorized as a distinct type of amyloidosis which is an abnormal aging process and does not carry the genetic transthyretin (TTR) mutation.[5] In addition to cardiac involvement, there is an increased incidence of bilateral carpal tunnel syndrome and spinal stenosis, as well as involvement of various ligaments and tendons.[6]

Interestingly, some ocular manifestations of amyloidosis differ among the subtypes of the disease. For example, patients with systemic AL amyloidosis have been reported to have extraocular manifestations such as conjunctival masses, persistent subconjunctival hemorrhage, temporal artery involvement, involvement of the extraocular muscles, as well as choroidal involvement.[7] In contrast, hereditary

transthyretin amyloidosis (ATTR) is known to be associated with vitreous involvement.[4, 8, 9] Furthermore, the onset of symptoms may vary between disease subtypes. For example, in patients with ATTR, the onset of glaucoma occurred 2.5 years after amyloid deposition was noted around the pupil.[10] In a large series of 513 patients with ATTR, Beirão et al. reported the earliest ocular manifestations as abnormal Schirmer tests and tear break-up times.[11] In addition, a few cases have been reported in which the vitreous opacities appear to be the initial ophthalmic manifestation.[12, 13] Nevertheless, those ocular manifestations such as choroidal angiopathy, retinal angiopathy, and secondary glaucoma develop progressively over time.[14]

There are very few published reports that have examined the histology of choroidal involvement.[15-17] Paton and Duke presented a histopathological study that described marked amyloid accumulation in the choroidal vessels and mild retinal vessel accumulation.[15] Kawaji et al. also reported histologic descriptions and found amyloid deposits both in choroidal and retinal vessels.[16] On the other hand, Ts'o et al conducted a detailed histopathological analysis of the eye of a deceased amyloid patient and observed scattered but extensive choriocapillaris occlusion in some cases as well as

moderate to large vessel involvement in other cases.[17] However, they did not find evidence of retinal vessel involvement.

To our knowledge, there are only a few reports in the literature of choroidal amyloidosis visualized using multimodal imaging.[16, 18-20] Therefore, in this study, we review the choroidal manifestations of eleven patients with systemic amyloidosis using a multimodal imaging system consisting of fundus photography, optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA). We further propose a grading system that categorizes choroidal features in association with the systemic severity of the amyloid involvement.

Methods

This study received Institutional Review Board approval from Mayo Clinic (Rochester, Minnesota, USA). The principles of the Declaration of Helsinki were followed. This study is a retrospective observational case series of eleven patients diagnosed with systemic amyloidosis (six patients with familial and one patient with wild-type transthyretin, three patient with light-chain amyloidosis, and one patient with AA

amyloidosis) presenting at Mayo Clinic (Rochester, Minnesota), Moorfields Eye Hospital (London, UK), and Kindai University Hospital (Osakasayama, Japan) from 2008 to 2020. The initial seven patients were those who had been sent to Dr Pulido for evaluation of their amyloidosis. Many of which were sent from the amyloidosis clinic at the Mayo Clinic. The subsequent cases were patients who were found retrospectively by asking internationally for cases with a confirmed diagnosis of systemic amyloidosis. All patient data used in the study adhered to local IRB and patient confidentiality requirements. Patient demographics and medical history were retrospectively reviewed and studied. Mutations in transthyretin (TTR) were identified by direct Sanger sequencing (Mayo Medical Laboratories).

Ophthalmic examination

Comprehensive ophthalmic examination included slit-lamp examination and pupil-dilated funduscopy. Multimodal imaging was deployed for all patients, including color fundus photography (Visucam 500; Carl Zeiss Meditec AG, Jena, Germany), ultra-wide-field fundus camera (Optos 200Tx, Optos, Dunfermline, UK), spectral-domain OCT (Spectralis OCT; Heidelberg Engineering GmbH, Dossenheim, Germany), FA, and ICGA (Spectralis HRA; Heidelberg Engineering GmbH, Dossenheim, Germany).

Each case was graded and then classified into one of three groups according to the severity of the choroidal findings as determined both by OCT and ICGA. The grading system of ICGA was modified according to the criteria proposed by Rousseau et al.[20] Furthermore, we focused on the choroidal features based on the OCT findings. ICGA images were overlaid to the *en face* OCT images, and we carefully evaluated the correspondence and superimposition of the hyperfluorescent spots on ICGA with the hyperreflective foci in the sectional OCT images. Our proposed grading system for choroidal angiopathy is summarized in **Table 1**.

Systemic evaluation

The severity of systemic amyloidosis in each organ was investigated along with the ophthalmic examination. Systemic and ocular evaluations were performed at similar time points. Systemic evaluations ranged from cardiac, liver, renal, gastrointestinal, to neural impairment. Examinations included echocardiogram, 99m-technetium pyrophosphate (PYP) scintigraphy, iodine-123-labelled serum amyloid P component (SAP) scintigraphy, blood examination (blood cell count and biochemistry, which includes a liver enzyme, estimated glomerular filtration rate), and neurologic examination. For the evaluation of systemic amyloidosis, we utilized the accepted

national Japanese amyloidosis guidelines, modifying them to enable scoring for each organ..[21] These guidelines were developed by Ando et al.[22] and consist of a scoring system as follows:

1. amyloid accumulation, yet asymptomatic

2. amyloid accumulation or clinically abnormal data with mild dysfunction in a single organ

3. amyloid accumulation or clinically abnormal data with mild dysfunction in multiple organs

4. amyloid accumulation and moderate dysfunction in single or multiple organs

5. amyloid accumulation with severe dysfunction in multiple organs

The systemic score was evaluated in each organ and summed in each case: score 0, no impairment; score 1, abnormal data yet asymptomatic; score 2, symptomatic complication; score 3, severe impairment (including organ transplantation). The maximum score for systemic grading is 15 (3 × 5).

Statistics

Statistical analysis was performed using JMP 14 (SAS Institute Inc., Cary, NC, USA) with data presented as the mean ± standard deviation. Mean systemic scores from choroidal grades 1 and 2 ere compared with that of choroidal grade 3 using a two-tailed Student *t*-test. Pearson's correlation analysis was utilized to investigate a relationship between choroidal grading score and systemic severity score. Statistical significance was predetermined at $p < 0.05$.

Results

Patient demographics and choroidal grading score

The study population consisted of eleven patients (six men and five women) with a mean (±SD) age of 61 ± 12.8 years. On ICGA, ten patients who underwent ICGA exhibited hyperfluorescent spots in the later stages. Hyperfluorescent spots noted to have a punctiform pattern were seen in four patients (40%). A pattern of hyperfluorescent punctate and linear patches (previously described as a focal pattern[20]) was seen in four patients (40%). A marked linear "firework" pattern[20] was seen in two patients (20%). All the findings were bilaterally symmetric. When the ICGA images

were overlaid to the *en face* OCT images, hyperfluorescent spots on ICGA corresponded with more hyperreflective foci than the usual reflectivity of choroidal vessels in the cross-sectional OCT images (**Figure 1A and B**). In the detailed observation of OCT using our grading system, hyperreflective foci were seen in the choriocapillaris and Sattler's layer in grade 1 (**Figure 2A**). Hypo- and hyperreflective choriocapillaris and partial loss of Sattler's layer were seen in grade 2 (**Figure 2B**). Patchy loss of choriocapillaris and Sattler's layer and dense hyperreflective Haller's layer were seen in grade 3 (**Figure 2C**). One patient (case 4) who had a punctiform pattern in ICGA had worse OCT findings. Thus, the choroidal score was evaluated as grade 2. Another patient (case 7) did not have ICGA, and the choroidal grading score was determined only by OCT features.

In summary, two patient (18%) were noted to have grade 1 choroidopathy, six patients (55%) had grade 2 choroidopathy, and three patients (27%) had grade 3 choroidopathy. Patient demographics with choroidal grading scores are listed in **Table 2**. Details of each case are described in the following sections.

Case 1

A 62-year-old Caucasian man diagnosed with wild-type ATTR and a negative genetic study was referred to our department in 2018. The patient had cardiac amyloidosis with positive PYP uptake but was asymptomatic, demonstrating preserved ejection fraction (systemic score 1). He did not have ocular vitreous amyloidosis, but ICGA showed hyperfluorescent punctate delineation of choroidal vessels in the later phases (choroidal grade 1; **Figure 3A**). OCT also showed hyperreflective foci in the choroid (**Figure 3B**). Coincidentally, the right eye had a simultaneous circumscribed choroidal hemangioma with overlying soft drusen.

Case 2

A 41-year-old Caucasian man presented to our department with a prior diagnosis of ATTR with Phe33Ile transthyretin mutation confirmed by genetic testing. Echocardiography showed increased concentric left ventricular wall thickness, but the patient was asymptomatic (systemic score 1). General workup revealed no other systemic involvement. He underwent a vitrectomy in the left eye in 2013 and the same in the right eye in 2014. Retinal architecture appeared normal. ICGA, in a later stage, showed hyperfluorescent punctate and linear patches (**Figure 4A**). OCT showed patchy

hypo- and hyperreflective choriocapillaris and partial loss of Sattler's layer (choroidal grade 2; **Figure 4B**).

Case 3

A 72-year-old Caucasian man presented to our department with a diagnosis of biopsy-proven AL amyloidosis. He had kidney amyloidopathy, however, other organs were not involved (systemic score 2). Hyperfluorescent punctate and linear patches were seen in the later frames of ICGA. OCT demonstrated cystoid macular edema with resolved subretinal fluid in both eyes (choroidal grade 2). Patchy hypo- and hyperreflective choriocapillaris and partial loss of Sattler's layer were observed in both eyes.

Case 4

A 68-year-old Caucasian man was referred to our department with a diagnosis of ATTR with Val30Met transthyretin mutation confirmed by genetic testing. He underwent liver transplantation in 1997. He also presented with amyloid autonomic neuropathy (systemic score 5). Cardiology evaluation showed no evidence of amyloid in the heart. The left eye showed some amyloid accumulation in the vitreous. The retinal morphology was unremarkable. Although ICGA showed only small hyperfluorescent

punctuates, OCT revealed more marked findings, including patchy loss of choriocapillaris and Sattler's layer (choroidal grade 2).

Case 5

A 44-year-old Caucasian woman was referred to our department with a diagnosis of ATTR with Glu54Gly transthyretin mutation confirmed by genetic testing. She underwent liver transplantation in 2011. She also had severe peripheral neuropathy and mild cardiac amyloidosis with preserved ejection fraction (systemic score 6). She had previously undergone vitrectomy in the left eye in 2016 for vitreous amyloidosis. In the later stages of ICGA, she demonstrated hyper- and hypofluorescent punctate and linear patches. OCT showed patchy hypo- and hyperreflective choriocapillaris and partial loss of Sattler's layer (choroidal grade 2).

Case 6

A 50-year-old Caucasian woman was referred to our department diagnosed with ATTR with Phe64Ser transthyretin mutation confirmed by genetic testing. She had definite cardiac amyloidosis as well as marked amyloid neuropathy, gastrointestinal tract involvement, and renal insufficiency (systemic score 7). She had prior bilateral vitreous

amyloidosis and underwent a vitrectomy in the right eye in 2016 and the same in the left eye in 2018. Although her retina appeared normal, ICGA revealed marked linear staining in the later stages (**Figure 5A**). OCT showed dense hyperreflective lesions in Haller's layer (choroidal grade 3; **Figure 5B**).

Case 7

A 64-year-old Caucasian woman was referred to our department with a diagnosis of ATTR with Asp18Glu transthyretin mutation confirmed by genetic testing. She had undergone liver-kidney-heart transplantation in 2005. She also had peripheral neuropathy (systemic score 10). She underwent vitrectomy in the right eye for vitreous amyloidosis in 2006. Retinal microaneurysms were observed in both eyes, and peripheral nonperfusion area was noted on FA. This patient was not examined with ICGA, however, OCT demonstrated dense hyperreflectivity around Haller's layer and patchy loss of choriocapillaris and Sattler's layer (choroidal grade 3).

Case 8

A 51-year-old Caucasian male was referred to Moorfields Eye Hospital (London, UK) with the diagnosis of Arg34Gly transthyretin mutation confirmed by genetic testing.

Systemic manifestation included cardiac amyloidosis and SAP scintigraphy showed small amyloid load in his spleen. Possible amyloid-related autonomic neuropathy and peripheral neuropathy was present with effects on both his hands and feet (Systemic Score 5). He presented with dense un-resolving vitreous floaters for which he underwent a right vitrectomy in 2011 and left vitrectomy in 2012. He also underwent Baerveldt tube implantation for secondary glaucoma in the right eye in 2017. ICGA showed hyper fluorescent punctate lesions in the later stages. OCT showed patchy hypo- and hyper-reflective choriocapillaris, and partial loss of Sattler's layer (Choroidal Grade 2).

Case 9

A 65-year-old Asian male was referred to Kindai University Hospital (Osakasayama, Japan) diagnosed with AA amyloidosis with negative genetic testing. Systemically, he had late gadolinium enhancement in the heart with elevated brain natriuretic peptide as 843pg/ml and abnormal renal function (lower estimated glomerular filtration rate) yet asymptomatic (Systemic score 2). ICGA showed hyper-fluorescent punctate delineation of choroidal vessels in the later phases. OCT showed hyper-reflective foci in the choroid. (Choroidal Grade 1).

Case 10

A 79-year-old Asian male was referred to Kindai University Hospital, diagnosed with AL (IgA-κ) amyloidosis. He had cardiac amyloidosis with positive PYP uptake. He also had abnormal renal function (lower estimated glomerular filtration rate), gastrointestinal involvement, peripheral neuropathy, and carpal tunnel syndrome (Systemic score 6). He had vitreous opacities in both eyes. In the later stages of ICGA, he demonstrated hyper-fluorescent punctate and linear patches. OCT showed patchy hypo- and hyper-reflective choriocapillaris, and partial loss of Sattler's layer (Choroidal Grade 2).

Case 11

A 75-year-old Asian female was referred to Kindai University Hospital diagnosed with AL (IgG-κ) amyloidosis. She presented with atrial flutter, gastrointestinal bleeding, abnormal renal function, ulnar nerve palsy and carpal tunnel syndrome (Systemic score 7). Ocular manifestation included conjunctival amyloidosis, blepharoptosis, dry eye, cataracts and vitreous opacities in both eyes. ICGA showed marked linear staining in the later stage. OCT demonstrated dense hyper-reflective lesions in Haller's layer (Choroidal Grade 3).

Systemic grading score

The systemic grading scores in each case are also summarized in **Table 2**. The systemic score in patients with choroidal grade 3 was significantly higher than that in patients with grade 1 and 2 (8.0 ± 1.7 vs. 3.5 ± 2.2, $p = 0.012$). Pearson's correlation analysis revealed significant correlation between choroidal grading score and systemic severity score (p=0.0014, Pearson's correlation co-efficient; ρ=0.83) **(Figure 6)**.

Discussion

Amyloidosis is associated with a broad spectrum of systemic complications, including cardiopathy, liver, renal, gastrointestinal, neuropathy, and ocular symptoms.[23] Amyloid depositions are well known to accumulate in the perivascular space.[24] In previous histological studies, amyloid deposition in the choroid starts from the replacement of the choriocapillaris, whereas retinal vessels are relatively spared in the early stage of the disease.[17, 25] Amyloid accumulation subsequently extends to the larger vessels.[16]

Using multimodal imaging, in vivo studies of systemic amyloidosis have demonstrated various types of hyperfluorescent staining patterns in late ICGA.[16, 18 ,26 ,27] Importantly, Rousseau et al. categorized these into the following three patterns: punctiform, focal, and a diffuse firework.[20] Because of the homology of the appearance of the posterior ciliary artery, it seems the case in the firework pattern that the choroidal arteries are predominantly affected, and those cases were associated with significantly higher polyneuropathy disability scores.[20] Similarly, in our cases, the "Marked linear" pattern was associated with significantly higher systemic scores.

The use of high-resolution anterior segment OCT for the evaluation of conjunctival amyloidosis revealed that amyloid deposition was seen as hyperreflective foci.[28] Rousseau et al. observed amyloid deposits only by ICGA,[20] but in the current study, we noted the correspondence of hyperreflective foci on OCT with the hyperfluorescent spots in ICGA. We have also noted that the choroidal tri-laminar structure (choriocapillaris, Sattler's, and Haller's) are relatively spared in the early stage and dense hyper-reflective Haller's layer, and delineated choriocapillaris and Sattler's layer were observed in the late stage of the disease. This is also supported by a previous histology study that the choriocapillaris was initially affected in a patient with systemic

amyloidosis without any ocular symptoms.[17] Thus, we speculated that the amyloid deposits in the microvessels, such as the choriocapillaris and the Sattler's layer, are affected before the larger Haller's layer and as the smaller vessels occlude then the larger vessels are affected over the time course of disease progression.

Hara et al. reported the results of a long-term retrospective follow-up study of 52 cases of ATTR patients after liver transplantation. Even after liver transplantation, eight patients (36%) developed vitreous opacities, and four patients (18%) developed glaucoma during follow-up. The researchers concluded that patients with ATTR who undergo liver transplantation continue to have a long-term risk of severe ocular manifestations such as vitreous opacities and glaucoma probably because of the mutant TTR synthesis in retinal pigment epithelium.[14] In animal studies, RPE[29] and ciliary pigment epithelium[30] are believed to be the tissue source of mutant TTR in the eye. Additionally, Koike et al. reported that the endothelial cell loss and occluded microvessels were significantly increased in the patients with ATTR suffering from polyneuropathy compared with patients with nutritional/alcoholic neuropathies.[31] The choroid appears to be a biomarker for systemic disease progression, yet it remains to be

proven whether the amyloid deposits in the choroid is from neighboring RPE, the endothelial cells, or from systemic circulation.

Roybal et al. reported amyloid choroidopathy in four patients with systemic amyloidosis and described the hyporeflective widened choriocapillaris band using spectral-domain OCT.[18] Tei et al also reported the same feature in a severe amyloid case and confirmed no signal in the choroidal capillary slab by OCT angiography.[19] We have noted that the cases in the literature with enlarged choriocapillaris bands also had dense hyperreflectivity in Haller's layer, which would then be categorized as the most severe grade in our choroidal grading system. Published cases of amyloidosis with ocular findings have also had renal insufficiency, and the glomerulus shares common histopathological features with the choroid.[32] The case presented by Tei et al underwent hemodialysis.[19] Thus, the widened choriocapillaris band might represent an end-stage feature of choroidal angiopathy, consistent with a high score of systemic severity.[33]

As the current study revealed an association between choroidal grading score and systemic severity, and there are many treatments for systemic amyloidosis currently available besides liver transplantation,[34, 35] the evaluation of patients with systemic amyloidosis using our choroidal grading system is useful and might serve as a

biomarker for systemic amyloid angiopathy. More multimodal imaging as OCT angiography would be warranted to evaluate the detailed choroidal features and further corroborative studies should be performed to evaluate the universal application of our grading system in association with systemic amyloid involvement.

Limitations of this study are the relatively small number of patients, heterogeneity of disease subtypes, and different amyloid proteins involved, that could possibly lead to different patterns of deposition and consequent systemic involvement.

Conclusion

We developed a grading system for choroidal amyloidosis using OCT combined with late ICGA. This grading system appears to be related to the systemic score. Although further studies on this topic are warranted, at this time, patients with suspected amyloidosis should be evaluated not only by routine ophthalmic techniques but also by OCT and ICGA.

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Figure legends

Figure 1. Correspondence of hyperfluorescent spots on indocyanine green angiography with hyperreflective foci on optical coherence tomography.

(A) A late-stage indocyanine green angiography (ICGA) image was superimposed onto the en face optical coherence tomography (OCT) image. The green horizontal line is placed through some of the hyperfluorescent ICGA spots indicated, and the corresponding spots are noted on the OCT by yellow arrows. (B) More hyperreflective foci in the choriocapillaris than the usual reflectivity of choroidal vessels were observed in the cross-sectional OCT, which corresponded with the hyperfluorescent spots in ICGA.

Figure 2. Choroidal features in patients with amyloidosis on optical coherence tomography.

(A) Hyperreflective foci were seen in the choriocapillaris and Sattler's layer, indicated by white arrows (Choroidal grade 1). (B) Hypo- and hyperreflective choriocapillaris and partial loss of Sattler's layer are seen in the white dotted circle. The partial

hyperreflective area around Haller's layer is indicated by black arrows (Choroidal grade 2). (C) The dense hyperreflective area around Haller's layer is shown in the black dotted circle (Choroidal grade 3).

Figure 3. A representative case of choroidal grade 1 (case 1).

(A) The black arrow shows the hyperfluorescent punctate staining in the later phase of indocyanine green angiography. (B) Optical coherence tomography showed hyperreflective foci in the choroid.

Figure 4. A representative case of choroidal grade 2 (case 2).

(A) Indocyanine green angiography in the later stages showed multiple hyperfluorescent punctate and linear patches. (B) Optical coherence tomography showed patchy hypo- and hyperreflective choriocapillaris and partial loss of Sattler's layer.

Figure 5. A representative case of choroidal grade 3 (case 6).

(A) Indocyanine green angiography showed marked punctate and linear staining in the later stage. (B) Optical coherence tomography showed dense hyperreflectivity around Haller's layer and loss of Sattler's layer and choriocapillaris.

Figure 6. Association between choroidal grading and systemic score.

Pearson's correlation analysis showed significant correlation between choroidal grading score and systemic severity score (p=0.0014, Pearson's correlation co-efficient; ρ=0.83)