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Angiographic dark choroid in systemic non-hereditary amyloidosis

Konstantin V. Astafurov, Andrew J. Barkmeier [1,*]

Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Purpose: To describe a novel finding of angiographic dark choroid in a patient with systemic non-hereditary amyloidosis.

Observation: A 43-year old female with systemic light-chain amyloidosis associated with advanced kidney disease presented with metamorphopsia and blurry vision in both eyes of 1 year duration. Examination revealed sub-retinal yellowish deposits in the central macula and mid-periphery with patchy RPE mottling bilaterally. OCT demonstrated thickened choroid with a widened hyporeflective sub-Bruch's choriocapillaris band. FAF showed hypoautofluorescence of the central maculae with hyperautofluorescence flecks perifoveally. Fluorescein angiography demonstrated normal vascular filling without leakage and peripheral microaneurysms. The FA also revealed a strikingly diminished diffuse lack of choroidal fluorescence throughout all angiographic phases in both eyes which has not been previously described in this condition.

Conclusionsand Importance: This case demonstrates that patients with systemic amyloidosis may exhibit attenuation of choroidal signal ("dark choroid") on fluorescein angiography, possibly due to accumulation of amyloid material in the sub-RPE space.

1. Introduction

The amyloidoses are a group of heterogeneous disorders characterized by tissue deposition of abnormally folded proteins leading to chronic tissue damage and dysfunction. Amyloid formation occurs when globular soluble proteins undergo misfolding and subsequently organize into insoluble fibrils with distinct affinity for Congo red stain with yellow-green birefringence under polarized light and rigid, non-branching appearance on electron microcopy.[1] Typically, amyloidoses are classified as either acquired primary (idiopathic) or secondary (due to an underlying systemic condition) and hereditary versus non-hereditary forms. The most common form of primary amyloidoses is the light-chain amyloidosis (AL) in which misfolded proteins are derived from the immunoglobulin light chain produced by clonally expanding plasma cells. Systemic amyloidosis associated with serum amyloid A protein deposition (AA) is the most common form of secondary amyloidosis due to an underlying chronic inflammatory or infectious process. Hereditary amyloidoses account for approximately 10% of all systemic amyloidoses with the amyloid derived from transthyretin (ATTR) being the most common in this group.[1]

The majority of amyloidoses result in systemic disease affecting multiple organs (most commonly kidney, heart, gastrointestinal tract, liver and lung), but amyloidoses may also localize to a particular tissue (e.g. cerebral amyloidoses such as Alzheimer's disease associated with beta-amyloid peptide deposition (Aβ) and Familial British dementia associated with amyloid-bri peptide (ABri) deposition, among others[1]). Systemic amyloidoses may affect ocular tissues, typically as orbital amyloidosis involving lacrimal glands or extraocular muscles. Certain corneal dystrophies are associated with a systemic disease (e.g. Lattice Corneal Dystrophy Type II which is associated with familial amyloidosis Finnish type [AGel amyloidosis], also known as Meretoja's Syndrome[2]) while others are recognized as primary localized hereditary amyloidoses (e.g. Gelatinous Drop-Like Dystrophy, Lattice Corneal Dystrophy Type II[2]).

Intraocular involvement in amyloidosis is most commonly seen as vitreous amyloidosis that typically occurs in familial transthyretin protein amyloidosis (ATTR). Reynolds et al.[3] published a longitudinal study of 108 patients with ATTR among whom 24% had signs of ocular disease. All of the affected individuals had vitreous amyloid deposition, with other intraocular structures affected less frequently: neurotrophic keratitis was seen in 8%, glaucoma in 19%, and tortuous retinal vessels in 15% of cases. No retinal or choroidal involvement was noted in that

* Corresponding author. Department of Ophthalmology, Mayo Clinic, Rochester, 200 First St. SW, Rochester, MN, 55905, USA.
E-mail addresses: kostyapiter@gmail.com (K.V. Astafurov), Andrew.Barkmeier@mayo.edu, kostyapiter@gmail.com (A.J. Barkmeier).
[1] Present address: Department of Ophthalmology, Rutgers Robert Wood Johnson Medical School/NJRetina, New Brunswick, NJ.

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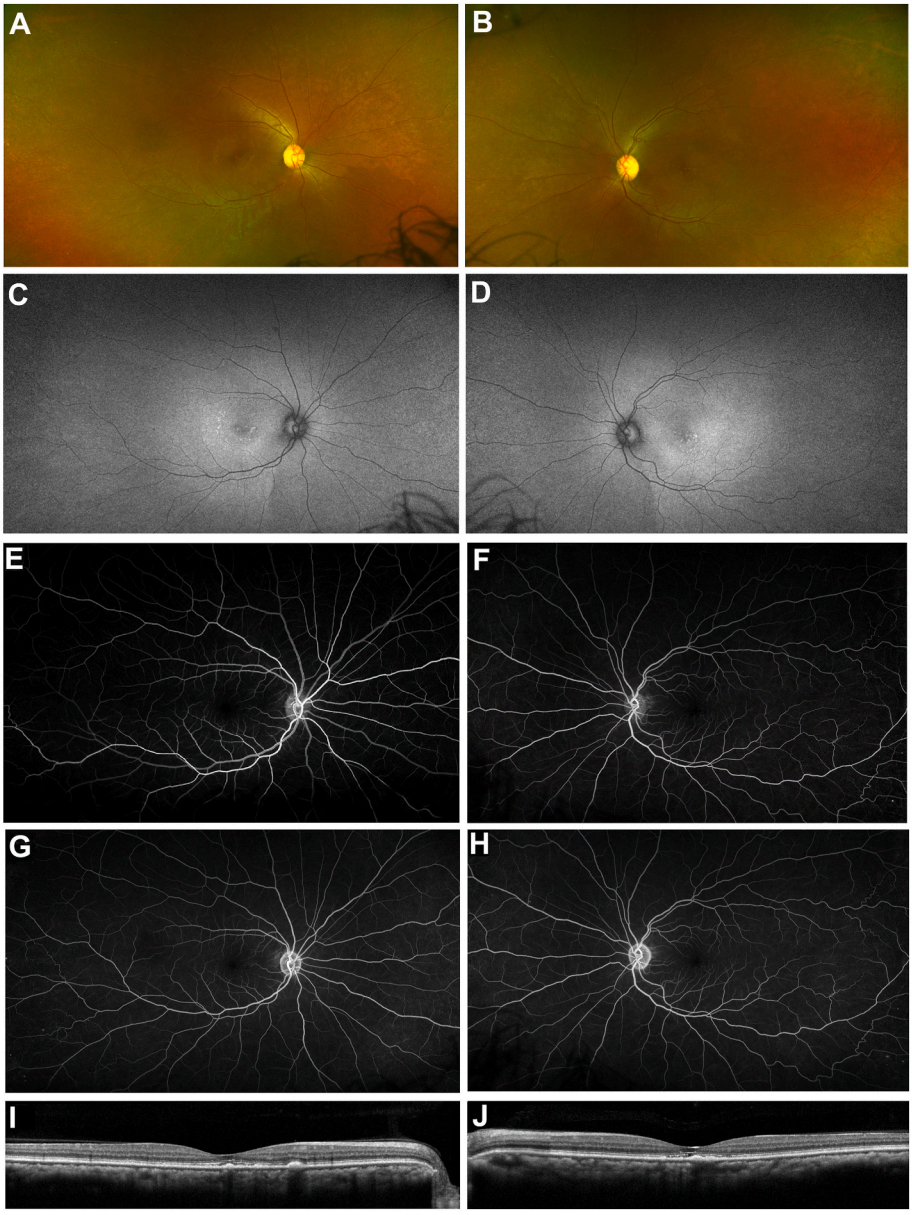

Fig. 1. Multimodal fundus imaging. Optos pseudocolor images of the right and left eyes (A and B, respectively) demonstrate drusenoid deposits in the perifoveal regions in both eyes. There are also few scattered drusenoid deposits in mid-periphery and RPE changes/atrophy in the posterior pole bilaterally. Fundus autofluorescence imaging demonstrates hypoautofluorescence of the central macula with hyperautofluorescent flecks perifoveally and in temporal macula in both eyes (C and D). Fluorescein angiogram reveals absence of fluorescein signal from choroidal circulation in both eyes in the early phase of the angiogram (laminar flow phase shown for the right eye, E, at 20 seconds; venous phase shown for the left eye, F, at 41 seconds) as well as in the late phases (G and H, for the right eye, at 8 min 27 seconds, and the left eye, at 8 min 40 seconds, respectively). The FA also revealed several peripheral retinal microaneurysms. Enhanced depth imaging optical coherence tomography (EDI-OCT) horizontal rasters of the macula reveal drusenoid deposits, a thickened hyporeflective choriocapillaris band, and thinning of the outer nuclear layer in both eyes (I and J). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

series. In general, involvement of the retina or the choroid is not typical in systemic amyloidosis with a limited number of cases reported.[4–7] This report describes a case of a patient with retinochoroidal involvement from systemic light-chain amyloidosis whose fluorescein angiography demonstrated dark choroid - a finding that has not has not been previously reported in this condition.

2. Case report

A 43-year-old female of Indian Asian descent with history of systemic light chain amyloidosis complicated by chronic stage 5 kidney disease presented to our retina clinic for evaluation of bilateral maculopathy. She was initially diagnosed with systemic amyloidosis by bone marrow biopsy 8 years prior which showed plasma cell population of 30% and was positive for Congo red staining. She underwent an autologous stem cell transplant. One year prior to presentation, she developed renal failure and was diagnosed with recurrence of amyloidosis. Initial treatment with cyclophosphamide/bortezomib/dexamethasone (CyBorD) was not tolerated, and she began daratumumab/bortezomib/dexamethasone therapy 3 months prior to presentation for retina evaluation. Additional past medical history included Factor X deficiency, hypertension, and anemia of chronic disease.

Visual acuity on presentation was 20/30 in the right eye and 20/25 in the left eye. She reported metamorphopsia and haziness of vision in both eyes for the past year since her most recent amyloidosis recurrence. IOP measured 18 mmHg in the right eye and 20 mmHg in the left eye. Extraocular motility, pupillary, and anterior segment examinations were unremarkable in both eyes. Fundoscopic examination revealed subretinal yellowish deposits in the central macula and mid-periphery bilaterally with patchy RPE pigmentary mottling in the posterior pole (Fig. 1A and B). There was no evidence of intra- or subretinal fluid or hemorrhages. Fundus autofluorescence (FAF) showed hypoautofluorescence in the central macula with hyperautofluorescence flecks perifoveally and in temporal macula (Fig. 1C and D). Fluorescein angiography (FA) showed normal arterial and venous filling without leakage in either eye. Several peripheral retinal microaneurysms were also observed. The FA also demonstrated a strikingly diminished diffuse lack of choroidal fluorescence throughout all angiographic phases in both eyes (Fig. 1E and F, G and H). Spectral domain optical coherence tomography (OCT) demonstrated thickened choroid (measuring 298 μm

Table 1
Prior reports of retino-choroidal involvement in systemic amyloidosis.

	Demographics	Amyloidosis type	Fundoscopy	FAF[a]	OCT[b]	FA[c]/ICG[d]
Roybal et al., 2015	4 females (37, 46, 62, and 74 years old)	-Primary with renal failure (1 patient). -Secondary with renal failure (3 patients), 2 patients with underling disease (Mediterranean fever and inflammatory bowel disease)	Drusenoid deposits (2 patients); scattered reticular pigmentary changes (1 patient), patchy chorio-retinal atrophy (2 patients)	Hyperautofluorescent flecks and drusen in macula and periphery; hypoautofluorescence in areas of atrophy; reticular hyperautofluorescence in the posterior pole	Thickened choriocapillaris band (4); thickened choroid (3); thinned ONL (4)	Not reported
Pece et al., 2000	A 59-year- old female	Primary, non-familial	Bilateral, diffuse, deep hemorrhages in the posterior pole with pigmentary mottling in the macular area	Not reported	Not reported	FA: pigmentary mottling, areas of hypofluorescence, hyperfluorescent streaks in the peripapillary region; ICG: hypofluorescent streaks radiation from the optic disc
Tei et al., 2019	A 43-year-old female	Secondary, underlying cryopyrine-associated periodic syndrome with renal failure	Vitreous opacities, pale optic discs and atrophy in the peripheral retina	Not reported	Thickened choriocapillaris band	Not reported
Mato et al., 2020	6 males and 5 females (mean age 61 ± 12 years)	Primary light-chain amyloidosis (3 patients), transthyretin amyloidosis (7 patients, 6 with familial and 1 with wild-type transthyretin), serum amyloid A protein amyloidosis (1 patient)	Retinal microaneurysms (1 patient); macular edema (1 patient); 1 incidentally found choroidal hemangioma	Not reported	Hyperreflective foci in choriocapillaris and Sattler's layer, dense hyperreflective areas in the Haller's layer.	FA: peripheral non-perfusion in 1 patient; peripheral microaneurysms in 1 patient no other abnormal findings were reported; ICG: hyperfluorescent linear patches and punctate lesions, hyperfluorescent punctate delineation of choroidal vessels
This case	A 43-year-old female	Primary light-chain amyloidosis with renal failure	Drusenoid deposits in the macula and mid-periphery; patchy PRE changes in the posterior pole	Hyperautofluorescent flecks and drusen in macula and periphery; hypoautofluorescence in areas of atrophy	Thickened choriocapillaris band; thickened choroid; thinned ONL	FA: angiographically dark or "silent" choroid; peripheral microaneurysms. ICG: not available

[a] FAF, fundus autofluorescence.
[b] OCT, optical coherence tomography.
[c] FA, fluorescein angiography.
[d] ICG, indocyanine green angiography.

OD and 329 μm OS with a widened hyporeflective sub-Bruch's choriocapillaris band measuring 32 μm OD and 35 μm OS (Fig. 1I and J). In addition, both eyes had thinning of the outer nuclear layer (ONL) demonstrated by OCT.

3. Discussion

Retino-choroidal involvement in systemic amyloidosis is relatively uncommon with only a handful of single case reports and case series described in the literature (Table 1). Typically, as observed in this case, examination demonstrates pigmentary changes, drusenoid deposits, as well as areas of atrophy that most significantly impact the posterior pole. *Mano* et al.[4] recently reported on 11 patients with systemic amyloidosis (3 with AL and 8 with ATTR) and proposed a grading scheme based on OCT and indocyanine green angiography (ICG) findings to classify the severity of choroidal involvement. The authors established that more severe stages of amyloid choroidopathy correlated with worse clinical scores of systemic disease. Similar to some prior reports,[5,7] macular OCT in our patient revealed a thickened sub-RPE/Bruch's hyporeflective band associated with relatively thickened choroid and thinning of the ONL.

The angiographic dark choroid was initially described by *Bonnin* et al.[8] in patients with macular dystrophies, and they proposed two possible explanations of this phenomenon: first, abnormal deposition of pathologic material blocking the transmission of the choroidal fluorescein signal, and second, non-filling of the choroid. The authors rejected the first possibility, reasoning that diffuse material accumulation underneath the retina, RPE, or Bruch's membrane would be visible on fundoscopy, which they had not observed. Subsequently, *Fish* et al.[9] examined 91 patients with posterior retinal dystrophies, 41% of whom had evidence of the dark choroid sign on fluorescein angiography. Their conclusion favored the first possibility that was described and rejected by *Bonnin* et al.; specifically, that accumulation of material absorbing the light in blue-green spectrum resulted in blocked choroidal fluorescence and explained the angiographic dark choroid sign. They also posited that choroidal non-filling would lead to severe outer retina pathology which was not seen clinically or functionally.[9]

Although retinochoroidal involvement in systemic amyloidosis represents a different pathologic process from that seen in inherited macular disorders, the potential explanation of the angiographic dark choroid sign in the former follows the same possibilities: blockage of signal from choroidal dye, or lack/diminution of dye perfusing through the choroidal circulation. Histopathologic reports and *in vivo* multimodal imaging raise the possibility that both factors may actually be involved. On histopathology, significant choriocapillaris amyloid deposition has been identified in patients with systemic amyloidosis as well as occlusion of some of the choriocapillaris vasculature.[10] The widened choriocapillaris hyporeflective band seen on our patient's OCT imaging may represent amyloid protein deposition capable of limiting choroidal fluorescein signal transmission. OCT-angiography (OCT-A) findings of diminished choroidal circulation have also been reported in amyloidosis, which may corroborate histopathologic findings of choriocapillaris occlusion.[7]

FA findings in systemic amyloidosis were first described in a single report by *Pece* et al.[6] and consisted of areas of hypofluorescence as well as hyperfluorescent streaks in the peripapillary region. However, no diffuse attenuation of choroidal background fluorescence was observed. Given significant variation in findings among clinical reports as well as among histopathologic studies, it appears that retinochoroidal involvement in systemic amyloidosis is a heterogeneous process. Such

heterogeneity could arise from the differences in the specific pathologic amyloid protein as well as from the differences in specific mutation of the same amyloid protein. As suggested by *Mano* et al.,[4] the retinochoroidal amyloidopathy is likely not a specific condition but rather a disease continuum of different severity levels. Furthermore, one needs to take into the account that most patients with reported retino-choroidal involvement in systemic amyloidosis often have advanced renal disease which might have contributed to amyloid-induced pathology.

In conclusion, in this report we describe a rare finding of angiographically dark choroid in a patient with advanced systemic non-hereditary amyloidosis. Dark choroid has been described prior in various inherited retinal disorders, but not in relation to a systemic condition. The pathophysiology of the observed finding is unclear, but may be related to blocked choroidal fluorescence as well as a possible contribution of choroidal vascular hypoperfusion. A limitation of our report is that ICG was not available to better discern between these possibilities. Further studies in patients with systemic amyloid disease carefully assessing structural retinal and choroidal changes and alteration in their vasculature using multimodal approach with OCT, FA, ICG and OCT-A may shed more light on the pathophysiology of this condition.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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