Angiographic dark choroid in systemic non-hereditary amyloidosis

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A R T I C L E   I N F O

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A B S T R A C T

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 subretinal 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.

Conclusion and 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 non-branching appearance on electron microscopy. 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.

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). 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) while others are recognized as primary localized hereditary amyloidoses (e.g. Gelatinous Drop-Like Dystrophy, Lattice Corneal Dystrophy Type II’).

Intraocular involvement in amyloidosis is most commonly seen as vitreous amyloidosis that typically occurs in familial transthyretin protein amyloidosis (ATTR). Reynolds et al. 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...
series. In general, involvement of the retina or the choroid is not typical in systemic amyloidosis with a limited number of cases reported. 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 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.)
examined 91 patients with posterior retinal dystrophies, 41% of whom
OD and 329 μm OS with a widened hyporeflective sub-Bruch’s chorio-
capillaris band measuring 32 μm OD and 35 μm OS (Fig. 11 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. 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, 5,7,10
macular OCT in our patient revealed a thickened sub-RPE/Bruch’s hypofl uorescent
band associated with relatively thickened choroid and thinning of the
ONL.

The angiographic dark choroid was initially described by Bonnin
et al. 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 fluores-
ccein signal, and second, non-filling of the choroid. The authors rejected
the first possibility, reasoning that diffuse material accumulation unde-
neath the retina, RPE, or Bruch’s membrane would be visible on
fundoscopy, which they had not observed. Subsequently, Fisch et al. 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 fluores-
cence and explained the angiographic dark choroid sign. They also
posit ed that choroidal non-filling would lead to severe outer reti na pa-
thology which was not seen clinically or functionally.9

Although retinochoroidal involvement in systemic amyloidosis rep-
resents a different pathologic process from that seen in inherited mac-
ular 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 multi-
modal imaging raise the possibility that both factors may actually be
involved. On histopathology, significant choricapillaris amyloid
deposition has been identified in patients with systemic amyloidosis as
well as occlusion of some of the choriocapillaris vasculature.10,11
The widened choriocapillaris hypofluorescent band seen on our patient’s OCT
imaging may represent amyloid protein deposition capable of limiting
choroidal fluorescenc 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.12

FA findings in systemic amyloidosis were first described in a single
report by Pece et al. 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 retinchoroidal involve-
ment in systemic amyloidosis is a heterogeneous process. Such

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

| Demographics | Amyloidosis type | Fundoscopy | FA/A \(^a\) | OCT \(^b\) | FA/ICG \(^c\) |
|--------------|----------------|------------|-----------|----------|---------------|
| 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 underlying 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; hypoafluorescence 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: pigmented motting, 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 cryopyrin-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), transthyrein amyloidosis (7 patients, 6 with familial and 1 with wild-type transthyrein), 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 microaneu rms 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; hypoafluorescence in areas of atrophy | Thickened choriocapillaris band; thickened choroid; thinned ONL | FA: angiographically dark or “silent” choroid; peripheral microaneu rms. ICG: not available |

\(^{a}\) FA, fundus autofluorescence.

\(^{b}\) OCT, optical coherence tomography.

\(^{c}\) FA, fluorescein angiography.

\(^{d}\) ICG, indocyanine green angiography.
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., 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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