

Long-term follow-up of a case of amyloidosis-associated chorioretinopathy

Koichi Nagura^{a,b}, Tatsuya Inoue^{a,*}, Jared Ching^c, Akinori Sato^a, Shohei Kitahata^a,
Maiko Maruyama-Inoue^a, Masaru Takeuchi^b, Kazuaki Kadonosono^a

^a Department of Ophthalmology and Micro-Technology, Yokohama City University, Kanagawa, Japan

^b Department of Ophthalmology, National Defense Medical College, Saitama, Japan

^c Department of Ophthalmology, Addenbrookes Hospital, Cambridge, UK

ARTICLE INFO

Keywords:

Amyloidosis

Chorioretinopathy

ABSTRACT

Purpose: To describe the findings of long-term follow-up of a case of amyloidosis-associated chorioretinopathy by multimodal imagings, including optical coherence tomography (OCT).

Observations: A 47-year-old woman who had been diagnosed as having systemic amyloidosis was found to have a best corrected visual acuity of 20/13 in both eyes at the age of 41, which subsequently decreased to 20/100 in the left eye and 20/20 in the right eye at age 47. Visual field examination demonstrated worsening of the central scotoma during the follow-up period. Funduscopy examination revealed bilateral white deposits along the choroidal vessels, which became more pronounced over time, along with diffuse pigmentary changes. The fluorescein angiography and indocyanine green angiography findings were consistent not only with atrophic lesions, but also with amyloid deposition (i.e., staining of the vessels).

At the baseline, macula OCT revealed a thick hyporeflective band at the choriocapillaris, however, at the last follow-up, it revealed an absent ellipsoid zone, and bilateral progressive retinal pigment epithelium irregularities in both eyes.

Conclusions: Patients diagnosed as having amyloidosis-related chorioretinopathy may have maintained visual function at the first detection of retinal amyloid deposition, and a number of years may elapse before the patient manifests visual deterioration.

1. Introduction

Amyloidosis is a clinical disorder characterized by extracellular deposition of insoluble abnormal fibrils in a variety of tissues.¹ The fibrils are derived from misfolded proteins that are usually soluble in their native state. Amyloidosis is classified into two major forms, localized and systemic. In localized amyloidosis, intercellular and/or extracellular amyloid deposition occurs in the organ or tissue in which the precursor protein is synthesized. In contrast, in systemic amyloidosis, the deposition is exclusively extracellular, with the precursor protein secretion occurring at a site distant from the major tissues of deposition, usually in multiple organs.² Systemic amyloidosis has historically been classified as primary (AL) or secondary (AA), depending on the biochemical properties of the protein itself.³ AL amyloidosis is generally considered as being idiopathic or caused by multiple myeloma, and is often associated with the deposition of AL amyloid fibrils formed of aggregates of

misfolded light chains. In contrast, reactive AA amyloidosis occurs secondary to chronic diseases such as diabetes, rheumatoid arthritis, chronic infections, and inflammatory bowel disease, where elevated serum amyloid A is converted to amyloid fibrils.^{4,5}

In a recent case of amyloidosis encountered by us, amyloidosis was associated with chorioretinopathy, and OCT showed a thick hyporeflective choriocapillaris band in the chorioretinal area.^{6,7} To the best of our knowledge, there are no reports of long-term observation of amyloidosis patients with ocular manifestations in the literature to date. Herein, we present the first report of long-term follow-up of a case of amyloidosis-associated chorioretinopathy by imaging studies, including OCT.

2. Case report

A 47-year-old female patient who had been diagnosed as having

* Corresponding author. Department of Ophthalmology and Micro-Technology, Yokohama City University, 4-57 Urafune, Minami-ku, Yokohama, 232-0024, Japan. Tel.: +81 45 253 5372; fax: +81 45 253 8490.

E-mail address: inouet-ky@umin.ac.jp (T. Inoue).

<https://doi.org/10.1016/j.ajoc.2020.100846>

Received 1 June 2020; Received in revised form 15 July 2020; Accepted 26 July 2020

Available online 2 August 2020

2451-9936/© 2020 The Authors.

Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

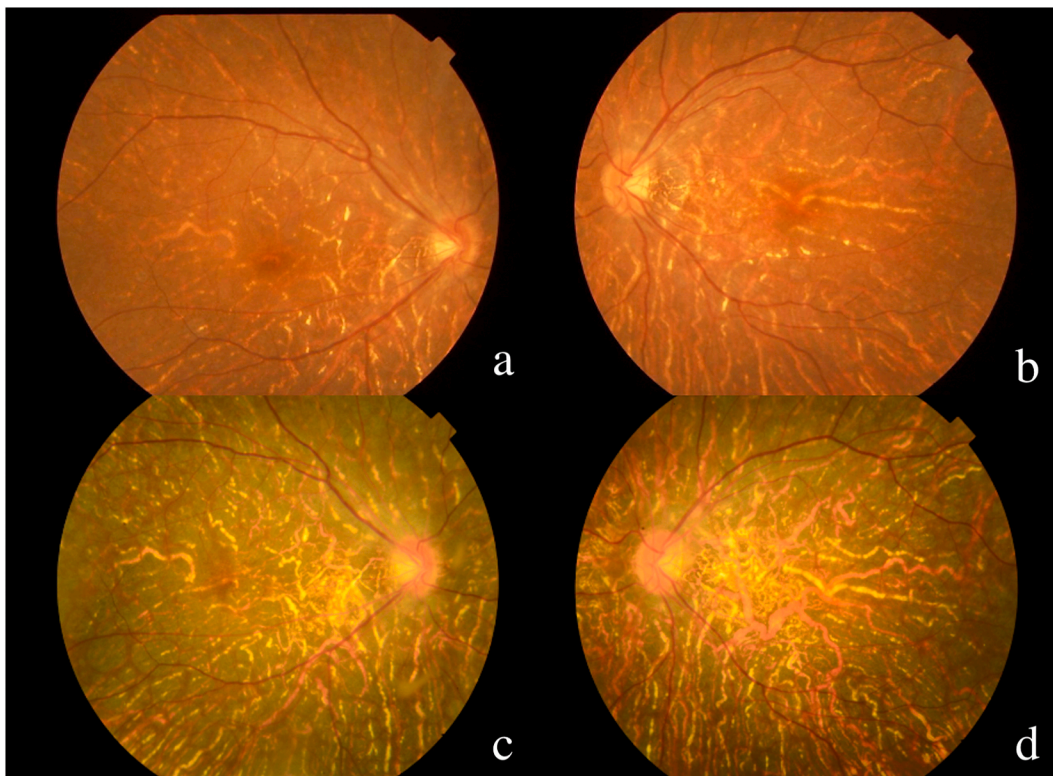


Fig. 1. Fundus photographs showing white deposits along the choroidal vessels in both eyes at the baseline (a, b). The white deposits were more pronounced at the last examination (c, d).

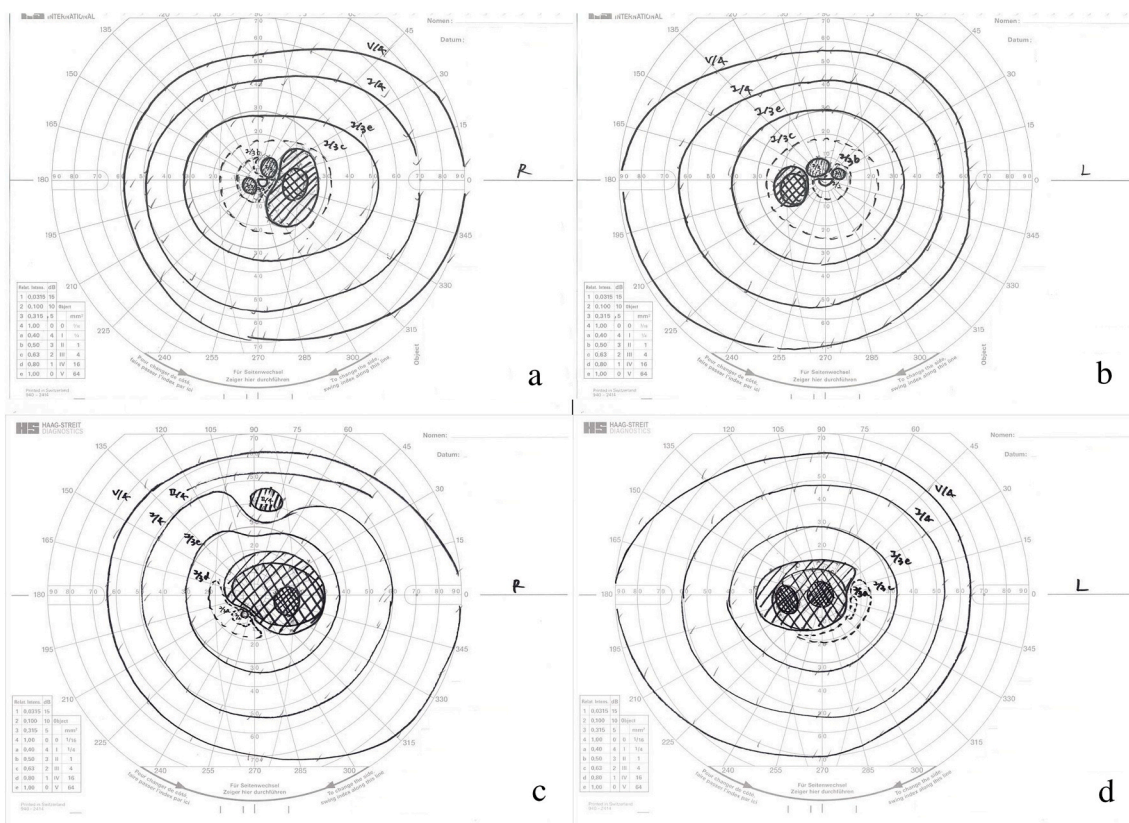


Fig. 2. Goldmann visual field testing demonstrated central scotomata in both eyes at the baseline (a, b) and bilateral enlargement of the scotomata at the last examination (c, d).

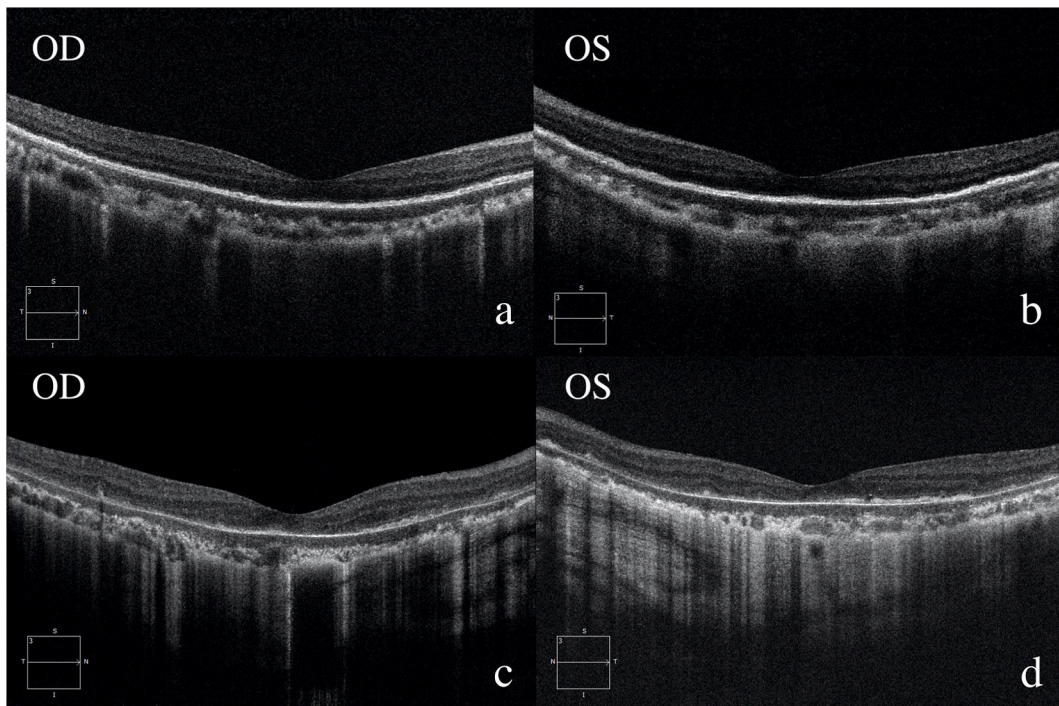


Fig. 3. Macular OCT images at the baseline (a, b) and at the last examination (c, d). Changes in the ellipsoid zone in both eyes are observed, along with atrophy of the outer retina.

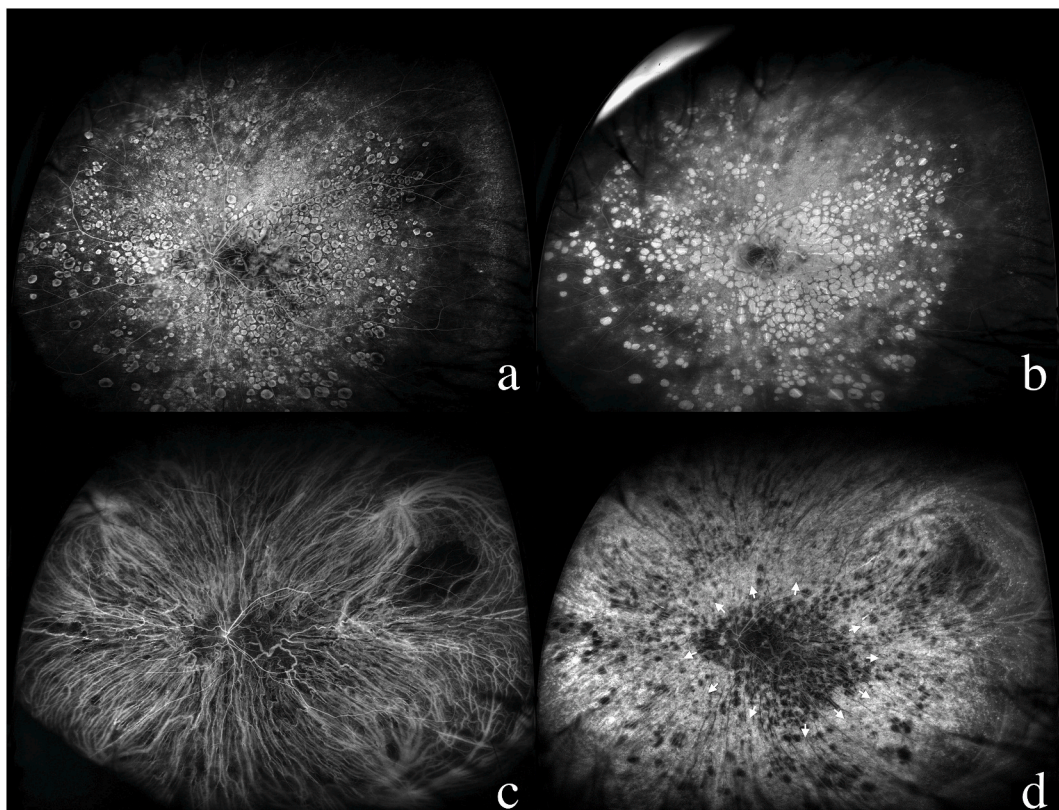


Fig. 4. FA and ICGA in amyloidosis-associated chorioretinopathy, which were performed when the patient was 47 years old. FA demonstrated hyperfluorescence in the location of the pigmentary changes (a; early phase of FA; b: late phase of FA). ICGA demonstrated hypofluorescence in the same region, hyperfluorescent lines along the choroidal vessels, hyperfluorescent pinpoints of leakage, and fleecy lesions (white arrow) in the periphery (c: early phase of ICGA; d: late phase of ICGA). FA: fluorescein angiography, ICGA: indocyanine green angiography.

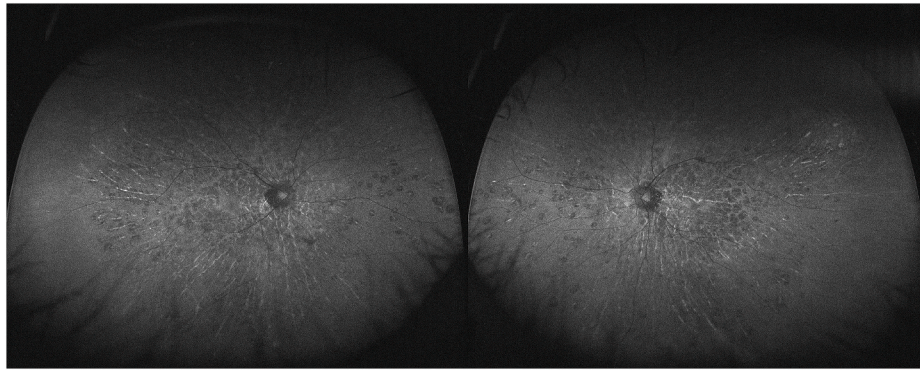


Fig. 5. FAF images in amyloidosis-associated chorioretinopathy. FAF imaging performed when the patient was 47 years old showed hypofluorescent scattered signals in the posterior pole in both eyes, consistent with the atrophic lesion on fundus examination. FAF: fundus autofluorescence.

systemic amyloidosis secondary to Crohn's disease when she was 25 years old presented to the Ophthalmology Clinic with a history of photophobia and impaired color vision. Her baseline best corrected visual acuity (BCVA) was 20/13 in both eyes at the age of 41 years. Corneal amyloid deposits were absent in both eyes on slit-lamp biomicroscopy, and the intraocular pressure was also normal in both eyes. There was no evidence of optic disc edema, peripapillary hemorrhages or cotton-wool spots on fundus examination. However, both eyes showed white deposits along the choroidal vessels (Fig. 1a and b), which became more and more pronounced with time during the follow-up period, eventually resulting in choroidal atrophy (Fig. 1c and d). The BCVA then deteriorated gradually to 20/16 by age 42 and to 20/20 by age 45. Subsequently, the BCVA deteriorated to 20/40 in the left eye by age 46 years, and to 20/100 in the left eye by age 47 years, while the BCVA in the right eye has continued at 20/20 until the present. Goldman visual field examination demonstrated bilateral central scotomata, which also appeared to progress over time (Fig. 2). At the baseline, macula OCT revealed a thick hyporeflective band at the level of the choriocapillaris, but no other abnormalities. However, macular OCT at the final visit revealed an absent ellipsoid zone (EZ), progressive retinal pigment epithelium (RPE) irregularities, and substantial thinning of the outer nuclear layer bilaterally. The central retinal thickness decreased from 145 μm at the baseline to 117 μm at the final visit. The central choroidal thickness and thickness of the hyporeflective band also decreased from 221 μm to 80 μm at the baseline to 166 μm and 68 μm at the final examination, respectively (Fig. 3).

Amyloid related abnormalities were found on fluorescein angiography (FA) and indocyanine green angiography (ICGA), which were performed when the patient was 47 years old. FA demonstrated hyperfluorescence in the same location as the pigmentary changes (Fig. 4b), whilst ICGA demonstrated hypofluorescence in the same region, hyperfluorescent lines along the choroidal vessels, hyperfluorescent pinpoint of leakage, and fleecy lesions in the periphery (Fig. 4d). Fundus autofluorescence imaging (FAF) also demonstrated patchy hypoautofluorescence at the macula, with hyperautofluorescent streaks (Fig. 5).

3. Discussion

Amyloidosis is known to cause a wide variety of ocular lesions.⁸ Common ocular manifestations of amyloidosis include amyloid deposition in the ocular adnexa, conjunctiva, cornea, trabecular meshwork and/or the vitreous, however retinal and choroidal involvement is rare.^{9–16} Histopathological analysis of amyloid deposition in the choroid has been reported in cases of systemic primary amyloidosis.^{17–20}

The authors found amyloid deposits in the choriocapillaris and choroidal vessels, but not in the retinal vessels. Further, the large choroidal vessel walls were thickened due to amyloid accumulation and

most of the choriocapillaris in the macula was occluded by amyloid deposits.

In the past, ICGA was adopted for the diagnosis and evaluation of amyloidosis chorioidopathy, with reports of the findings in cases of non-familial amyloidosis.²¹ Identification of pinpoint, fleecy and streak-like patterns of hyperfluorescence along the choroidal vessels in the late phase of ICGA has been reported, suggesting the presence of deposits in the choriocapillaris stroma, RPE and choroidal vessels. Furthermore, hypofluorescence in the macula in the late ICGA phase, may be suggestive of choroidal vascular occlusion secondary to amyloidosis.^{21,22} These findings are consistent with the findings in our patient reported here.

The specific combination of pachychoroid features and a widened choriocapillaris was first reported by Roybal et al. in a case series of 4 patients with systemic amyloidosis.⁷ Characteristic features of amyloid-associated chorioretinopathy on spectral domain OCT include a widened choriocapillaris band, choroidal infiltration and thinning of the outer nuclear layer, and these changes were associated with a decline in visual function. The authors surmise that amyloid infiltration and occlusion may disturb the RPE and photoreceptor function and eventually lead to outer retinal atrophy.

In contrast, in one case of choroidal amyloidosis, supported by the histopathological findings, extensive obstruction of the choriocapillaris was found with sparing of the retinal vessels and intact visual acuity.²³ This patient was asymptomatic, and the overlying retina was reported as morphologically normal.

Therefore, whilst the characteristic chorioretinal changes of amyloidosis-associated chorioretinopathy have been elucidated, the changes in the retinal findings over time have remained unknown.

To the best of our knowledge, ours is the first report of long-term follow-up of a patient with amyloidosis-associated chorioretinopathy; the patient showed gradual visual loss corresponding to the pathological changes over time observed by multi-modal imaging, including macula OCT. Our long-term observations revealed gradual EZ and RPE irregularities along with atrophy of the outer retina.

4. Conclusions

Long-term follow-up of our patient with amyloidosis-related chorioretinopathy suggested that the visual function may be intact at the time of detection of retinal amyloid deposition, and that a number of years may elapse before visual deterioration becomes manifest.

4.1. Informed consent

Written informed consent to publish the case report was not obtained, although the patient provided oral consent for publication. This report does not contain any personal information that could lead to

identification of the patient.

Funding

No funding or grant support.

Declaration of competing interest

The following authors have no financial disclosures to make:

References

1. Pepys MB. Amyloidosis. *Annu Rev Med*. 2006;57(1):223–241.
2. Blancas-Mejia LM, Ramirez-Alvarado M. Systemic amyloidosis. *Annu Rev Biochem*. 2013;82:745–774. <https://doi.org/10.1146/annurev-biochem-072611-130030>.
3. Serra I, Oller B, Manosa M, et al. Systemic amyloidosis in inflammatory bowel disease: retrospective study on its prevalence, clinical presentation, and outcome. *J Crohns Colitis*. 2010;4(3):269–274. <https://doi.org/10.1016/j.crohns.2009.11.009>.
4. Westermarck P, Benson MD, Buxbaum JN, et al. Amyloid: toward terminology clarification. Report from the nomenclature committee of the international society of amyloidosis. *Amyloid*. 2005;12(1):1–4. <https://doi.org/10.1080/13506120500032196>.
5. Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid diseases. *Biochim Biophys Acta*. 2005;1753(1):11–22. <https://doi.org/10.1016/j.bbapap.2005.08.014>.
6. Reynolds MM, Veverka KK, Gertz MA, et al. Ocular manifestations of systemic amyloidosis. *Retina*. 2018;38(7):1371–1376. <https://doi.org/10.1097/IAE.0000000000001901>.
7. Roybal CN, Sanfilippo CJ, Nazari H, et al. Multimodal imaging of the retina and choroid in systemic amyloidosis. *Retin Cases Brief Rep*. 2015;9(4):339–346. <https://doi.org/10.1097/ICB.0000000000000215>.
8. Hashemian H, Jabbarvand M, Khodaparast M, Khalilipour E, Esfehiani HR. Ocular presentations of amyloidosis. *Amyloidosis*. 2013:85.
9. Leibovitch I, Selva D, Goldberg RA, et al. Periocular and orbital amyloidosis: clinical characteristics, management, and outcome. *Ophthalmology*. 2006;113(9):1657–1664.
10. Mora-Horna ER, Rojas-Padilla R, López VG, Guzmán MJ, Ceriotta A, Salcedo G. Ocular adnexal and orbital amyloidosis: a case series and literature review. *Int Ophthalmol*. 2016;36(2):281–298.
11. Tei M, Maruko I, Uchimura E, Iida T. Retinal and choroidal circulation determined by optical coherence tomography angiography in patient with amyloidosis. *BMJ Case Rep*. 2019;12(2). <https://doi.org/10.1136/bcr-2018-228479>.
12. Ando T, Oshitari T, Saito M, et al. A Case of Conjunctival Amyloidosis with Repeated Subconjunctival Hemorrhage. vol. 2017. Case reports in ophthalmological medicine; 2017.
13. Nelson GA, Edward DP, Wilensky JT. Ocular amyloidosis and secondary glaucoma. *Ophthalmology*. 1999;106(7):1363–1366.
14. Azari AA, Kanavi MR, Girgis D, Saïpe N, Potter HD, Albert DM. Amyloid deposits in temporal artery mimicking temporal arteritis in a patient with multiple myeloma. *JAMA ophthalmology*. 2013;131(11), 1488–1488.
15. Sandgren O. Ocular amyloidosis, with special reference to the hereditary forms with vitreous involvement. *Surv Ophthalmol*. 1995;40(3):173–196.
16. Cheung CMG, Cheng CL, Farzavandi S. Retinal and choroidal angiopathy and electrophysiological disturbance in a case of amyloid AA. *Eye*. 2010;24(6):1117–1119.
17. Ts'o MO, Bettman JW. Occlusion of choriocapillaris in primary nonfamilial amyloidosis. *Arch Ophthalmol*. 1971;86(3):281–286.
18. Schwartz MF, Green WR, Michels RG, Kincaid MC, Fogle J. An unusual case of ocular involvement in primary systemic nonfamilial amyloidosis. *Ophthalmology*. 1982;89(4):394–401.
19. Paton D, Duke JR. Primary familial amyloidosis*: ocular manifestations with histopathologic observations. *American journal of ophthalmology*. 1966;61(4):736–747.
20. Kawaji T, Ando Y, Nakamura M, et al. Ocular amyloid angiopathy associated with familial amyloidotic polyneuropathy caused by amyloidogenic transthyretin Y114C. *Ophthalmology*. 2005;112(12), 2212–e1.
21. Attia S, Kahloun R, Mbarek S, et al. Indocyanine green angiography findings in patients with nonfamilial amyloidosis. *Journal of ophthalmic inflammation and infection*. 2012;2(4):199.
22. Pece A, Yannuzzi L, Sannace C, Sforzolini BS, Brancato R. Chorioretinal involvement in primary systemic nonfamilial amyloidosis. *American journal of ophthalmology*. 2000;130(2):250–253.
23. Juarez C, Jampol LM, Serjeant G. Choroidal amyloidosis: a case report. *Perspectives in Ophthalmology*. 1979;3(2):141–145.