



Contrasting presentations of the same disease: A comparison of two cases of amyloidosis presenting with eyelid involvement

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ABSTRACT

Purpose: Localized amyloidosis can affect numerous tissues throughout the body and can also affect a variety of peri-ocular tissues including the conjunctiva, extra-ocular muscles, peri-orbital soft tissue, and lacrimal gland. We report two cases of amyloidosis presenting with eyelid involvement.

Observations: The first case represented a more subtle presentation of skin thickening with a pre-septal cellulitis, while the second case had a dramatic presentation of edema evolving into tissue dehiscence and spontaneous hemorrhage with ongoing angioedema and systemic coagulopathy.

Conclusions and importance: The two cases of biopsy-proven orbital/peri-ocular amyloidosis demonstrate the different clinical presentations that may go from the subtle to dramatic, depending on which peri-ocular tissues are affected and to what degree. Standards for treatment of amyloidosis remain conservative initially with surgery or radiation recommended only for refractory cases, but additional therapies are under investigation. Clinicians should have high clinical suspicion for amyloidosis with findings such as skin thickening or significant periorbital edema and should always consider tissue biopsy and further workup for amyloidosis if the findings worsen or do not resolve with treatment of more common conditions such as cellulitis.

1. Introduction

Amyloidosis is a rare disease, which infrequently presents with involvement of the eyelid. We report two unique cases of biopsy-proven amyloidosis of the eyelid with starkly contrasting clinical features at the time of presentation; one presenting with mild eyelid skin thickening and the other with rapid eyelid hemorrhaging. These case reports serve to illustrate the variability to which amyloidosis with eyelid involvement can present.

2. Findings

2.1. Case 1

A 76-year-old Caucasian male without any significant past medical history presented to the emergency department with a 1-week history of worsening edema and erythema of his face and neck. His symptoms began after he sustained an abrasion of his right cheek while shaving.

At presentation he was noted to have significantly more right sided than left sided periorbital edema, erythema, and generalized facial, neck, and upper chest edema (Fig. 1). He complained of tenderness to palpation around the right orbit. A CT scan of the orbits revealed peri-orbital swelling without orbital involvement. The remainder of his ophthalmologic evaluation was unremarkable. Systemic workup showed leukocytosis (initial white blood cell count of 22,200/mm³), negative blood cultures, and slightly prolonged prothrombin time (16.5 sec).

He was treated with 14 days of broad-spectrum IV antibiotics (clindamycin) and topical erythromycin ointment for presumed pre-septal cellulitis. He also received methylprednisolone, dexamethasone, famotidine, and diphenhydramine for possible allergic reaction or angioedema causing his neck edema. He was discharged several days later with significant improvement in his edema as the presumed cellulitis component resolved. He was seen in follow up and was noted to have mild myogenic ptosis of the right upper eyelid and right upper and lower eyelid skin thickening with a yellow tinge (Fig. 2). A biopsy of the right

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Fig. 1. Case 1 – Initial Presentation. Significantly more right sided than left sided periorbital edema, and erythema.



Fig. 2. Case 1 – Follow Up. Significant improvement in his edema after treatment with broad-spectrum IV antibiotics and topical erythromycin. Mild myogenic ptosis of the right upper eyelid and right upper and lower eyelid skin thickening with a yellow tinge. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

upper eyelid skin was obtained and showed skin and subcutaneous tissue with chronic inflammation and focal minute deposits of amyloid, that demonstrated apple-green birefringence with polarized light on Congo red stain. The minimal amount of amyloid present prevented any further studies for amyloid typing.

At the time of this report, the patient is undergoing further evaluation for systemic amyloidosis with echocardiography, abdominal fat biopsy, and bone marrow biopsy prior to initiation of therapy.

2.2. Case 2

An 81-year-old African American female with a past medical history of MGUS and intermittent facial/periorbital swelling presented to the emergency department with worsening bilateral periorbital edema, periorbital edema, and upper and lower eyelid ecchymosis, worse on the

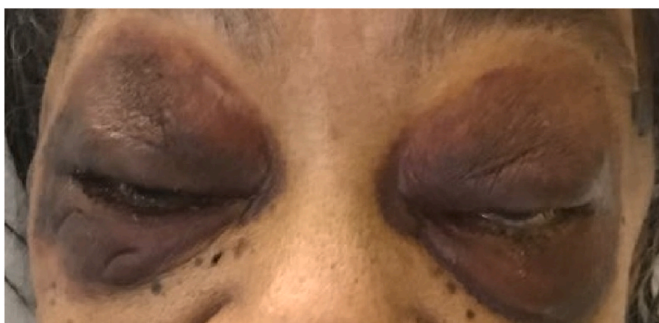


Fig. 3. Case 2 – Initial Presentation. Facial and periorbital swelling, bilateral periorbital edema, and upper and lower eyelid ecchymosis, worse on the right than on the left.

(Fig. 3). Intraocular pressures were elevated to the 40s bilaterally. She also noted recent worsening of recurrent dysphagia and hoarseness. She had been seen intermittently in the eye clinic for periorbital swelling and bilateral restrictive strabismus but had not returned for several years. The patient was noted to have tense, bullous edema and ecchymosis of the right upper and lower eyelids and mild edema of the left upper and lower eyelids.

With minimal manipulation of the eyelids, edema and ecchymosis rapidly progressed bilaterally, resulting in spontaneous soft tissue dehiscence and hemorrhaging of the right upper eyelid (Fig. 4). The patient was taken to the operating room emergently for debridement and exploration. Hemostasis was achieved, and a biopsy specimen of the right upper eyelid showed skin and subcutaneous tissue with hemorrhage and abundant amorphous eosinophilic material (Fig. 5). The material stained in a pale red/orange color on Congo Red special stain and showed apple-green birefringence under polarizing microscopy, confirming the presence of amyloid (Fig. 6). Additional workup revealed a systemic coagulopathy with low fibrinogen, thrombocytopenia, elevated fibrin split products, and elevated D-dimer which was thought to be secondary to systemic involvement of amyloidosis. C1 inhibitor protein levels, factor X activity, and thromboelastometry were all normal. Blood cultures and a respiratory culture and gram stain were also negative.

The patient subsequently was found to be hyper somnolent and unable to protect her airway. Attempted intubation was unsuccessful secondary to angioedema and upper airway bleeding, with friable tissue also concerning for amyloid involvement. An emergent tracheostomy was performed and the patient received dexamethasone for the angioedema and cryoprecipitate for her coagulopathy. Due to her open periorbital wounds, altered mental status, and intermittent hypotension, the patient was started on empiric antibiotics with vancomycin and piperacillin-tazobactam. A subsequent video swallow study showed silent aspiration. After goals of care discussions with the patient's family, the patient was transitioned to hospice care. She passed away several months later, presumably from complications of aspiration.

3. Discussion

Amyloidosis represents a spectrum of diseases characterized by extracellular deposition of hyaline material in various tissues throughout the body.¹ Greater than 20 such proteins, which aggregate into misfolded, insoluble fibrils, have been identified. Amyloidosis can be classified as either localized or systemic.² Systemic amyloidosis, which is more common than localized amyloidosis, involves widespread deposition of proteins such as immunoglobulin light or heavy chains, transthyretin, serum amyloid A, apolipoprotein A-I, beta-2 microglobulin, and leukocyte chemotactic factor-2. Transthyretin amyloidosis and familial amyloidosis are two types of systemic amyloidosis that



Fig. 4. Case 2 – Spontaneous Hemorrhage. Spontaneous soft tissue dehiscence and hemorrhaging of the right upper eyelid after minimal manipulation of the eyelids.

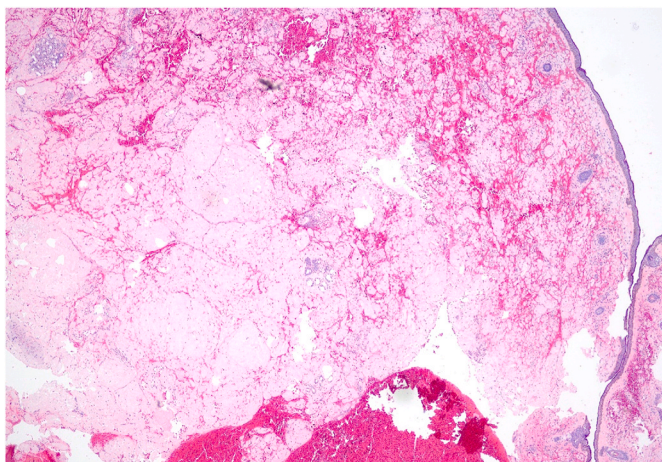


Fig. 5. Case 2– Hematoxylin-eosin staining. Hematoxylin-eosin staining reveals areas of hemorrhage and abundant homogenous amorphous eosinophilic material (H&E X40).

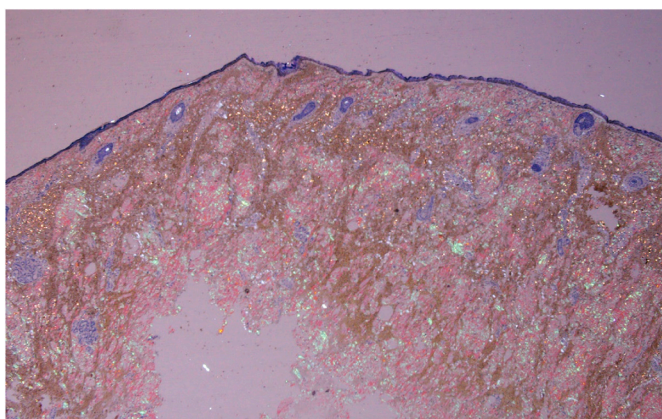


Fig. 6. Case 2 – Congo Red Stain. Polarized microscopy reveals the characteristic apple-green birefringence of the amyloid deposits (Congo Red x 100). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

more frequently involve the eye.³ In contrast, localized amyloidosis is most frequently characterized by local deposition of immunoglobulin light chains (usually kappa or lambda) and is referred to as localized light chain amyloidosis.⁴ Localized amyloidosis can affect numerous tissues throughout the body, including the eyelid/peri-ocular structures, cardiac atrea, larynx, ureter, and skin.

Amyloid affecting ocular and peri-ocular structures is rare and was first reported by Zimmerman and Smith in 1966.⁵ Peri-ocular/orbital amyloidosis can affect a variety of peri-ocular tissues including the conjunctiva, extra-ocular muscles, peri-orbital soft tissue, and lacrimal gland. It can present in a variety of ways, with the most common signs and symptoms being an eyelid mass or tissue infiltration and resultant ptosis. However, masses and tissue thickening or edema have been reported in varied sites such as the conjunctiva, tarsal plate, and lacrimal gland. Even more rarely, amyloid can deposit along vessels in the choroid and retina.⁶

Less frequent presentations include pain, proptosis, motility deficits, and diplopia (secondary to mass effect or infiltration of extra ocular muscles), and subcutaneous hemorrhage or purpura.^{7–10} Acquired hemostatic disorders have been reported to cause bleeding in systemic amyloidosis, providing a possible explanation for the hemorrhage seen in Case 2. Compressive and infiltrative optic neuropathies are rare.^{11,12} The cases described serve to illustrate the wide variability of presenting

symptoms and symptom severity, with one patient presenting with rapidly progressive periocular hemorrhage requiring emergent surgical intervention, and the other presenting with acute periorbital edema followed by chronic eyelid thickening and mechanical ptosis.

The gold standard for the diagnosis of amyloidosis is tissue biopsy, with the sample showing the characteristic apple-green birefringence when stained with Congo-red. Additional pathologic and histologic characteristics of amyloid include metachromasia with crystal violet dye, fluorescence with thioflavin T staining under ultraviolet light, and the presence of a typical filamentous appearance when examined under electron microscopy.¹³ Communication with the pathologist prior to biopsy is crucial. Discussing the possibility of amyloid prior to obtaining the biopsy can guide the surgeon in determining the amount of tissue needed for diagnosis and can aid the pathologist in implementing the proper staining and examination techniques. Time to diagnosis can be crucial, as demonstrated by Case 2 in which early referral to hematology and likely systemic therapy probably would have altered the disease course.

The mainstays of conservative management for orbital/peri-ocular amyloidosis include observation, lubrication, protection of ocular surface, and management of secondary intra-ocular pressure elevation (both medically and surgically).⁷ As in Case 1, patients presenting with concomitant infection such as pre-septal cellulitis should additionally receive a standard antibiotic regimen. Refractory cases may be managed with surgical debulking.⁷ Recently, the use of external beam radiation (either alone or in conjunction with surgical debulking) has shown some success in small case series.¹³

Novel therapeutic approaches for ocular amyloidosis target the various tissues affected. For conjunctival amyloidosis, liquid nitrogen cryotherapy has been studied as an adjunct to surgical excision.¹⁴ Amyloidosis presenting with vitreous opacities, such as in transthyretin amyloidosis, should be managed with primary complete, extensive vitrectomy with scleral depression.¹⁵ Laser therapy with retinal photocoagulation has also been performed for retinal and vitreous amyloid deposits.¹⁶ A number of treatments are also under investigation for systemic amyloidosis. Oral proteasome inhibitors (e.g., ixazomib) are being studied for refractory or relapsed systemic primary amyloidosis.¹⁷ Studies of monoclonal antibodies that bind to amyloid proteins have been less promising.¹⁸ Other systemic therapies in trials include a small molecule stabilizer of the transthyretin tetramer and intravenous siRNA and anti-sense oligonucleotides which can reduce transthyretin production.^{19–21}

4. Conclusions

The two cases of biopsy-proven orbital/peri-ocular amyloidosis described above serve to illustrate the wide-ranging variability of presentation of this rare disease. Clinical presentation may go from the subtle to dramatic, depending on which peri-ocular tissues are affected and to what degree. As demonstrated by the above cases, identification of amyloidosis as a diagnosis requires the clinician to have high clinical suspicion and a tissue biopsy done early. The variability of presentation, coupled with lack of exposure to the disease, due to its rarity and relative paucity of literature available, can contribute to missed/delayed diagnoses. Delayed diagnosis may lead to progression of the disease and significant visual and systemic sequelae, as is especially evident by the clinical course of the patient in case 2. While rare, amyloidosis should be considered in patients who present with a variety of orbital and peri-ocular findings as outlined above.

Patient consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

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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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References

- Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2012 recommendations from the nomenclature committee of the International Society of amyloidosis. *Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis*. 2012;19(4):167–170. <https://doi.org/10.3109/13506129.2012.734345>.
- Pepys MB. Amyloidosis. *Annu Rev Med*. 2006;57:223–241. <https://doi.org/10.1146/annurev.med.57.121304.131243>.
- Badar T, D'Souza A, Hari P. Recent advances in understanding and treating immunoglobulin light chain amyloidosis. F1000 Faculty Rev-1348. Published 2018 Aug 29 *F1000Res*. 2018;7. <https://doi.org/10.12688/f1000research.15353.1>. Google Search. Accessed July 21, 2022 https://www.google.com/search?q=Badar+T%2C+D%27Souza+A%2C+Hari+P.+Recent+advances+in+understanding+and+treating+immunoglobulin+light+chain+amyloidosis.+F1000Res.+2018%3B7%3AF1000+Faculty+Rev-1348.+Published+2018+Aug+29.+doi%3A10.12688%2Ff1000research.15353.1&rlz=1C5CHFA_enUS913US913&oq=Badar+T%2C+D%27Souza+A%2C+Hari+P.+Recent+advances+in+understanding+and+treating+immunoglobulin+light+chain+amyloidosis.+F1000Res.+2018%3B7%3AF1000+Faculty+Rev-1348.+Published+2018+Aug+29.+doi%3A10.12688%2Ff1000rese arch.15353.1&aqs=chrome..69i57.665j0j7&sourceid=chrome&ie=UTF-8.
- Merlini G, Westermarck P. The systemic amyloidoses: clearer understanding of the molecular mechanisms offers hope for more effective therapies. *J Intern Med*. 2004; 255(2):159–178. <https://doi.org/10.1046/j.1365-2796.2003.01262.x>.
- Smith ME, Zimmerman LE. Amyloidosis of the eyelid and conjunctiva. *Arch Ophthalmol Chic Ill*. 1960;75(1):42–51. <https://doi.org/10.1001/archophth.1966.00970050044009>, 1966.
- Aryasit O, Preechawai P, Kayasut K. Clinical presentation, treatment, and prognosis of periocular and orbital amyloidosis in a university-based referral center. *Clin Ophthalmol Auckl NZ*. 2013;7:801–805. <https://doi.org/10.2147/OPTH.S41857>.
- Leibovitch I, Selva D, Goldberg RA, et al. Periocular and orbital amyloidosis: clinical characteristics, management, and outcome. *Ophthalmology*. 2006;113(9):1657–1664. <https://doi.org/10.1016/j.ophtha.2006.03.052>.
- Malik UF, Kapre S. Periorbital purpura in a 66-year-old man: clue for spot diagnosis. *QJM Mon J Assoc Phys*. 2010;103(2):127–129. <https://doi.org/10.1093/qjmed/hcp101>.
- Colucci G, Alberio L, Demarmels Biasutti F, Lämmle B. Bilateral periorbital ecchymoses. An often missed sign of amyloid purpura. *Hämostasologie*. 2014;34(3):249–252. <https://doi.org/10.5482/HAMO-14-03-0018>.
- Erie JC, Garrity JA, Norman ME. Orbital amyloidosis involving the extraocular muscles. *Arch Ophthalmol Chic Ill*. 1960;107(10):1428–1429. <https://doi.org/10.1001/archophth.1989.01070020502019>, 1989.
- Finlay KR, Rootman J, Dimmick J. Optic neuropathy in primary orbital amyloidosis. *Can J Ophthalmol J Can Ophthalmol*. 1980;15(4):189–192.
- Kisser U, Heichel J, Gliem A. Rare diseases of the orbit. *Laryngorhinootologie*. 2021; 100(Suppl 1):S1–S79. <https://doi.org/10.1055/a-1384-4641>.
- O'Donnell B, Wuebbolt G, Collin R. Amyloidosis of the conjunctiva. *Aust N Z J Ophthalmol*. 1995;23(3):207–212. <https://doi.org/10.1111/j.1442-9071.1995.tb00158.x>.
- Fraunfelder FW. Liquid nitrogen cryotherapy for conjunctival amyloidosis. *Arch Ophthalmol Chic Ill*. 1960;127(5):645–648. <https://doi.org/10.1001/archophth.2008.535>, 2009.
- Beirão NM, Matos E, Beirão I, Costa PP, Torres P. Recurrence of vitreous amyloidosis and need of surgical reintervention in Portuguese patients with familial amyloidosis ATTR V30M. *Retina Phila Pa*. 2011;31(7):1373–1377. <https://doi.org/10.1097/IAE.0b013e318203c0c2>.
- Kawaji T, Ando Y, Hara R, Tanihara H. Novel therapy for transthyretin-related ocular amyloidosis: a pilot study of retinal laser photocoagulation. *Ophthalmology*. 2010;117(3):552–555. <https://doi.org/10.1016/j.ophtha.2009.07.042>.
- Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood*. 2017;130(5):597–605. <https://doi.org/10.1182/blood-2017-03-771220>.
- Wechalekar A, Antoni G, Al Azzam W, et al. Pharmacodynamic evaluation and safety assessment of treatment with antibodies to serum amyloid P component in patients with cardiac amyloidosis: an open-label Phase 2 study and an adjunctive immuno-PET imaging study. *BMC Cardiovasc Disord*. 2022;22(1):49. <https://doi.org/10.1186/s12872-021-02407-6>.
- Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79(8):785–792. <https://doi.org/10.1212/WNL.0b013e3182661eb1>.
- Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med*. 2013;369(9):819–829. <https://doi.org/10.1056/NEJMoa1208760>.
- Benson MD, Kluge-Beckerman B, Zeldenrust SR, et al. Targeted suppression of an amyloidogenic transthyretin with antisense oligonucleotides. *Muscle Nerve*. 2006;33(5):609–618. <https://doi.org/10.1002/mus.20503>.