Case Report

Conjunctival Amyloidosis: A Report of Two Cases with Review of Literature – 2000–2020

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Abstract

Amyloidosis is a complex multisystem disorder characterized by deposition of an aberrant protein in tissues and results in disruption of the normal organ function. Localized amyloidosis is a rare disorder. It commonly affects the head-and-neck region, and only 4% of these lesions are encountered in the orbital region. Hence, conjunctival amyloidosis is a very rare entity. It is thought to be a manifestation of local immunologic disorders. Amyloidosis of conjunctiva is more often localized with no other systemic features. Here, we present two cases of unilateral conjunctival amyloidosis, one with extensive calcification. Conjunctival amyloidosis must be considered in the differential diagnosis of conjunctival neoplasms. Histopathological examination and apple-green birefringence on polarized microscopy with Congo red stain remain the gold standard for diagnosing this entity.

Keywords: Amyloidosis, Congo red, conjunctiva

Introduction

Amyloidosis is a complex multisystem disorder characterized by deposition of an aberrant protein in tissues and which results in disruption of the normal organ function. Although amyloidosis is presently classified as light and amyloid A protein amyloidosis, its classification into localized or systemic is still clinically significant due to grave consequences of the latter.[1,2] Localized amyloidosis is a rare disorder. It commonly affects the head-and-neck region, and only 4% of these lesions are encountered in the orbital region. Hence, conjunctival amyloidosis is a very rare entity. Conjunctival amyloidosis is thought to be a manifestation of a local immunologic disorder secondary to chronic infection or trauma to the eye or a hereditary familial disorder.[1,3] It is more often localized with no other systemic features.[3] Here, we present two cases of unilateral conjunctival amyloidosis, one with extensive calcification.

Case Reports

Case 1

A 50-year-old man presented to the eye outpatient department with a complaint of swelling in the upper and lower eyelids of the right side. There was no history of preceding chronic ophthalmic complaint. An ill-defined, pale yellow swelling was noted over both the lids of the right eye [Figure 1a]. On examination of the palpebral conjunctiva, these swellings appeared waxy yellow and were firm to hard in consistency. No other ocular defect was identified. Hematologic and biochemical investigations were within normal limits. Excision biopsy of both the eyelid lesions was done to rule out malignancy. Histopathological examination showed abundant acellular eosinophilic extracellular material in the subepithelial conjunctival tissue along with extensive areas of calcification [Figure 1b and c]. The eosinophilic deposits stained purple–violet with crystal violet stain and displayed apple-green birefringence with Congo red stain on polarized microscopy [Figure 1d]. A final diagnosis of localized conjunctival amyloidosis, right eye was offered. The patient is asymptomatic and doing well after 6 months of follow-up.

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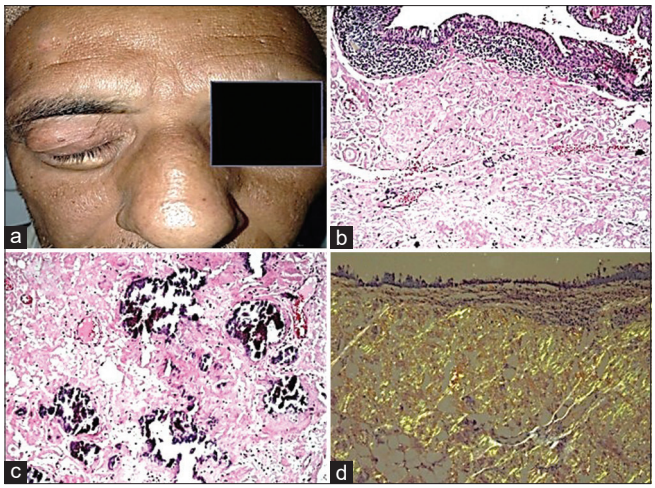

Figure 1: Case 1: (a) A 50-year-old male with swelling in the upper and lower eyelids. (b) (×100): H and E section showing acellular, pink, hyaline extracellular substance in subepithelial conjunctival tissue. (c) (×100) H and E sections showing extensive areas of calcification within amyloid deposits. (d) (×100): Congo red staining shows apple-green birefringence under polarizing light, confirming amyloid

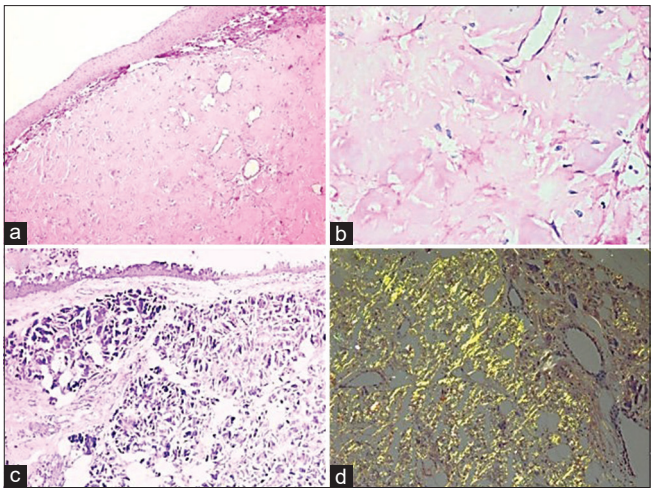

Figure 2: Case 2: (a) (×100) and (b) (×400): H and E section showing acellular, pink, hyaline extracellular substance in the subepithelial conjunctival tissue. (c) (×100): Crystal violet staining shows purple–violet deposits. (d) (×100): Congo red staining shows apple-green birefringence under polarizing light, confirming amyloid

Case 2

A 55-year-old woman presented with a painless progressive mass in the left lower eyelid for 8–9 years. There were no other ocular complaints. On local examination of the left eye, a yellow, firm, nontender, freely mobile mass with irregular margins was noted attached to the lower fornix. The mass was excised and sent for histopathological examination. Microscopy revealed the presence of acellular, pink, hyaline extracellular substance in the subepithelial tissue, suggesting amyloid deposition [Figure 2a and b]. On staining with crystal violet, the deposits appeared purple–violet [Figure 2c] and revealed pathognomonic apple-green birefringence under polarizing light on Congo red staining, confirming amyloid deposition [Figure 2d]. Subsequent clinical examination and relevant investigations did not reveal any evidence of systemic involvement. A final diagnosis of localized conjunctival amyloidosis, left lower eyelid, was given. The patient is asymptomatic and doing well after 9 months of follow-up.

Discussion

The term "amyloidosis" was coined by Virchow in 1854, and it is characterized by deposition of hyaline extracellular material into various tissues throughout the body.[4] The amyloid protein gets deposited as insoluble fibrils which gives "apple-green" birefringence under polarized light with Congo red staining, diagnostic of amyloidosis.[1]

Ocular involvement of amyloidosis, though rare, has been reported involving the adnexa, extraocular muscles, levator palpebrae muscle, conjunctiva, cornea, lens with capsule, anterior uvea, trabecular meshwork, vitreous, and retina.[5]

Although rare, conjunctival amyloidosis is the most common nonfamilial ophthalmological manifestation of amyloidosis.[6] It is usually a primary, localized process, which presents as a mass lesion.[3] Patients may also present with general eye discomfort, stickiness of eye, or subconjunctival hemorrhage due to friability of vessels caused by amyloid deposits.[1] Characteristically waxy yellow or red lesions are seen in the late stage of the clinical course.[3] Rarely, in chronic lesions, extensive areas of calcification and ossification can be found which gives the lesion a hard consistency and hence a false clinical impression of tumor.[7] Biopsy is usually done to rule out malignancy. Histopathological findings and apple-green birefringence on polarized microscopy with Congo red stain highlighting the classic areas point toward the right diagnosis.

Case 2 had the classical clinical presentation of localized conjunctival amyloidosis, however, in Case 1, the lesion was hard in consistency which led to the suspicion of malignancy. Furthermore, the microscopic findings of Case 1 were unusual, as on microscopy, it showed extensive areas of calcification within the amyloid deposits. Amyloid fibrils have affinity for calcium, and calcified amyloid deposits are known to occur in both primary and secondary amyloidoses, but the molecular process and significance of such calcified deposits remain unknown. This, however, represents chronicity of the lesion.[7]

The mainstay of treatment is conservative with observation or lubrication with artificial tears or gels. Surgical excision has proved to be controversial due to risk of recurrence and hemorrhage.[5] Fraunfelder *et al*. reported liquid nitrogen cryotherapy to be a safe and effective therapeutic option, however, further study for its widespread use is warranted.[8] After surgical excision, both patients are doing well and are asymptomatic on 6 months and 9 months of follow-up.

On an extensive review of the literature, we found isolated primary conjunctival amyloidosis to be reported in 64 cases in the last 20 years (2000–2020) [Table 1].[1,3,5,8,9-35] Cases

Table 1: Characteristics of patients with primary localized amyloidosis involving only conjunctiva reported in literature (2000-2020)[1,3,5,8,9-35]

Author	Year	Age (years)/ sex	*n*	Side	Location	Presentation	Treatment	Stable/ recurrence
Lee *et al*.[9]	2000	38/female	1	Bilateral	UP + LP	RSH	Conservative	Stable
Cheong-Leen[10]	2001	24/male	1	Left	BUL	SH	Not available	Not available
Van Cleynenbreugel *et al*.[11]	2002	67/male	1	Left	UP + LP	Mass, hemorrhage	Excision biopsy + cryotherapy	Stable
Biewend *et al*.[12]	2006	65/?	1	Left	BUL	Conjunctival mass	Conservative	Recurrence
Demirci *et al*.[5]	2006	45-69, male (1), female (2)	3/6	Right (2), Left (1)	BUL (2), fornix (1)	Conjunctival mass (3), SH (1)	Excision + cryotherapy (2), incisional biopsy (1)	Stable (2), recurrence (1)
Leibovitch *et al*.[13]	2006	60 (38-79), male (5), female (8)	13/24	Bilateral (3), ? (10)	?	Mass (13), ptosis (8), pain (3)	Observation (8), excision (5)	Stable (11), recurrence (2)
Seider *et al*.[14]	2006	63/female	1	Right	Palpebral + BUL + fornix + semilunar fold	Ptosis + conjunctival mass	Incisional biopsy + ptosis repair	Stable
Gauba *et al*.[15]	2006	30/female	1	Right	Lower fornix	RSH + conjunctival mass	Surgery	Recurrence
Mesa-Gutiérrez *et al*.[16]	2008	57/female	1	Left	LP	Conjunctival mass	Excision	Stable
Bozkurt *et al*.[17]	2008	40/female	1	Left	BUL	Conjunctival mass	Incisional biopsy	NA
Fraunfelder[8]	2009	50-70, male (2), female (2)	4	Right (3), Left (1)	UP (2), BUL (1), BUL + UP (1)	Pseudoptosis + epiphora (2), pseudoptosis (1), epiphora (1)	Excision + cryotherapy (3), cryotherapy (1)	Stable (2), recurrence (2)
Naxer *et al*.[18]	2011	68/male	½	Right	Palpebral	Ptosis	Excision	?
Al-Nuaimi *et al*.[19]	2012	38, 53, female (2)	2/10	Bilateral (1), Left (1)	UP + LP (1), BUL + LP (1)	Ptosis (1), RSH (1)	Surgery (2)	Recurrence (2)
Ray *et al*.[20]	2012	41/male	1	Left	BUL	Growth	Excision + cryotherapy	-
Aryasit *et al*.[21]	2013	31/female	1/6	Left	?	Irritation, eye pain	Incisional biopsy	Recurrence
Chakraborti *et al*.[22]	2014	19/male	1	Bilateral	UP + LP	Right painless ptosis	Excision, cryotherapy	-
Suesskind *et al*.[3]	2015	44,58, male (1), female (1)	2/6	Right (1), left (1)	BUL (2)	Mass (2), SH (1)	Excision (2)	Recurrence (1), ? (1)
Hufendiek *et al*.[23]	2015	73/female	1	Left	BUL + lower fornix	Conjunctival mass	Excision	S
Mora-Horna *et al*.[1]	2015	18-84, female (2), ? (3)	5/14	Bilateral (2), left (2), right (1)	BUL (2), UP (1), UP + LP (1), ? (1)	RSH (2), ptosis + eyelid swelling (2), decreased visual acuity (1)	Incisional biopsy (5)	Recurrence (1)
Arai *et al*.[24]	2016	31, 43 female (2)	2	Left (2)	UP (1), 2nd ?	Ptosis + SH + mass (2)	Incisional biopsy (2)	-
Meduri *et al*.[25]	2016	55/female	1	Bilateral	LP	Mass + SH ectropion in left eye	Excisional biopsy + cryotherapy	-
Hamill *et al*.[26]	2017	48/female	½	Bilateral	UP + LP	Mass + ptosis + SH	Biopsy + ptosis repair	Stable
Ando *et al*.[27]	2017	43/male	1	Bilateral	BUL	SH	Partial biopsy	-
Byers *et al*.[28]	2018	52/male	1	Left	LP	Swelling and SLL of right orbit	Surgical debulking	-
Blandford *et al*.[29]	2018	62/female, NA	5/10	Left (1), NA (4)	BUL (1), NA (4)	Conjunctival mass (1), NA (4)	Excision (1), NA (4)	Stable (1), NA
Prager *et al*.[30]	2018	11-70, male (2), female (1)	-	Bilateral (1), left (1), right (1)	BUL (2), BUL + palpebral + fornix (1)	Red eye (1), RSH (1), hemorrhagic conjunctival lesion (1)	Excisional biopsy + cryotherapy (2), excision (1)	Recurrence (1)
Charles *et al*.[31]	2018	61/male	1	Bilateral	BUL	Redness, tearing	Excision	Stable
Noh *et al*.[32]	2019	19/male	1	Right	BUL	Conjunctival mass	Excision	-
Zloto *et al*.[33]	2019	?/male	1	?	?	Subconjunctival yellow deposits	Excision	Stable

Contd...

Table 1: Contd...

Author	Year	Age (years)/ sex	*n*	Side	Location	Presentation	Treatment	Stable/ recurrence
Medel Jiménez *et al*.[34]	2018	52/female	¼	Right	LP	Conjunctival mass	Excision	Stable
Dammacco *et al*.[35]	2019	NA	4/41	Left (1), NA	BUL (3), UP (1)	Nodule (3), thickening (1)	NA (4)	NA

BUL: Bulbar, UP: Upper palpebral, LP: Lower palpebral, SH: Subconjunctival hemorrhage, RSH: Recurrent SH, NA: Not available, SLL: Small lymphocytic lymphoma

of isolated primary amyloidosis involving only conjunctiva were included. Cases with extension into other orbital structures, for example, eyelid components such as tarsal plates, levator palpebrae muscle, cornea, or periorbital deep tissues, with confirmed systemic involvement or where systemic workup was not done to rule out systemic disease were excluded.

There were 64 cases in total, including 21 males and 31 females (in 12 cases, sex was not available). The mean age of the patients was 54.6 years (range: 11–84 years) (age not available in 9 cases). Conjunctival involvement was on the left side in 20 cases, followed by the right side (13 cases) and bilateral involvement (13 cases) (data not available in 18 cases). Predominant conjunctival site involved was bulbar (20 cases) followed by palpebral (16 cases) > fornix (2) = diffuse (2) = bulbar and palpebral (2) > bulbar and fornix (1). Both upper and lower palpebral conjunctivae were involved in 5 cases (data not available in 21 cases). The most common clinical feature was conjunctival mass (40) followed by ptosis (16) and subconjunctival hemorrhage (15). Recurrent subconjunctival hemorrhage was seen in 6 cases. Other features included pain (4), epiphora (4), pseudoptosis (3), redness (2), decreased visual acuity (1), and ectropion (1) (no data in 4 cases). Only excision/surgical treatment was done in 20 cases, followed by incisional biopsy (13), excision and cryotherapy (11), and only cryotherapy in 1 of the cases. Conservative management including observation was done in 10 cases (no data in 9 cases). Recurrence was seen in 13 cases. Calcification was not seen in any of these cases.

To conclude, the present cases are being presented owing to rarity of localized conjunctival amyloidosis. Furthermore, one of the cases shows an even rarer finding, i.e. the presence of extensive areas of calcification. Conjunctival amyloidosis must be considered in the differential diagnosis of conjunctival neoplasms. Histopathological examination and apple-green birefringence on polarized microscopy with Congo red stain remain the gold standard for diagnosing this entity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and their confidentiality and anonymity will be maintained.

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Conflicts of interest

There are no conflicts of interest.

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