Original Article

Orbital and adnexal amyloidosis: Thirty years experience at a tertiary eye care center

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Purpose: The aim of this work was to study the clinical presentation, management and outcomes of orbital and adnexal amyloidosis. **Methods:** This retrospective analysis included all the patients diagnosed with orbital and adnexal amyloidosis between January 1990 and December 2019. Positive staining with Congo Red and apple-green birefringence on polarized light microscopy established the diagnosis. Data analyzed included demographic profile, varied presentations, management, and outcome. **Results:** Thirty-three eyes of 26 patients were included. The male:female ratio was 1:1. The mean age of the study population was 42.6 ± 16 years. The median duration of symptoms was two years. Unilateral involvement was seen in 19 eyes (right = 11, left = 8). The most common presenting feature was acquired ptosis. Eyelid was the most commonly affected site followed by orbit and conjunctiva. Two patients had systemic involvement in the form of multiple myeloma and lymphoplasmacytic lymphoma. Complete excision was done in seven (26.9%) cases while 19 (73.1%) cases underwent debulking. Three patients underwent ptosis surgery. The median duration of follow-up was 1.5 years. Three cases had recurrence and underwent repeat surgery. **Conclusion:** Orbit and adnexa is a rare site for amyloidosis. It is usually localized; however it can occur as a part of systemic amyloidosis. Eyelid is the most common site of involvement and patients usually present as eyelid mass or ptosis. Complete excision is difficult and most of the patients usually undergo debulking surgery. All patients should undergo screening for systemic amyloidosis

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Amyloidosis refers to a group of disorders characterized by the extracellular deposition of amyloid which is an aggregate of amorphous, insoluble, misfolded protein fibrils, arranged in β-pleated sheet formation. It demonstrates positive Congo Red staining on histopathology and apple-green birefringence on polarized light microscopy. The term 'amyloid' was first introduced by Rudolph Virchow in 1854. Amyloidosis is classified as local or systemic based on the extent of involvement, and primary or secondary based onthe underlying etiology. At present, at least 36 different types of amyloid are known depending upon the type of precursor protein.[1-5]

Localized amyloidosis comprises in-situ production of amyloid fibrils at a single site. Systemic amyloidosis involve multiple organs simultaneously including heart, kidney, liver, gastrointestinal tract, nerve, skin and soft-tissue causing their dysfunction and subsequent failure. The kidneys are the most commonly affected organs and cardiac involvement leads to increased morbidity and mortality.[6]

Orbital and adnexal amyloidosis is uncommon, has varying presentations and can be the first sign of systemic involvement. Hence ruling out systemic association in all such cases is mandatory.[6-9] The reported sites of orbital and adnexal amyloidosis are the eyelids, conjunctiva, extraocular muscles including levator palpebrae superioris (LPS), lacrimal gland, lacrimal sac and orbital fat. Because of the rarity of the condition, only a few large series have been reported with much literature limited to case reports and smaller case series. There is still a paucity of literature on this enigmatic disorder and this study was aimed at adding to the existing literature.[7,9-13] To the best of the authors' knowledge this is the first study on orbital and adnexal amyloidosis from India and the second largest series in the world spanning over three decades. This study aims to throw light on the clinical presentations, management and outcomes of the orbital and adnexal amyloidosis in Indian patients.

Methods

A retrospective review of all patients with a histopathological diagnosis of orbital and adnexal amyloidosis between January 1990 and December 2019 was carried out. Patient consent and the Institutional review board approval were

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obtained. The study adhered to the tenets of the Declaration of Helsinki.

Histopathological diagnosis of amyloidosis was confirmed based on the deposition of hyaline material seen on hematoxylin and eosin (H and E) staining and demonstration of apple-green birefringence under cross-polarized light after Congo red staining. Immunohistochemistry was done to detect the precursor protein wherever required. The tests to rule out systemic involvement included complete blood count, peripheral blood smear, liver function test, prothrombin time, β2 microglobulin assay, renal function test, serum immunofixation electrophoresis (IFE) with measurement of the free light chain (FLC), bone marrow aspiration, urine electrophoresis, chest x-ray, electrocardiogram, echocardiography and ultrasonography of the abdomen. All these investigations were carried out under the guidance of a hemato-oncologist and immunologist after confirmation of the diagnosis.

Data analyzed included demographic details, onset and duration of symptoms, site of involvement, surgical procedures with their outcomes and recurrences and follow up duration.

Percentage and frequency was calculated for categorical data and the mean, standard deviation and the range was calculated for numerical data. Statistical analysis was accomplished with Statistical Package for Social Sciences (SPSS Inc. Chicago, IL, version 22.0).

Results

Thirty-three eyes of 26 patients were included in the study. The male:female ratio was 1:1 (13 each). The mean age of the study population was 42.6 ± 16.0 years (Range 9-72 years). The median duration of the symptoms was 2 years (Range 2 months -15 years). Eleven patients had right eye involvement (42.3%), the left eye was involved in 8 patients (30.7%) while 7 (27%) cases had bilateral involvement. Out of 33 eyes in our study, eyelid was the most common site (n = 25, 75.8%) followed by orbit (n = 6, 18.2%), conjunctiva (n = 2, 6%). Out of the 7 cases with the bilateral presentation, 6 cases had eyelid involvement while one had orbital involvement. Upper and lower eyelids were involved in 11 eyes each while 3 eyes had involvement of both the eyelids. Upper eyelid amyloid deposition manifested as ptosis (n = 12), lid mass (n = 5), eyelid thickening (n = 3), entropion (n = 1) and periorbital ecchymosis (n = 1) [Fig. 1a]. Lower lid infiltration presented as a mass that bled on mild touch (n = 5) and entropion (n = 1) [Fig. 1b and c]. Out of the 6 eyes with orbital amyloidosis, diffuse soft tissue infiltration was observed in three and lacrimal gland involvement in one, two eyes had extraocular muscle involvement (superior rectus and lateral rectus muscle). Orbital amyloidosis presented in the form of proptosis (n = 4), periorbital swelling (n = 2) [Fig. 1d], the eye with SR involvement had hypotropia and the case of LR involvement presented as incomitant esotropia mimicking lateral rectus palsy. Two eyes had pure conjunctival involvement and both had involvement of medial bulbar conjunctiva [Fig. 1e and f]. Eighteen patients (69.2%) had no known systemic co-morbidities while hypertension (n = 2), type 2 diabetes mellitus (n = 2), hypothyroidism (n = 2), multiple myeloma (n = 1) and lymphoplasmacytic lymphoma (n = 1) were the associated systemic ailments in the remaining patients. Three patients had a significant past medical history in the form of rheumatic fever, malaria and pulmonary tuberculosis (pTB) respectively. The family history of all 26 patients was unremarkable. Complete excision was performed in 7 cases (26.9%) including the two cases with conjunctival amyloidosis and the one with lacrimal gland involvement. Debulking +/- cryotherapy was done in the rest of the 19 cases (73.1%). Three patients underwent ptosis surgery and the patient with hypotropia underwent strabismus surgery at a later stage. All biopsied specimens demonstrated eosinophilic deposits on hematoxylin and eosin stain, positive Congo Red staining and apple-green birefringence on polarized light microscopy [Fig. 2a-c]. Immunohistochemistry (IHC) revealed the presence of AA amyloid fibril in one case with a past history of pulmonary tuberculosis. Biopsied tissue from the case with lymphoplasmacytic lymphoma who had lacrimal gland involvement was subjected to IHC and it displayed positivity for CD20, CD3 and CD 138. A review of the consultation records with the hemato-oncologist revealed the absence of systemic amyloidosis in our cohort of patients. The median duration of the follow-up period was 1.5 years (Range 6 months – 29 years). Recurrence was noted in the eye with SR involvement, in a case of lower lid amyloidosis and in another case where the lesion was misdiagnosed as pterygium and excision with conjunctival autograft was done. Debulking with cryotherapy was done for the first case and excision with cryotherapy was performed in the last case respectively and no recurrence was noted at their last follow up. Our results are summarized in Table 1.

Discussion

This study is the first case series of orbital and adnexal amyloidosis reported from the Indian subcontinent. It reveals that amyloidosis predominantly occurs in the middle-age group with no gender predilection. Amyloid deposition can be unilateral as well as bilateral and has a varied clinical presentation depending on the site involved. Eyelid is the most frequently affected site followed by orbit and bulbar conjunctiva. Complete excision/debulking +/- cryotherapy is the management of choice and gives satisfactory outcomes. Orbital and adnexal amyloidosis is mostly a localized disorder, however, ruling out systemic involvement is necessary.

Amyloidosis has been described as a heterogeneous group of disorders featuring the characteristic extracellular deposition of Congo Red stain-positive, amorphous, insoluble protein fibrils with a β-sheet configuration that exhibit apple-green birefringence on polarized light microscopy. Amyloid fibril deposition can occur as a localized aggregation in a single tissue or it may be a multi-system disseminated amyloidosis, where abnormal proteins build up in multiple organs. Based on the underlying etiopathogenesis, it can be classified as primary or secondary. The latter develops as a complication of chronic inflammatory or infectious conditions like rheumatoid arthritis and tuberculosis. There are atleast 36 types of amyloid fibrils that have been discovered in human beings.[1,3-5]

Orbital and adnexal amyloidosis is an infrequent form of localized amyloidosis that can occur as a part of systemic

amyloidosis as well. In this study, we found that orbital and adnexal amyloidosis is mostly seen in the early 4th decade of life which is consistent with the findings of Aryasit *et al*. and Al Hussain *et al*.[14,15] However, few studies from other regions have reported the 5th and the 6th decade as the age of onset.[3,7,9,10,12,13] Unlike other studies that have noted a female preponderance we noticed an equal sex distribution.[3,9,10,12,14] The mean duration of the symptoms and signs in our study was 2 years which is in agreement with the findings of several other studies.[9,10,12,14] It indicates the slow nature of the amyloid deposition and the

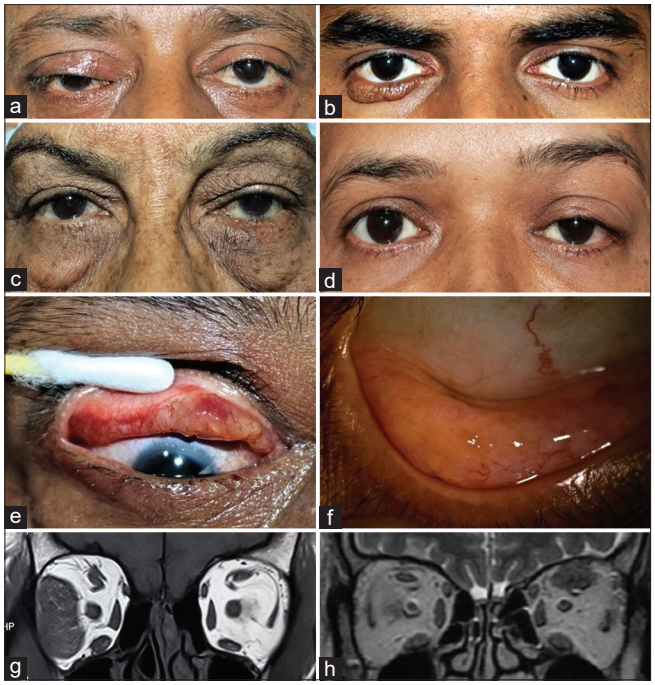

Figure 1: (a) Acquired progressive ptosis in the right eye due to amyloid deposition. (b) Localized amyloidosis presenting as eyelid massin the right lower eyelid. (c) Left lower eyelid amyloid presenting as entropion. (d) Left orbital amyloidosis presenting with periorbital swelling and proptosis. (e) Amyloid deposition involving the palpebral conjunctiva and the tarsal plate in a patient presenting with acquired ptosis. (f) Amyloid deposition in the left lower lid involving the palpebral and bulbar conjunctiva. (g) MRI orbit showing enlarged Right lateral rectus muscle, isotense on T2 W Image due to amyloid infiltration. (h) MRI orbit showing Left superior rectus muscle involvement in amyloidosis

Table 1: Demographic details, clinical presentations and management outcome

Sample size	*n*=26
Mean age	42.6±16.0 years (Range 9-72 years)
Gender	Male=13 (50%) Female=13 (50%)
Median duration of symptoms	2 years (Range 2 months -15 years)
Laterality	Right eye (11, 42.3%) Left eye (8, 30.7%) Bilateral (7, 27%)
Site of deposition	Eyelid (25 eyes, 75.8%) Orbit (6 eyes, 18.2%) Conjunctiva (2 eyes, 6%)
Clinical presentation	Ptosis (12, 36.4%) Eyelid mass (10, 30.3%) Proptosis (4, 12.1%) Eyelid thickening (3, 9.1%) Entropion (2, 6.1%) Periorbital swelling (2, 6.1%) Squint (2, 6.1%) Recurrent subconjunctival hemorrhage (1, 3%) Pterygium (1, 3%)
Clinical diagnosis	Amyloidosis (11, 33.4%) Acquired ptosis (7, 21.2%) Eyelid neoplasia (4, 12.1%) Orbital lymphoma (3, 9.1%) Chalazion (3, 9.1%) Cicatricial entropion (2, 6.1%) Xanthogranuloma (1, 3%) Lateral rectus palsy (1, 3%) Pterygium (1, 3%)
Management	Complete excision +/- cryotherapy (7, 26.9%) Debulking +/- cryotherapy (19, 73.1%)
Systemic ailments	Hypertension (2, 7.7%) Type 2 Diabetes Mellitus (2, 7.7%) Hypothyroidism (2, 7.7%) Multiple myeloma (1, 3.8%) Lymphoplasmacytic lymphoma (1, 3.8%)
Systemic amyloidosis	Nil
Median duration of follow up	1.5 years (Range 6 months - 29 years)
Recurrence	3

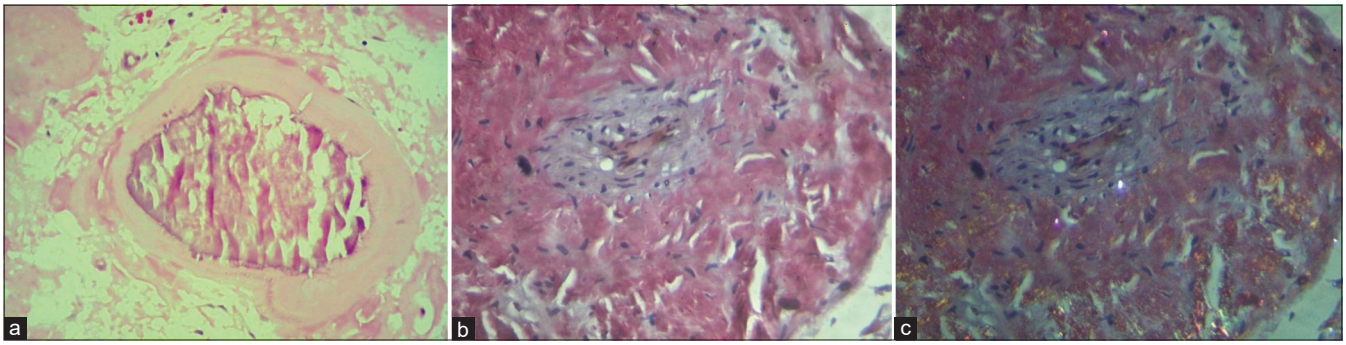

Figure 2: (a) H and E photomicrograph (40x) showing eosinophilic amyloid deposits. (b) The amyloid deposits displaying positivity for Congo Red stain. (Reproduced with permission from Canadian Journal of Ophthalmology, Elsevier Publications). (c) Demonstration of apple-green birefringence by the amyloid deposits under cross-polarized light. (Reproduced with permission from Canadian Journal of Ophthalmology, Elsevier Publications)

delay in the diagnosis due to the varied clinical presentation. A case of repeated ptosis surgery in patient with acquired progressive ptosis due to undetected localized upper eyelid amyloidosis has been reported in literature.[10] In our series, few cases of eyelid amyloidosis were misdiagnosed as aponeurotic ptosis and one case of conjunctival amyloidosis was misdiagnosed as pterygium initially [Table 1].

Previous literature mostly reports orbital and adnexal amyloidosis as a unilateral presentation. However, a small percentage is characterized by bilateral involvement and this corroborates with our findings.[9,10,12,14] Our study yielded eyelid as the most frequent site for amyloid deposition which is in agreement to that reported by Kang *et al*., Aryasit *et al*. and Al Hussain *et al*. respectively.[10,14,15] On the contrary, a review by Mora-Horna *et al*. comprising 64 cases have reported the conjunctiva as the most common site for orbital and adnexal amyloidosis.[12] Our series comprised of only two cases of conjunctival amyloidosis both involving the medial bulbar conjunctiva. One of them presented with recurrent subconjunctival hemorrhage. The other one was initially misdiagnosed as pterygium and excision with conjunctival autograft was done. The recurrent lesion produced symblepharon leading to restricted adduction and diplopia. We noted that few of our cases of eyelid amyloidosis had involved the tarsus and palpebral conjunctiva to a varying extent.

While Kang *et al*. had observed a predilection for the upper eyelid in their series, we had almost equal involvement of both the eyelids.[10] Orbital soft tissue is a favorable site for amyloid deposition as well, a finding which agrees with the work of Taban *et al*.[3] In one of our cases of orbital amyloid, the lateral rectus muscle was infiltrated and it mimicked LR palsy. On Magnetic Resonance Imaging (MRI) it appeared as fusiform enlargement of the muscle and displayed isointense to hypointense signal in both T1 and T2 weighted images [Fig. 1g and h]. The myriad clinical presentation may mislead the diagnosis, hence in acquired progressive ptosis, acquired squint in adulthood and recurrent subconjunctival hemorrhage, one must look for amyloid deposition.[16,17]

In our series, one of the patients with eyelid amyloidosis had multiple myeloma and another patient with lacrimal gland involvement had lymphoplasmacytic lymphoma. Goshe *et al*. and Glass *et al*. reported orbital amyloidosis and conjunctival amyloidosis respectively in multiple myeloma patients. The occurrence of lymphoproliferative disorder in orbital amyloidosis involving the lacrimal gland has been published in the literature.[18-21]

The standard treatment for amyloid deposits is debulking/excision biopsy with cryotherapy. Its unique characteristic feature of Congo Red positivity and apple-green birefringence on polarized light microscopy confirms the diagnosis.[5,7-9,14] The possibility of co-existing systemic involvement should be ruled out in each and every case. Dammacco *et al*. had studied the ocular involvement in amyloidosis and found that localized AL amyloidosis was more frequent (78.6%) followed by systemic AL amyloidosis (16.2%) and multiple myeloma associated AL amyloidosis (10.7%). Reynolds *et al*. reported ocular involvement in 11.8% patients with AL amyloidosis and they found ophthalmic manifestation was the initial presentation in 5%of the cases in that group.[22,23] In our study spanning over 3 decades, we observed a progressive advancement in the investigative modalities for systemic amyloidosis. Thirty years back, an abdominal fat biopsy or rectal biopsy was needed whereas, in recent years less invasive methods like serum electrophoresis, urine electrophoresis and bone marrow biopsy alongwith blood investigations form the baseline investigations to screen for systemic involvement. The investigations used to screen for systemic amyloidosis have been summarized in Table 2.

This study has a median duration of follow up of 1.5 years which is less as compared to the other series.[7,9,10,14] In our series, one patient who was misdiagnosed as pterygium and underwent pterygium excision had a recurrent lesion at six months. Another patient who had eyelid amyloidosis involving LPS and had undergone debulking presented to us with progressive ptosis after 27 years. She had concurrent hypotropia and imaging showed infiltration of superior rectus muscle as well. Debulking of mass along with LPS resection was done. The patient later underwent strabismus surgery for residual hypotropia which also resulted in improvement of the final globe and lid position. She had shown no signs of recurrence at her last follow up after 1 year.

Adjunctive radiotherapy has been observed to provide a long-lasting effect due to its action against plasma cells.[7-9,12,14,15,24] However we feel that it should be reserved for cases where the mass is quite large resulting in disfigurement, has shown poor response to surgery or is associated with lymphoma. We did not give radiation to any of our patients. The present case series is the first from the Indian subcontinent and the second largest series till date. However, it has a few limitations. Immunohistochemistry was not available at our institute in the initial few years of our study; later on it could be done only in select cases as many of them refused due to financial constraints. Hence, our assumption that only one case had secondary amyloid deposition could be an understatement. The median follow up of our study is 1.5 years which is less than other studies in the literature. The overview of the major case series published till date has been provided in Table 3.

Conclusion

Orbital and adnexal amyloidosis is a rare form of localized amyloid aggregation. It can also occur as a part of disseminated systemic involvement. In India, it is prevalent in the 4th decade and does not have any gender predilection. The clinical

Table 2: List of investigations to screen for systemic amyloidosis

Blood tests	Complete Blood Count Serum immunoelectrophoresis B 2 microglobulin Liver Function Tests Serum Urea and Creatinine
Urine test	Urine immunoelectrophoresis Bence Jones protein 24 hr urinary protein
Bone marrow Biopsy	
Ultrasound abdomen	
Chest X-Ray	
Electrocardiography	
Echocardiogram	

Table 3: Review of literature

Study	Sampl size (*n*)	Gender	Mean age (years)	Mean/Median duration of symptoms	Laterality	Most Common Site	Management	Systemic amyloidosis (*n*)	Mean/Median duration of follow up	Recurrence (*n*)
Kang *et al.*, 2020	41	M=12, F=29	66 (Range 19-87)	24 months	UL=30, 73% BL=11, 27%	Eyelid	Incision biopsy (*n*=41), Repeat debulking (*n*=21), Ptosis surgery (*n*=6), Squint surgery (*n*=1), DCR (*n*=1) Orbital wall decompression (*n*=1)	4	8 years	21
Mendel Jimenez *et al.*, 2019	4	M=1, F=3	52	Not specified	UL=4	Eyelid	Orbital biopsy (*n*=2), Excision (*n*=1), Endo DCR + biopsy (*n*=1)	1	8 months	Not specified
Horna-Mora *et al.*, 2016	14	M=2, F=12	56.4 (Range 18-84)	49.3 months (Data of 2 patients unavailable)	UL=13, 92.9% BL=1, 7.1%	Conjunctiva	Incision biopsy (*n*=11), Excision biopsy (*n*=3),	Nil (Data of 6 patients unavailable)	55 months (Data not available for 5 patients)	3 (Data of 5 patients unavailable)
Aryasit *et al.*, 2013	6	M=1, F=5	39.7 (Range 15-79)	31 months	UL=5, 83.3% BL=1, 16.7%	Eyelid	Surgical excision (*n*=5)	Nil	41 months	2
Al Hussain *et al.*, 2013	6	M=2, F=4	46.3 (Range 25-75)	12.8 years	UL=6	Eyelid	Surgical excision (*n*=2), Ptosis surgery (*n*=3), Observation (*n*=1)	Nil	Not specified	2
Al Nuami *et al.*, 2012	10	M=6, F=4	63.1 (Range 38-86)	Not specified	UL=6, 60% BL=4, 40%	Conjunctiva	Conservative management with lubricants and BCL (*n*=4), Surgical intervention (*n*=6)	1	54 months	Nil
Leibovich *et al.*, 2006	24	M=9, F=15	57 (Range 27-85)	37 months	UL=19, 79.2% BL=5, 20.8%	Periocular tissue	Observation (*n*=8), Debulking (*n*=7), Excision (*n*=5), Adjuvant RT (*n*=1), Ptosis surgery (*n*=5)	1	39 months	5
Present study 2020	26	M=13, F=13	42.6 (range 9-72 years)	2 years	UL=19, 73% BL=7, 27%	Eyelid	Surgical excision (*n*=7), Debulking + cryotherapy (*n*=19)	Nil	18 months	3

M: Male, F: Female, UL: Unilateral, BL: Bilateral, NA: Not available, DCR: Dacryocystorhinostomy, RT: Radiotherapy, BCL: Bandage Contact Lens

presentation is myriad based on the involved site and may be misleading at times. Eyelid, orbital soft tissue and conjunctiva are the common sites of amyloid deposition. Hence, middle aged patients with acquired ptosis, incomitant squint or recurrent subconjunctival hemorrhage should be examined for localized amyloidosis. Screening for systemic involvement is necessary and these patients need periodic follow up to monitor the progression of the lesion and recurrence.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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