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## Ocular Presentations of Amyloidosis

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/53910>

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### 1. Introduction

Amyloidosis is a term used for some clinical disorders that result from deposition of insoluble amyloid fibrils in extra- and intracellular spaces leading to many tissue dysfunctions and disrupt tissue architectures in human body. These set of disorders with similar pathophysiology, and involvement of metabolic pathways result in protein deposition in different tissue.[1-3]

Amyloid deposits in various groups of amyloidosis have these common findings:

1. Homogeneous granular, filamentous eosinophilia in hematoxylin and eosin staining.
2. Metachromasia in crystal violet staining.
3. Ultraviolet fluorescence in Thioflavin-T staining
4. Orange-red staining with Congo red, which exhibits two additional properties – Birefringence (ability to rotate polarized light by 90°) and Dichroism (red to green color change under polarized light).

These amyloid proteins can be classified into:

- a. Immunoglobulin light chains (AL) in primary systemic amyloidosis.
- b. Amyloid A protein (AA) in secondary amyloidosis.
- c. Transthyretine in familial amyloidosis.
- d. A protein known as Amyloid P component (AP ). These conditions may be primary or secondary, localized or systemic, and familial or nonfamilial. Primary systemic amyloidosis includes so many clinical disorders like heart failure, gastrointestinal tract in-

volvement, neuropathies, and other disorders. Secondary systemic amyloidosis results from chronic inflammatory diseases such as tuberculosis or syphilis. [4-8]

Various ocular structures may be involved in any subgroup of systemic amyloidosis, as well as in localized amyloidosis limited to the eye. We will discuss in detail in this chapter about ocular manifestations of amyloidosis. Table-1 summarizes ocular involvements of different subgroups of amyloidosis.

Structure	Involvement	Amyloidosis Classification	Comment
Eyelids ,Orbit & Adnexa	Waxy eyelid papules with purpura,	Primary Systemic	
	Proptosis, diplopia, Ptosis, accommodative paresis	Primary localized, primary systemic	
	Keratoconjunctivitis sicca, upper lid mass	Primary localized, primary systemic, secondary systemic	
Conjunctiva	Tumefactive or diffuse yellow infiltrative masses	Primary localized, secondary localized, primary systemic	
Cornea	Polymorphic Amyloid Degeneration	Primary localized	Secondary to climatic Effects
	Primary Gelatinous Drop-Like Dystrophy	Primary localized	Autosomal-Dominant Inheritance
	Lattice Stromal Dystrophy (Type I, III)	Primary localized	Autosomal-Dominant Inheritance
	Lattice Stromal Dystrophy (Type II = Meretoja Syndrome )	Primary systemic	Autosomal-Dominant Inheritance with Systemic Symptoms
Anterior Chamber	Particulate glaucoma	Heredofamilial (neuropathic)	
	Scalloped pupils, amyloid particles pupillary margin	Heredofamilial (neuropathic), primary systemic	
Retina and Vitreous	Fundus abnormalities, decreased vision	Heredofamilial, I and II (neuropathic)	

Table 1. Amyloidosis presentations in different ocular tissue

1.1. Periorbital and orbital amyloidosis

Ophthalmic presentations of Amyloidosis are not a common entity. Amyloidosis can affect any ocular and periocular structures with multifarious clinical presentations so reaching to correct diagnosis is often an arduous task. Periocular and orbital amyloidosis is generally a slowly progressive disease, but it potentially can lead to devastating ocular complications.

The most common signs and symptoms include: visible or palpable periocular mass or tissue infiltration and ptosis. Other less common signs are; pain or periocular discomfort, recurrent periocular subcutaneous haemorrhages, keratoconjunctivitis sicca, ocular motility disturbances, pupillary abnormalities, proptosis and globe displacement. Proptosis may result from a localized orbital mass or from diffuse amyloid infiltration. Mild pain or painless

status in clinical presentations of ocular amyloidosis can differentiate this disease from idiopathic inflammatory pseudotumor.[9-11]

In this section different involvements of periorbital tissues by amyloidosis will be discussed in detail.

## 2. Eyelid involvement

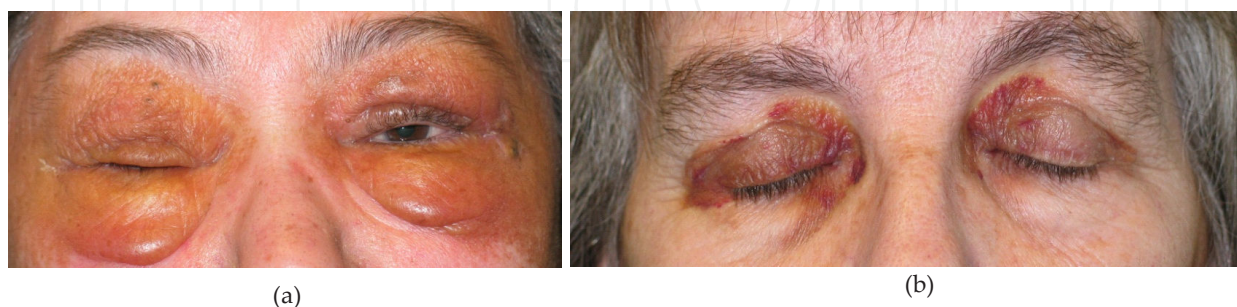
Dermal and ocular amyloidosis can affect eyelid skin either as a part of primary systemic amyloidosis or secondary to dermal conditions like basal cell carcinoma, Bowen's disease and seborrhoeic keratosis.

Nodular or diffuse deposits of amyloid in eyelids are either unilateral or bilateral. Eyelids can be either isolated site of involvement or get involved beside the other sites (e.g. scalp, head and neck or axillae).

Eyelid skin is the preferred site of amyloid deposits both in primary and secondary (reactive) amyloidosis; so unlike other periocular amyloidoses, eyelid skin involvement indicates systemic workup for presence of systemic disease and even some ophthalmologists believe that cutaneous involvement of the eyelid is a sign of primary systemic amyloidosis unless otherwise proved; on the other hand periocular involvements that spares eyelid skin is probably localized.

Amyloid protein deposits in the eyelid skin vessel walls and secondarily increase their fragility, making them very susceptible to hemorrhage after minor trauma (or even spontaneously), so waxy eyelid papules with hemorrhagic appearance can be diagnostic clue of systemic amyloidosis.

Dermatologic conditions like basal cell carcinoma, Bowen's disease, and seborrheic keratosis can lead to secondary localized forms of amyloid deposits in the eyelids although this condition is a histopathologically incidental finding.



**Figure 1.** Waxy eyelid papules (A ) with hemorrhagic appearance (B ) in systemic amyloidosis Sophie R Silverstein MB BChir MA; Primary, systemic amyloidosis and the dermatologist: Where classic skin lesions may provide the clue for early diagnosis; Dermatology Online Journal 11 (1): 5

Primary localized cutaneous amyloidosis of eyelid is not a common condition and can be overlooked easily. In this condition we can see Amyloid light chains (AL) deposits in the tissue. As this condition is usually associated with B-cell or Plasma cell proliferation so plasma cell dyscrasia must be excluded.[9,11,12-16]

### 3. Orbital involvement

Orbital involvement is more common in primary compared to secondary amyloidosis and is rare in hereditary/familial or senile amyloidosis. Localized amyloidosis is a rare condition usually affecting head and neck region and only 4% of them involve orbital region. Although some sight threatening complications like secondary glaucoma and optic neuropathy have been reported, orbital localized amyloidosis is usually considered a benign condition with a slowly progressive nature.

Two types of localized orbital amyloidosis have been described. One type presents with progressive proptosis and limitation of ocular movements and is associated with bilateral nodular infiltration of extraorbital muscles and nearby adnexal tissues. Second form is rare cases of Amyloidoma that occurs usually in anterior orbital region next to lacrimal glands. These Amyloidomas have yellow waxy appearances with fragile consistency that shows calcification in orbital CT-scan. [10, 17-22]

Ptosis and Ophthalmoplegia are two common clinical presentations of periocular involvement that can occur coincidentally or respectively (ophthalmoplegia may follow the ptosis by weeks or months). These two manifestations are due to infiltration and secondary necrosis of extraocular muscles, including levator and Muller's Muscles.

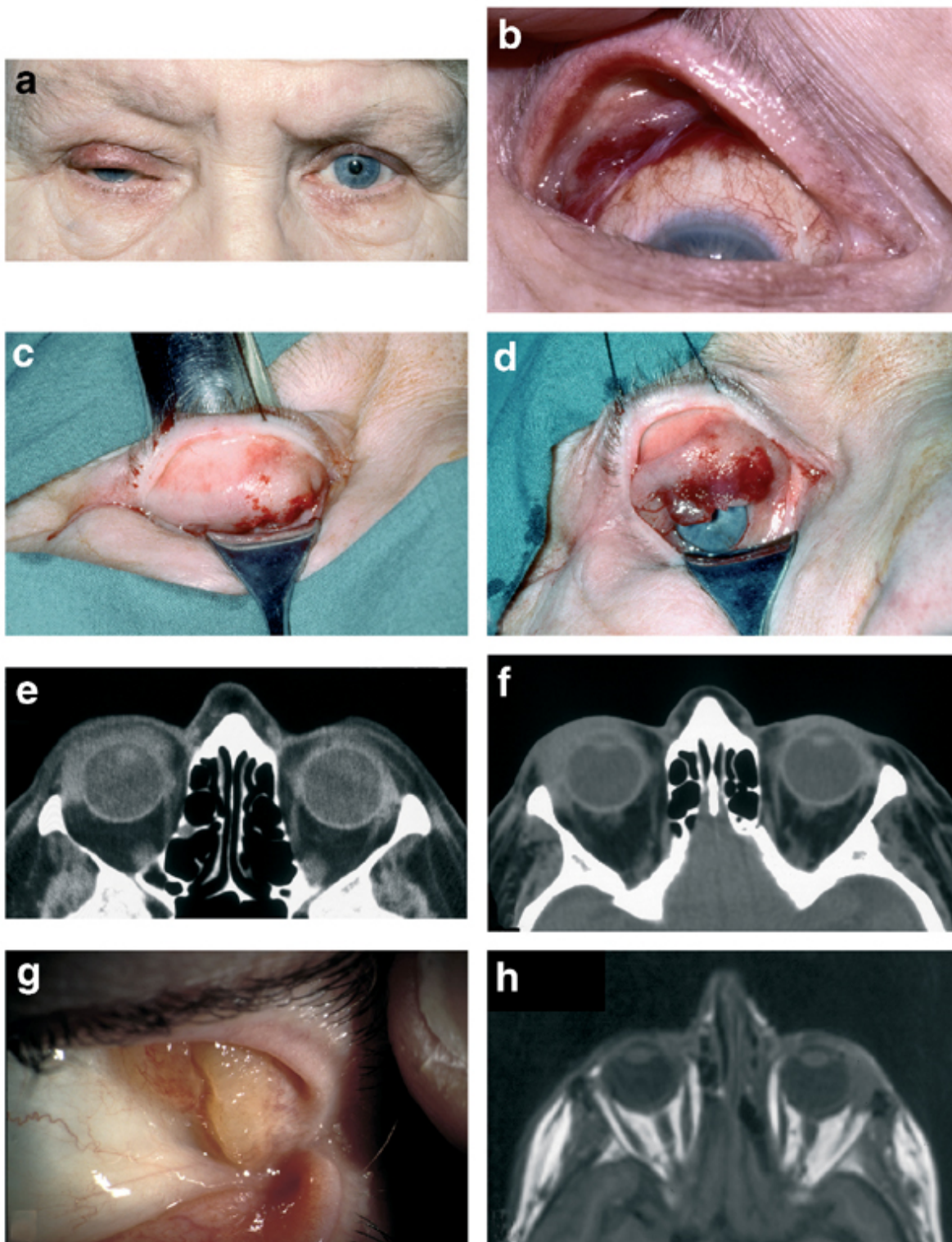
Although Extra-Ocular muscle involvements can present with proptosis, ocular motility restrictions or diplopia, in some cases no prominent signs suggestive of this involvement can be found and Orbital imaging is necessary to make the accurate diagnosis.[9-11,23]

Lacrimal gland involvement is not common in amyloidosis and most commonly presents with hard and mobile Superior-temporal orbital mass, rarely fixated to periocular bones. Other manifestations include proptosis, ocular motility disorders, keratoconjunctivitis Sicca and mild pain.

Amyloid deposits in systemic Amyloidosis involve lacrimal glands bilaterally, whereas primary localized amyloidosis usually affects them unilaterally. Lacrimal Gland involvement can mimic disorders like vascular malformations, dacryoadenitis, or lacrimal gland neoplasms.

Computed tomography and MRI although not diagnostic but are important in localizing the involved orbital structures. Lacrimal gland involvement on orbital CT scan usually presents as a homogenous mass, with a slightly higher density than brain with involvement of nearby extra-ocular muscles, although sometimes lobulated gland with areas of calcification and orbital wall erosion can be seen.





**Figure 2.** Patient-1. (a) Right-sided ptosis. (b) Orbital mass prolapsing through the right upper fornix. (c) and (d) Intra-operative photographs at the time of biopsy. (e) First CT orbits showing the right-sided orbital mass. (f) Repeat CT 9 years later showing the mass to be unchanged. Patient-2. (g). Translucent, yellow, and nodular orbital mass prolapsing through the left upper fornix. (h) MRI of orbits showing the mass in the left orbit. S Dinakaran, A D Singh and I G Rennie: Orbital amyloidosis presenting as ptosis; Eye (2005) 19, 110–112. doi:10.1038/sj.eye.6701411

Although both CT and MRI can be useful in detecting the involvement of periocular tissue in amyloidosis, CT scan is generally more informative than MRI because of the higher sensitivity in detecting specific bone changes and calcifications.

The mass effect can cause globe displacement. Extraocular muscle enlargement, soft tissue infiltration/mass, and calcifications are also characteristic findings on imaging and are seen almost always in orbital involvement.

Other signs of extra-ocular muscle involvement include highly irregular nodular enlargement of muscles with extension to nearby fat tissue with a reticular pattern, fusiform enlargement of muscles with islands of calcification. Extraocular muscle tendons usually are spared. and muscle involvement may be either unilateral or bilateral. [ 9,11,22-26]

#### **4. Optic nerve involvement**

Although orbital amyloidosis rarely involves optic nerve primarily, orbital or muscular amyloid masses especially those located at the orbital apex can involve optic nerve secondarily and can lead to vision loss. Moreover compressive optic neuropathy secondary to dural infiltration is another cause of optic nerve involvement. As a rule, the neuropathic amyloidosis spares the optic nerve.[9-11]

#### **5. Conjunctival involvement**

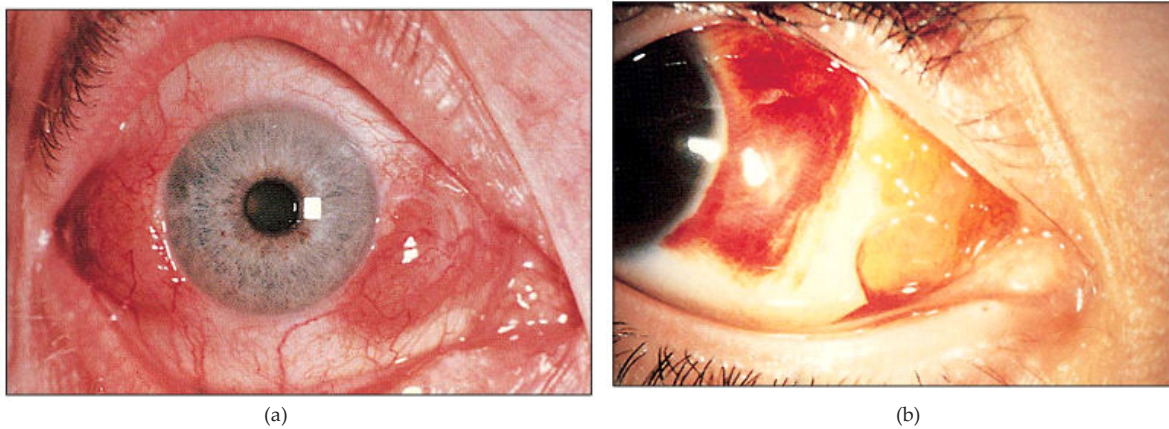
A primary localized form of Amyloidosis is Amyloid plaque deposition in substantia propria of the conjunctiva that usually occurs in healthy young and middle-aged persons with no sex predilection.

The conjunctiva can either be the only site of involvement or involve as well as other structures like the orbicularis oculi or levator muscles. Nodular or diffuse amyloid deposits in these structures can clinically present with Salmon patch nodules and blepharoptosis. Conjunctival amyloidosis usually involves the fornixes (superior fornix more than inferior) and tarsal conjunctiva. Amyloid deposits may be unilateral or bilateral and have firm or rubbery and waxy appearance.

Conjunctival deposits are usually painless, but may cause epiphora or significant local swelling and irritation. Recurrent subconjunctival haemorrhages is another presenting symptom of conjunctival amyloidosis that can be missed easily and is usually due to increased fragility of orbital vasculature secondary to amyloid deposits.

Although initial systemic evaluation for primary systemic amyloidosis in patients with conjunctival deposits is usually negative, progression of a local primary-amyloidosis to a systemic disease has been reported and should be kept in mind when following a presumed localized amyloid patient. Although disorders like trachoma, recurrent bacterial conjunctivi-

tis, or immune conjunctival involvements like GVHD can lead to secondary conjunctival Amyloidosis, this is not a common phenomenon.



**Figure 3.** A. Tumefactive conjunctival amyloidosis. B. Nodular amyloid infiltration of the conjunctiva with spontaneous hemorrhage. Albert & Jakobiec's Principles & Practice of Ophthalmology- 3rd Ed, 2008, Vol 3, chapter 331, Page 4524, 4525

In review of literatures some reports can be seen about conjunctival amyloid deposits after recent strabismus surgery and conjunctival involvement secondary to reactive systemic amyloidosis in rheumatoid arthritis.[9-11, 27-33]

## 6. Management of periocular and ocular amyloidosis

For diagnosis of periorbital and orbital amyloidosis usually tissue biopsy is required and Congo red staining shows characteristic red-green dichroism in unidirectional polarized light.

The first step in management of periocular amyloidosis is determining the type of disease and coincidental systemic involvement. Some treatment modalities like Surgical debulking, radiotherapy and observation have been described for localized amyloidosis but surgical debulking remained mainstay of treatments in patients with symptomatic diseases including ocular motility disturbances, compressive optic neuropathy, and unacceptable cosmetic appearance.

In patients with medical contraindications for surgery or with extensive infiltrative disease, radiotherapy either with or without surgical debulking may be useful.

Observation is a choice of treatment in asymptomatic or mildly symptomatic patients with localized amyloidosis.

Because complete surgical excision of periocular masses is not possible in most patients, and some case reports showed significant progression after surgical debulking, often symptom



revealing treatments for restoration of visual functions and prevention of ocular complications is the goal of treatment.

For Extensive conjunctival infiltration close follow-up is the best option because surgical removal and other modalities are not effective for these lesions.[9-11]

## 7. Anterior chamber involvement

Anterior chamber involvement is usually accompanied by vitreoretinal involvement in hereditary systemic amyloidosis. Clinical manifestations in this form of involvement include white flocculent debris in aqueous, anterior lens capsule and on the iris surface and scalloped pupil borders that indicate amyloid deposition in iris stroma or disruption of parasympathetic innervation of the iris sphincter.

Hallmark of ocular amyloidosis presenting in anterior chamber is amyloid glaucoma that is very similar to pseudoexfoliation syndrome and only microscopic studies can differentiate these entities. A close relationship between the onset of glaucoma and pupillary abnormalities has been described in this condition. This is a unilateral asymmetric condition with multiple mechanisms involved in its pathophysiology. Increased episcleral venous pressure secondary to perivascular amyloid deposition and increased resistance to aqueous outflow are two probable mechanisms of increased intra-ocular pressure (IOP) in this situation. Familial amyloid polyneuropathy (FAP) is often complicated with glaucoma and vitreous opacity.

As previously mentioned amyloid deposition on the pupil border is a strong predictor of glaucoma. It is proposed that fringed pupil may be secondary to high amount of amyloid deposit on the pupil border and these deposits may involve trabecular meshwork, reduce aqueous outflow and secondarily increase intra-ocular pressure (IOP).

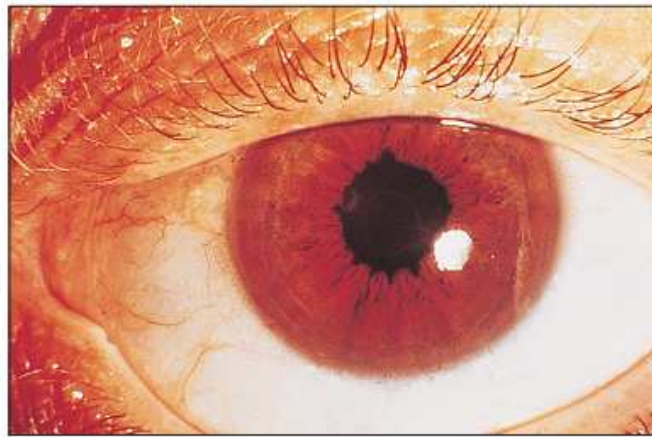
Medical management with aqueous suppressants is treatment of choice to decrease IOP but vitrectomy may have some benefits in aphakic eyes. [34-40]

## 8. Iris involvement

As in amyloid glaucoma, iris stromal deposits originated from blood vessels in amyloidosis is associated with vitreoretinal diseases and usually occur in familial amyloid polyneuropathy (FAP ).

Scalloped border pupils have been found to be the classic sign of iris involvement in amyloidosis, although not a pathognomonic sign.

Secondary localized Amyloidosis has been reported after conditions like recurrent or chronic uveitis and rare disease like ocular leprosy.



**Figure 4.** Scalloped pupil seen in hereditary familial neuropathic amyloidosis. From Lessell S, Wolf PA, Benson MD, Cohen AS: Scalloped pupils in familial amyloidosis. Reprinted from the New England Journal of Medicine, 1975; 293:914–915.

Histopathological review of eyes from patients with rheumatoid arthritis has showed amyloid deposition in iris and posterior uvea. More than the iris, the choroid may also be infiltrated with amyloid in patients with primary systemic amyloidosis.

There are some reports of pupillary abnormality such as pupillary deformity, decrease in pupillary reaction to light, and amyloid deposition in the pupillary border. [34-35,41,42]

## 9. Vitreoretinal involvement

Vitreous Amyloidosis as a rare condition usually presents in Familial Amyloid Polyneuropathy (FAP) but isolated vitreous deposits in the absence of a family history (primary nonfamilial amyloidosis of the vitreous) are extremely rare. FAP usually results from mutations in transthyretin (TTR) gene and is the most common form of hereditary amyloidosis. Although TTR (also known as prealbumin) is usually produced in the liver, retinal pigment epithelium and choroid plexus of brain can synthesize this protein too. TTR transfers thyroxine and retinol binding proteins in plasma.

Vitreous opacities, manifested as bilateral (but highly asymmetric) cobweb-like or sheet-like veils or string of pearls white opacities are the most common presentations of this condition, and density of these opacities determines severity of visual symptoms. These symptoms include glare, floater, blurred vision and acute decrease in vision secondary to dislocation of these opacities to the visual axis. These vitreous opacities usually spread from cortical vitreous to the center and are often the only sign of ocular involvement but can be in association with other signs like Iris deposits, choroidal infiltration and amyloid glaucoma. Unfortunately this condition can be misdiagnosed easily with uveitis, vitritis, intra-ocular lymphoma, and vasculitis. In FAP, vitreous opacity incidence is variable between 5.4% and 35%. Vitreous involvement in FAP may be accompanied by other organs involvement so systemic workup is necessary.

Retinal vessels usually appear normal in vitreous involvement, although sometimes these opacities may involve perivascular regions and appear as focal plaques, tortuosity, beading or vascular sheathing. Retinal vasoocclusive accidents that appear as cotton-wool spots and neovascularizations have been reported too.



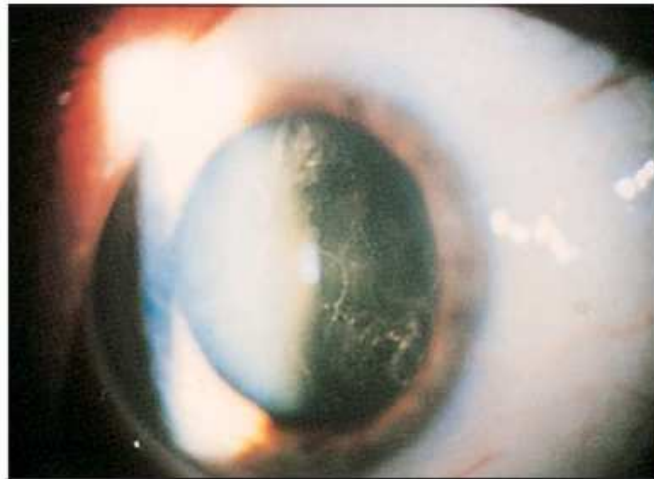
**Figure 5.** Congo red preparation of amyloid infiltration of outer retinal vessel wall. From Schwartz MF, Green WR, Michels RG, et al: An unusual case of ocular involvement in primary systemic nonfamilial amyloidosis. *Ophthalmology* 1982; 89:394–401.



**Figure 6.** Typical lens footplates seen in advanced vitreous amyloidosis (deposits aligning themselves on posterior lens capsule). From Doft BH, Machemer R, Skinner M, et al: Pars plana vitrectomy for vitreous amyloidosis. *Ophthalmology* 1987; 94:607–611.

Retinal hemorrhages with dot and linear shapes may be seen. In angiography, retinal vascular involvement present with blockage from vasocclusive abnormalities and focal or diffuse leakage that is more prominent in posterior pole than retinal periphery. Another clinical presentation of vitreous amyloidosis is central vitreous opacities that make footplate-like opacities on the posterior lens capsule.

In OCT (optical coherence tomography) veil like vitreous opacities shows needle-shaped deposits on the retinal surface that extend to the vitreous cavity and immunohistochemistry studies demonstrate amyloid-light chain deposits.



**Figure 7.** Magnified view of vitreous opacification. From Schwartz MF, Green WR, Michels RG, et al: An unusual case of ocular involvement in primary systemic nonfamilial amyloidosis. *Ophthalmology* 1982;89:394–401.

Treatment modalities for vitreous amyloidosis is limited to vitrectomy and leads to significant visual improvement, but unfortunately opacities can reoccur in one-fourth of patients over months. Incomplete vitrectomy proposed as the reason of this amyloid reaccumulation. Tight adhesion of these opacities to the perivascular regions potentially can lead to formation of retinal breaks during surgery.

Glaucoma as an independent condition in vitreous amyloidosis or concurrently developed complication, can be managed with filtering surgery at the time of vitrectomy or at any time postoperatively.[43-55]

## 10. Amyloidosis of the cornea

The Cornea as an important transparent structure of human visual system can be affected in Systemic and localized amyloidosis, either as a primary site of Amyloid deposition or secondarily.

*Primary localized corneal amyloidosis* consists of two localized inherited corneal involvements, gelatinous droplike dystrophy and lattice corneal dystrophy types I and III. In these dystrophies the amyloidosis is localized to the cornea without systemic manifestations.

*Primary systemic amyloidosis* is known as lattice corneal dystrophy type II (LCD II), (also known as familial amyloidotic polyneuropathy type IV, or Meretoja syndrome.)



*Secondary localized corneal amyloidosis* has been observed in a variety of corneal and ocular diseases such as trichiasis, trachoma, leprosy, sarcoidosis, interstitial keratitis, phlyctenular keratitis, uveitis, chronic post-traumatic inflammation, glaucoma, and keratoconus.

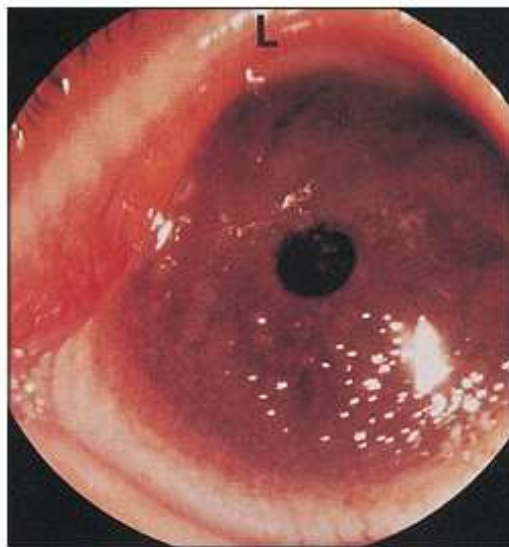
*Secondary systemic amyloidosis* does not affect the cornea.[56-59]

## 11. Gelatinous drop-like corneal dystrophy

Gelatinous drop-like corneal dystrophy (GDCD), (also known as: Lattice corneal dystrophy type III, Familial subepithelial corneal amyloidosis, primary familial amyloidosis of the cornea) is a rare corneal dystrophy, first described by Nakaizumi in 1914 and mainly affects Asian descent but can occur in diverse ethnic groups throughout the US, Europe and Asia.<sup>14,15</sup>

Inheritance pattern of this dystrophy is Autosomal Dominant and its gene (TACSTD2 gene) located on 1p32. Although more than 25 mutations in TACSTD2 gene encoding *Tumor-associated calcium signal transducer 2* have been described, some patients with this corneal dystrophy don't have this mutation suggesting genetic heterogeneity and probability involvement of other genes in this autosomal recessive disease.

This dystrophy presents in young adulthood (within the 1st and 2nd decades) and tends to be slowly progressive.



**Figure 8.** Primary, gelatinous droplike dystrophy of the cornea. From Ohnishi Y, Shinoda Y, Ishibashi T, Taniguchi Y: The origin of amyloid in gelatinous drop-like corneal dystrophy. *Curr Eye Res* 1982–1983; 2:225–231.

Cornea of these patients on slit-lamp biomicroscopy shows gelatinous white deposits of amyloid in the subepithelial and Bowman's layer, giving a multilobulated mulberry-like appearance to the cornea. These deposits spread laterally and deeply within the stroma with time and

can make larger nodular lesions leading to photophobia, vision loss and foreign body sensation. These lesions marked on with fluorescein staining and sometimes superficial vascularization appears on the cornea. Severe vision loss is secondary to coalescence of these deposits on the cornea surface. Some cases of cataract have been reported in young patients with this dystrophy. Fusiform appearance of deposits in corneal stroma of some patients resembles Lattice Corneal Dystrophy (LCD) and some ophthalmologists categorize Gelatinous Drop-like dystrophy as LCD type III. In this disease, the amyloid contains lactoferrin, but the disease is not linked to the lactoferrin gene.

Treatment is with repeated superficial keratectomy because of early recurrences on corneal grafts. In GDCD, the response to both lamellar and penetrating keratoplasty as well as to a superficial keratectomy is unsatisfactory as amyloid deposition recurs in the graft within about 5 years. Soft contact lenses are effective in managing the abnormal epithelial permeability to decrease recurrences.[56-69]

## 12. Lattice Corneal Dystrophy (LCD)

Lattice corneal dystrophy is the second form of inherited localized amyloidosis and is the most common form of corneal stromal dystrophies. This dystrophy typically is a bilateral disease with an autosomal dominant inheritance which presents at the first and second decade of life with symptoms like recurrent corneal erosion and decreased vision.

The term of Lattice for this dystrophy has been originated for the network of thin and delicate interdigitating branching opacities of the cornea in two separate common types of this stromal dystrophy. Lattice Corneal Dystrophy type 1 (LCD I) and its variants are due to a specific mutation in the TGFBI gene and patients with this form of corneal dystrophy have no systemic manifestations, but in LCD type II systemic manifestations are inevitable part of corneal disease and this form resulting from a mutation in Gelsolin (GSN) gene.

Five subtypes of LCD have been identified, we will discuss in this section about Lattice corneal dystrophy type I, II, III. Other sub-types of this dystrophy are very rare disorders. [56,70,75]

### 12.1. Lattice dystrophy type (I)

This type of LCD is the most common form and also known as Biber-Haab-Dimmer corneal dystrophy. LCD1 usually presents its manifestations at the end of the first decade of life, but occasionally it begins in middle life and rarely in infancy and typically is a bilateral disease although occasional unilateral involvement may occur. Corneal sensation is often decreased and the network of interdigitating corneal filamentous opacities has some similarity to nerves, although these lesions are not apparent in all affected members of families with LCD1. Although LCD 1 is seen most often in the western world but some cases have been reported from Bulgaria, Spain and China.

Characteristics	Lattice Corneal Dystrophy			Gelatinous drop-like corneal dystrophy
	Type I	Type II	Type III	
Usual age at onset	<10 years	>20 years	>40 years	<20 years
Visual acuity	Markedly impaired by age 40–60 years	Usually good until after age 65 years	Impaired after 60 years	Markedly impaired by age 10–30 years
Systemic amyloidosis	No	Yes	No	No
Mode of inheritance	Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal recessive
Facies	Normal	Masklike facial expression, blepharochalasis, floppy ears, protruding lips	Normal	Normal
Nervous system	Normal	Cranial and peripheral nerve palsies	Normal	Normal
Skin	Normal	Dry, itchy, and lax with amyloid deposits	Normal	Normal
Cornea	Delicate interdigitating network of filaments; no lines present at early stage; lines difficult to see at late stage	Thick and radially oriented lines	Thick lines	Multiple prominent subepithelial nodules
Episodic corneal erosion	Yes	Yes	No	No

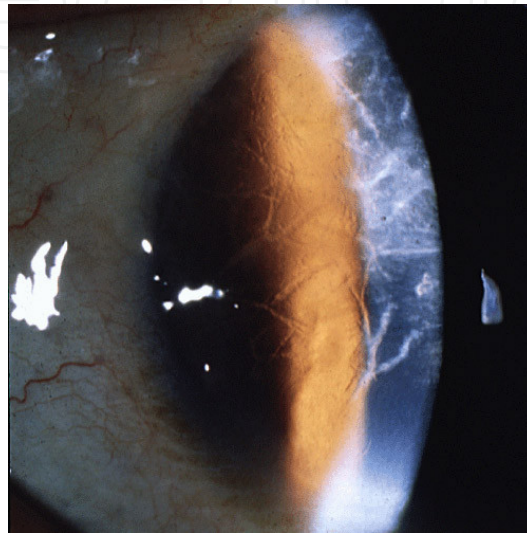
From Hida K, Tsubota K, Kigasawa K, et al: Clinical features of a newly recognized type of lattice dystrophy. *Am J Ophthalmol* 1987; 104:241–248, 1987.

**Table 2.** Comparison of Inherited Varieties of Corneal Amyloidosis.

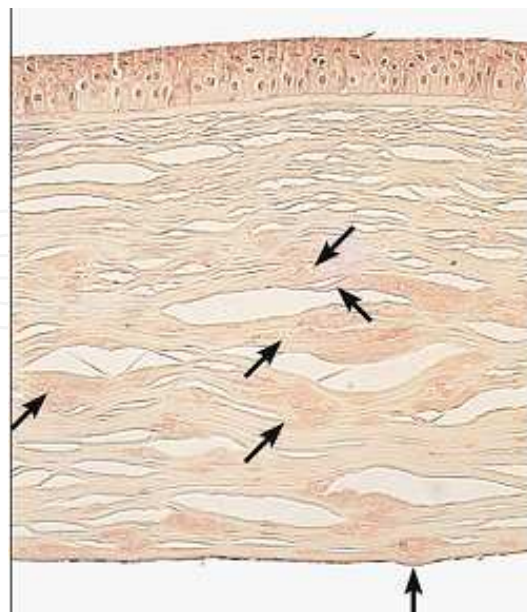
At the time of presentation in the first or second decade of life Rod-like fine glassy opacities in the anterior stroma appear and over time this opacities become denser and combine together and make a network of linear branching and interdigitating opacities. These opacities usually are denser anteriorly and centrally but peripheral cornea is usually spared and classical branching lattice figures may not be present in all cases. The lines are relatively fine, as opposed to the more ropy opacities seen in lattice dystrophy Type III.

LCD I in light microscopy reveals Amyloid deposits in anterior stroma and subepithelial region that may lead to poor adhesion between corneal epithelium and stroma and secondary recurrent corneal erosion. Other pathologic features of this dystrophy in light microscopy include epithelial atrophy and disruption, degeneration of basal epithelial cells, and focal thinning or absence of Bowman layer increasing progressively with age and presence of an eosinophilic

layer between the epithelial basement membrane and Bowman layer. Stromal deposition of the amyloid substance can lead to distortion of the corneal lamellar architecture. Amyloid deposition in this dystrophy shows typical Amyloid histopathologic features including metachromasia with crystal violet; ultraviolet fluorescence (yellow-green) with Thioflavin T; and orange-red staining with Congo red and stain with periodic acid-Schiff, and Masson's trichrome, exhibits dichroism and birefringence previously mentioned in this chapter.

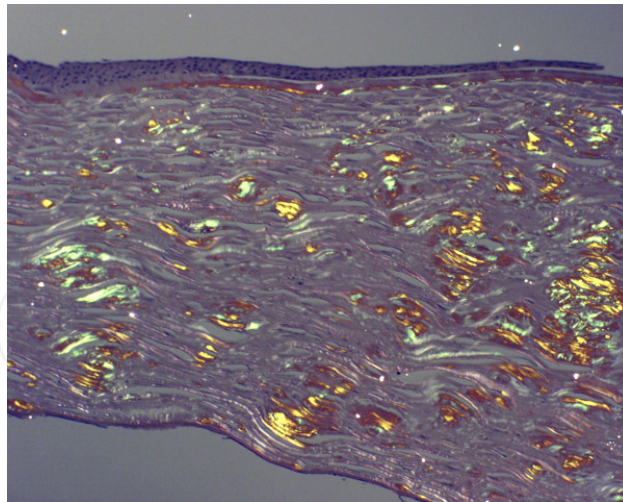


**Figure 9.** Lattice corneal dystrophy type I. Klintworth Orphanet Journal of Rare Diseases 2009 4:7 doi: 10.1186/1750-1172-4-7



**Figure 10.** Lattice dystrophy Type 1. Histopathology using Congo red stain shows the amyloid accumulation throughout the stroma (arrows Yanoff & Duker: Textbook of Ophthalmology, 3rd ed.)





**Figure 11.** Lattice corneal dystrophy type I variant. Deposits of amyloid throughout the corneal stroma due to a p. Ala546Asp mutation in the TGFBI gene in a patient with a variant of LCD type 1. Eifrig DE Jr, Afshari NA, Buchanan HW IV, Bowling BL, Klintworth GK: Polymorphic corneal amyloidosis: a disorder due to a novel mutation in the TGFBI (BIGH3) gene. *Ophthalmology* 2004, 111:1108-1114

Diagnosis of LCD I is based on clinical findings. As mentioned before; this dystrophy has an autosomal dominant inheritance and is due to mutation in the TGFBI gene resulting in isolated amyloid deposition in the cornea without any systemic manifestation.

Recurrent corneal erosions as a common complication of this dystrophy can be managed with options like therapeutic contact lenses, superficial keratectomy or phototherapeutic keratectomy. Despite the fact that this dystrophy may recur in the corneal grafts, severe cases of lattice dystrophy with decreased vision can be treated with lamellar keratoplasty (DALK) or Penetrating Keratoplasty (PK).[56,70-79]

## 12.2. lattice dystrophy type II

(Familial amyloid polyneuropathy Type IV (Finnish type), also known as Meretoja's syndrome)

This dystrophy as a part of systemic disease involves corneal stroma bilaterally and is similar to LCD I, histopathologically and clinically but fine glass-like lines are randomly scattered, radially oriented, less numerous, and more delicate, than those in LCD I. Stromal lattice lines in this dystrophy reach to the peripheral cornea and limbus and central cornea is almost spared in contrast to LCD I. Although corneal sensitivity and nerve density is reduced in this type of LCD, Lattice lines are not related to corneal nerves. Patients with this disease are at increased risk of Open-Angle Glaucoma.

This dystrophy is secondary to the GSN (Gelsolin) gene mutation located on chromosome 9. Gelsolin is an actin severing protein and the abnormal Gelsolin molecule leads to deposition of highly amyloidogenic protein throughout the body. Amyloid deposits in this systemic disease can be seen in the conjunctiva, sclera, and ciliary body, along the choriocapillaris, in the ciliary nerves and vessels, and in the optic nerve. Extraocularly, amyloid is detected in

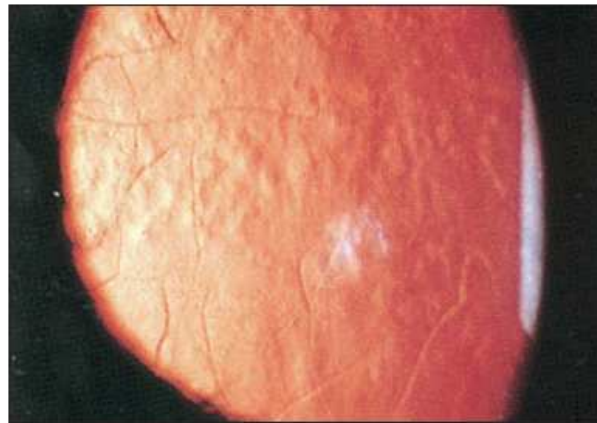
arterial walls, peripheral nerves, and glomeruli. The amyloid in this condition is related to Gelsolin and does not stain for type AA or AP.

LCD II present usually after second decade of life but patients that are homozygous for mutated GSN gene may reveal symptoms earlier. Recurrent corneal erosions are not a common complication in LCD II and vision loss does not significantly occur before sixth decade of life. The pathology is similar to lattice dystrophy Type I. Light microscopy shows amyloid in the lattice lines as a discontinuous band under Bowman layer and within the sclera.



**Figure 12.** Mask like facies of patient with familial amyloid polyneuropathy type IV (Meretoja, Finnish type). From Purcell JJ Jr, Rodrigues M, Chishti MI, et al: Lattice corneal dystrophy associated with familial systemic amyloidosis. *Ophthalmology* 1983;90:1512–1517.)

Treatment modalities are similar to LCD type I, but exposure keratopathy secondary to facial neuropathy in some patients may need additional considerations. [56,80-87]



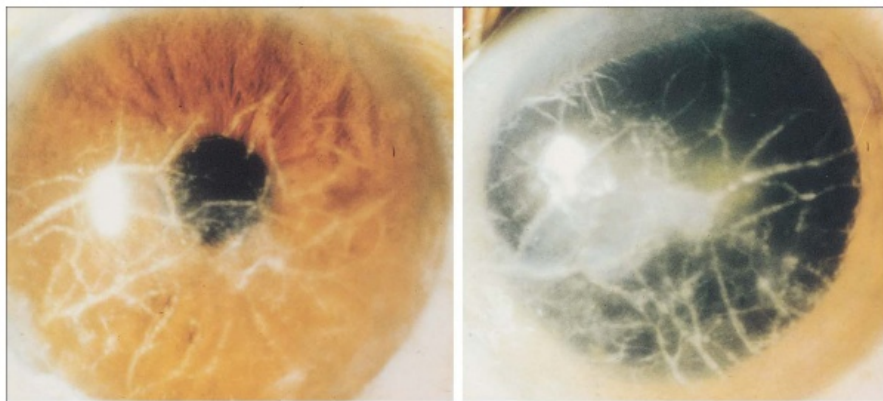
**Figure 13.** Corneal deposits of Meretoja's syndrome (lattice type II, familial amyloidotic polyneuropathy type IV). Note the location along the course of corneal nerves. From Purcell JJ, Jr, Rodrigues M, Chishti MI, et al: Lattice corneal dystrophy associated with familial systemic amyloidosis. *Ophthalmology* 1983;90:1512–1517.

### 12.3. Lattice dystrophy type III & IV

Lattice dystrophy Type III is an autosomal recessive disease that presents often after fourth decade of life (later than LCD type I). Lattice lines in this dystrophy are thicker than type I and corneal erosions rarely occur. Amyloid usually deposits in the superficial stroma and beneath the Bowman's layer and also can be found in mid-stroma.

LCD IIIA has been described with autosomal dominant inheritance and corneal changes similar to LCD type III; but in this subtype recurrent corneal erosions are more prevalent. This disorder is due to a defect in the keratoepithelin gene, demonstrated at various codons.

LCD IV is a late-onset corneal dystrophy that has been reported in Japanese population and is secondary to mutation in TGFBI gene. In this subtype of LCD amyloid deposition is in deeper stromal layers of cornea.[88-91]

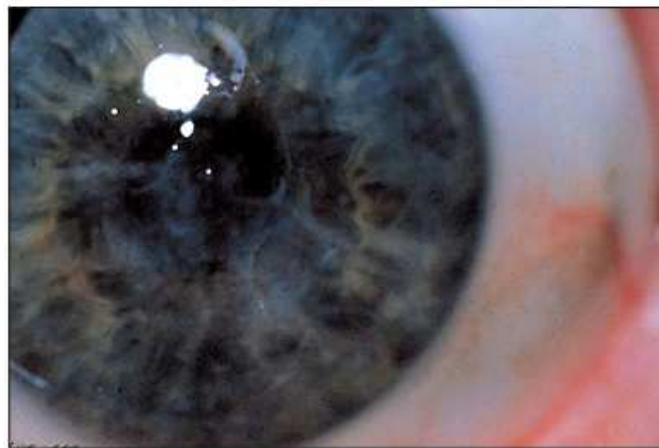


**Figure 14.** Thick ropey lattice lines in patient with LCD III. From Hida T, Tsubota K, Kigasawa T, et al: Clinical features of a newly recognized type of lattice corneal dystrophy. *Am J Ophthalmol* 1987; 104:241-248.

### 13. Polymorphic amyloid degeneration

This is a specific type of corneal amyloid degeneration that generally occurs after fifth decade of life. This condition is usually bilateral and incidental finding in elderly without much affect on vision. In slit-lamp biomicroscopy deposits with punctate glass-like appearance can be seen in central corneal stroma with extension to descemet's membrane. Sometimes these deposits resemble lattice dystrophy although usually these deposits are less denser than LCD. Histopathologically there is a similarity between polymorphic degeneration and LCD. The reason of this degeneration has not been clearly described and no treatment is usually required for this patients.

Climatic proteoglycan stromal keratopathy is another condition similar to spheroidal degeneration of cornea first time described in Saudi Arabia. Patients with this condition have bilateral oval, central horizontal haziness in anterior stroma that may accompany with refractile stromal lines but does not usually affect vision. In histopathologic review of these patients proteoglycan and amyloid deposits have been found.[92,93]



**Figure 15.** Polymorphic amyloid degeneration of the cornea. From Ohnishi Y, Shinoda Y, Ishibashi T, Taniguchi Y: The origin of amyloid in gelatinous drop-like dystrophy. *Curr Eye Res* 1982–1983; 2:225–231.

### 14. Secondary localized amyloidosis

Wide variety of chronic ocular disorders can lead to corneal amyloid deposition including; keratoconus, trachoma, phlyctenulosis, leprosy, bullous keratopathy (of any etiology), prolonged contact lens wear, trichiasis, uveitis, and severe retinopathy of prematurity with glaucoma.

Amyloid Deposits secondary to these conditions are usually subepithelial and appear as cream-colored nodules very similar to Gelatinous-drop like corneal dystrophy. Corneal vascularization in relation to primary disorder can be seen. Genetic work up must be done to rule out systemic inherited amyloidosis.



Keratoconjunctivitis sicca may be associated with amyloidosis with several mechanisms. The first mechanism is lacrimal gland infiltration in primary localized amyloidosis, with secondary hyposecretion of tears. The second mechanism is orbital nerve infiltration with associated autonomic neuropathy. Reactive (secondary) systemic amyloidosis has been reported with Sjögren syndrome, a condition frequently heralded by dry eyes. Finally, a systemic immunocyte dyscrasia, with or without systemic amyloidosis may result in neoplastic infiltration of the lacrimal gland and associated dry eye.[94-96]

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