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Progressive bilateral localized Amyloidosis of the Eyelids/Conjunctiva –Four Years after MALT lymphoma

Clinical History:

In 2018, a 58-year-old patient was diagnosed at an external clinic with a B-cell-dominant, clonal lymphocytic infiltration of the left lower eyelid. Histology confirmed marginal zone lymphoma of the MALT (mucosa-associated lymphoid tissue) type, accompanied by nodular amyloid deposits. Orbital MRI ruled out deeper extension. The patient underwent local surgical excision without adjuvant radiotherapy.

In June 2022 four years later, the patient was referred in our clinic due to progressively thickened, ptotic upper eyelids and yellowish nodular conjunctival lesions bilaterally. Visual acuity had declined significantly over the previous year, primarily due to severe ocular surface disease.

Ophthalmological examination revealed a visual acuity of 0.8 in the right eye and 0.6 in the left eye, intraocular pressure of 18 mmHg (right) and 17 mmHg (left), ptotic, thickened upper eyelids, nodular yellowish changes in the conjunctiva (bilaterally), and meibomian gland dysfunction. Apart from early cataract formation in both eyes, the anterior segments were otherwise unremarkable. Fundus examination was age-appropriate in both eyes.

MRI of the orbits and brain excluded orbital mass lesions.

In September 2022 two conjunctival biopsy specimens are made.

Ocular Pathology (September 2022):

Macroscopy:

Two mucosal tissue fragments, gray-brown in colour, with a maximum diameter of 3 mm.

Microscopy:

Histologically, two conjunctival biopsy specimens are present (from the superior nasal bulbar conjunctiva on the left side and the lateral fornix on the right side): both showing identical histological features.

Each specimen consists of conjunctival tissue covered by flattened, stratified, non-keratinizing squamous epithelium. Within the epithelium, several grouped goblet cells are observed. The substantia propria is extensively infiltrated by dense, Congo red-positive, birefringent amyloid deposits.

Immunohistochemistry:

Immunohistochemical staining was performed for further characterization of the amyloid material. The deposits showed positivity for lambda light chains with both antibody clones ULI-LAT and HAR, as well as for the P component. Staining for amyloid A, transthyretin (ATTR), and AL-kappa remained negative.

Electron Microscopy:

Ultrastructural analysis confirms the presence of amyloid deposits. These appear as non-branching, randomly arranged fibrils measuring approximately 7–12 nm in diameter, consistent with the characteristic ultrastructural features of amyloid.

Diagnosis: Localized AL amyloidosis, lambda type

Systemic Workup (October 2022)

- No evidence of monoclonal gammopathy in serum or urine
- Normal renal and cardiac function
- Biopsies of bone marrow, abdominal fat, and labial gland: no amyloid deposits
- Lip biopsy ruled out Sjogren's syndrome

Clinical Progression (Late 2022 – Mid 2023)

Despite intensive topical therapy (lubricating eye drops, anti H1 eye drops), the patient developed:

- Worsening ptosis, especially impacting the visual field
- Chronic follicular conjunctivitis and blepharitis
- Refractory ocular itching
- Allergy testing without evidence of type I sensitization: Prick test negative, total IgE and specific IgE against house dust mites unremarkable
- MRI: asymmetrical contrast enhancement of the upper lids, no muscle infiltration

Rebiopsy and Local Radiotherapy

- Supratarsal conjunctival biopsy (June 2023): Recurrence of MALT lymphoma (CD20+, lambda light chain restriction) with AL amyloidosis
- **Predictive marker analysis:**
 - CD20 (Rituximab target): Strong positive
 - CD38 (Daratumumab target): Largely negative except for a few plasma cells
 - BCL2 (Venetoclax target): Strong and diffuse positivity
 - Ki-67 (general predictor of chemosensitivity): 2%
- Radiotherapy: 2 × 2 Gy to each eye (July and September 2023)
- Temporary improvement, but insufficient long-term control

Systemic Immunochemotherapy (January 2024)

Due to persistent symptoms and ptosis-related visual field obstruction:

- Systemic treatment with 8 cycles of Rituximab + 12 cycles of Lenalidomide
- Good response after 3 months: significant reduction in eyelid swelling and avoidance of work disability
- After 7 months: Reduced amyloid deposits, improved sicca symptoms, early nuclear cataracts noted
- After 12 months: Visual acuity improved to 0.6 (RE) and 0.8 (LE); lid swelling markedly reduced; minimal conjunctival scarring; almost complete resolution of yellowish deposits

Planned Surgery

- May 2025: Bilateral surgical debulking of residual eyelid tissue under continued Rituximab therapy and perioperative antibiotic prophylaxis

Discussion:

This case underscores the diagnostic and therapeutic challenges in managing localized AL (light chain) amyloidosis of the conjunctive and eyelids, occurring in the context of recurrent ocular MALT lymphoma. Amyloidosis encompasses a heterogeneous group of diseases characterized by extracellular deposition of insoluble protein fibrils, typically resulting from protein misfolding. These deposits can be systemic or localized, with clinical significance varying accordingly.

Orbital and adnexal amyloidosis is uncommon only a few large series have been reported with much literature limited to case reports and smaller case series (1,2,3). In the ocular region, localized amyloidosis most frequently involves the eyelids and conjunctiva, presenting with ptosis, eyelid thickening, and nodular, yellowish conjunctival lesions, as seen in this patient. While ocular amyloidosis can occasionally

be the first manifestation of systemic disease, it is more often localized and associated with chronic inflammatory or neoplastic conditions such as MALT lymphoma [1].

Histopathologic analysis in our case confirmed lambda light chain-restricted AL amyloidosis, with no systemic involvement based on extensive clinical, serologic, and histopathologic evaluation. The localized deposition of amyloid in the conjunctiva and eyelids was secondary to recurrent MALT lymphoma, a phenomenon that is rare but documented in the literature [2,3,4]. Therefore, ruling out systemic involvement is essential in all such cases. Despite the initially localized nature of the disease and absence of systemic findings, the patient experienced significant morbidity, including progressive ptosis, refractory ocular surface inflammation, and visual impairment.

Although low-dose local radiotherapy (2x2 Gy) offered temporary relief, it failed to achieve sustained control - contrasting with prior reports suggesting good outcomes after fractionated doses of 20–30 Gy [5,6]. In our case, six months of follow-up showed only transient benefit, highlighting the variable responsiveness of such lesions to radiation.

The decision to initiate systemic immunochemotherapy was guided by histological confirmation of lymphoma recurrence, as well as functional impairment. The treatment regimen of Rituximab plus Lenalidomide was chosen based on existing evidence supporting its efficacy in extranodal marginal zone lymphomas, including ocular MALT lymphomas [7]. Rituximab targets CD20+ B-cells, while Lenalidomide exhibits immunomodulatory and anti-angiogenic effects, which may also contribute to the regression of amyloid deposits.

Our patient demonstrated excellent clinical response with systemic therapy, showing marked reduction in eyelid swelling, resolution of amyloid deposits, and functional improvement. This supports the notion that systemic therapy, although typically reserved for disseminated lymphoma, can have significant benefit in selected cases of recurrent localized disease with secondary amyloidosis.

Finally, the planned surgical debulking of residual eyelid tissue will aim to further optimize lid function and cosmetic outcomes. Post-treatment surgery may play a complementary role in managing residual fibrosis or mass effect once the active inflammatory and neoplastic processes are controlled.

References

1. Banerjee P, Alam Set al. Orbital and adnexal amyloidosis: Thirty years experience a tertiary eye care center. *Indian J Ophthalmol*2021;69:1161-1166.
2. Dammacco R, Merlini G et al. Amyloidosis and Ocular involvement: an Overview. *Semin Ophthalmol*2020;35:7-26.
3. Demirci H, Shields CL et al. Conjunctival amyloidosis:Report of six cases and review of the literature. *SurvOphthalmol*2006;51:419–33.
4. Mora-Horna ER, Rojas-Padilla R et al. Ocular adnexal and orbital amyloidosis: a case series and literature review. *Int Ophthalmol*2016;36:281-298.
5. Prager AJ, Habib LA et al. Long-Term Follow-Up of 4 Patients with Conjunctival Amyloidosis. *Ocul Oncol Pathol*2018;4:313-317.
6. Martel A., Oberic A. Moulin A. et al. Clinical, radiological, pathological features, treatment and follow-up of periocular and/or orbital amyloidosis: Report of 6 cases and literature review. *J Fr Ophthalmol*2018;41:492-506.
7. Yang L, Yanju L et al. Efficacy and safety of lenalidomide in the treatment of B-cell non-Hodgkin lymphoma. *Discov Oncol* 2024;5;15(1):105.