

Clinical and histopathological aspects in two cases of ligneous conjunctivitis

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Abstract

Ligneous conjunctivitis represents a very rare form of chronic membranous conjunctivitis, with unknown etiology; less than 200 cases have been reported in the literature, most of them in infants and children. After 40 years, this condition appears in exceptional circumstances. We present, in this study, two patients (of 55 and 64 years old) with very severe forms of ligneous conjunctivitis, certified by histopathological examination, one of them being previously diagnosed with Lyell's syndrome. The histological examination in ligneous conjunctivitis is important for diagnostic but also to elucidate the etiopathological context. A discontinued hyperplastic conjunctiva with numerous nuclear abnormalities and marked intra- and inter-cellular edema was characteristic for both cases. The epithelium layer presents large area of extension into the connective tissue, in the form of cysts and gland-like structures, or creating deep epithelial lacunas, with goblet cells. The connective subepithelial tissue presents diffuse inflammatory infiltration, with round cells, especially near vessels. Inside the conjunctival tissue, big hyaline areas with rare cellularity are detected. The amorphous deposits containing fibrillar material are also present. At the level of pseudomembranes, we recorded a massive exudation of fibrin with an inflammatory cellular infiltration, and large areas containing an amorphous eosinophilic hyaline material. The association of ligneous conjunctivitis with Lyell's syndrome in one of our patients suggests its immuno-allergic etiology.

Keywords: ligneous conjunctivitis, mast cell, Lyell's syndrome.

Introduction

Ligneous conjunctivitis is an extremely rare form of chronic membranous conjunctivitis, characterized by "wood-like" lesions of the conjunctiva that produce in most cases, chronic corneal ulcerations with decreased vision [1]. It was previously described in young children, with a slight predominance in females; an autosomal recessive inheritance pattern is apparent in some cases [2]. In old persons, this condition appears exceptional, but several cases have been already presented in literature [3].

In a period of 25 years, in the Emergency County Hospital of Craiova, Romania, we diagnosed two cases of ligneous conjunctivitis in old persons, both of them characterized by severe evolution and tendency to recur, despite the medical and surgical treatment.

Case presentations

Case No. 1

Patient S.R., 64 years old, presented history of bilateral inflammation of the palpebral portion of the conjunctiva, with hypersecretion and formation of pseudomembranes. In the both eyes, numerous thick, yellowish-white, fibrous pseudomembranous layer of conjunctival

proliferation had developed, spreading from the inner side of the upper and lower eyelids of both eyes.

Ophthalmological examination:

- Right eye visual acuity: 0.9;
- Left eye visual acuity: 0.9;
- Right eye ocular pressure: 17 mmHg;
- Left eye ocular pressure: 16 mmHg.

Biomicroscopic examination presented thick, yellowish-white pseudomembranes and conjunctival proliferation with ligneous induration on the conjunctiva, especially located on the upper eyelids. Cornea is transparent, medium anterior chamber, clear aqueous humor, normal iris design, and posterior cortical lens densification. Fundus eye examination showed normal optic nerve head, retinal arteriosclerosis, and degenerative lesions of the peripheral retina.

General examination – without similar lesions involving other membranes.

Vital signs: body temperature 36.6°C, pulse 62 beats/min., respiratory rate 14 breaths/min., the blood pressure 150/70 mmHg.

Lungs and heart auscultation – without clinical modifications; soft abdomen, no hepatosplenomegaly.

Laboratory data in normal limits.

The pseudomembranes have been removed surgically with local treatment with antibiotics, corticosteroids, and

cyclosporine, and histopathological examination has been performed.

The study of bioptic material has been performed on 5 µm sections, in Hematoxylin–Eosin (HE) and Masson's trichrome stainings. The histological examination of pseudo-membranes of the eyes exhibited massive exudation of fibrin with an inflammatory cellular infiltration, a disrupted epithelium, and areas containing an amorphous, eosinophilic, hyaline material. A moderate vascular chronic inflammatory-cell infiltrate with numerous mast cells is present in the perivascular spaces. The conjunctival epithelium presents disseminated epithelial ulceration with hyperplasia and extension of the epithelial layer into conjunctival structures. We also noticed diffuse inflammatory conjunctival infiltration, and numerous small vessels with irregularities of their caliber and very thin wall. Hyaline areas with rare cellularity and fibrillar material are also present. These findings confirm the diagnosis of ligneous conjunctivitis in this patient (Figure 1).

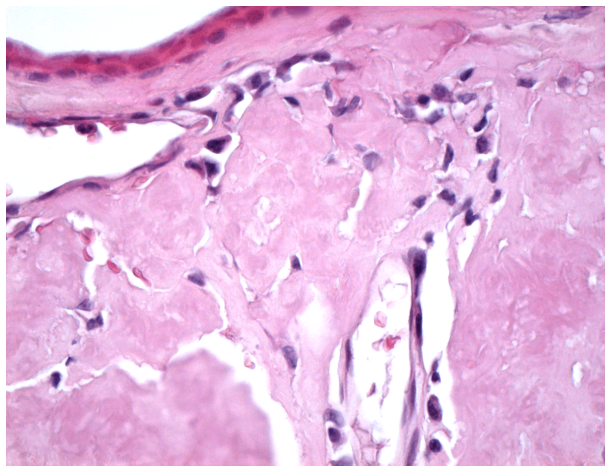


Figure 1 – Patient S.R., ligneous conjunctivitis: infiltration with hyaline material; under the epithelial tissue, the conjunctival structure appears dense and infiltrated with inflammatory perivascular cells. HE staining, ×200.

The patient was treated by local antibiotics, steroids and topical sodium cromoglycate (inhibitor of mediator release from the mast-cell granules). The evolution was moderate favorable after therapy, that supports the theory that mast cells are involved in the pathogenesis of ligneous conjunctivitis, but after excision, the membranes had the tendency to reappear.

Case No. 2

Patient I.M., 55 years old, has been hospitalized in the Clinic of Ophthalmology by hyperplastic chronic conjunctivitis, and recurrent corneal ulcerations. Symptoms appeared in the last two years, when patient noticed on the lower tarsal conjunctiva, several prominent and recurrent vesicles, associated with symptoms of irritation, grittiness, photophobia. When we decided hospitalization, patient presented intense chemosis, eyelid edema, subconjunctival hemorrhages and a deep inferior corneal infiltration on the right eye. These symptoms increased in intensity in the last period, despite any treatment, and the inflammation extended to the orbital tissue, with axial moderate exophthalmia.

Ophthalmological examination:

- Right eye visual acuity: 0.8;
- Left eye visual acuity: 1;
- Right eye ocular pressure: 23 mmHg;
- Left eye ocular pressure: 15 mmHg.

Biomicroscopic examination presented on the right eye a ligneous induration on the conjunctiva, that appears hyperplastic and intense hyperemic. In the lower fornix, conjunctiva presents chemosis, and subconjunctival hemorrhages. On the left eye, several macropapillae with nodular aspect are restricted in the inferior fornix.

Fundus eye examination showed normal optic nerve head, constricted arteries, and dilated venules, Salus–Gunn sign stage II, normal retina.

General examination presented papular exanthema, purpuric macules and polycyclic erythematous placards disseminated on hands, legs and face that rapidly progress and the skin begins to sag from the body and it is peeled off in great swaths. They also severely affected the mucous membranes, the mouth anal and genital mucosa, lesions characteristic for Lyell's syndrome. The diagnostic was certified by dermatological examination.

Vital signs were the body temperature 38.6°C, pulse 74 beats/min., respiratory rate 18 breaths/min., the blood pressure 140/80 mmHg.

No abnormalities were detected on chest X-ray and electrocardiogram studies.

Laboratory data: hemoglobin (Hb) 11.68 g/dL, hematocrit (Ht) 0.38%, leukocytes 5400/mm³, non-segmented neutrophils (NNs) 3, segmented neutrophils (SNs) 64, eosinophils (E) 1, lymphocytes (L) 28, monocytes (M) 4, glycemia 1.32 g/L, total proteins 47 g/L, albumin 33 g/L, creatinine, electrolytes, bilirubin were unremarkable.

The treatment was instituted immediately, by using prednisone 1 mg/kg body weight, antiallergic therapy, immunotherapy, vitamin therapy, general and local anti-biotherapy and local anti-inflammatory non-steroid and steroid drugs. Surgical treatment has been performed from the beginning: the indurated conjunctiva has been removed, and histopathological exam has been performed. Evolution was satisfactory with epidermization occurring in about 10 days, and moderate favorable ocular evolution after three weeks of treatment.

The study of bioptic material has been performed on 5 µm sections, in HE and Masson's trichrome stainings. Histological examination of the membranous conjunctival lesions shows extensive epithelial ulceration with hyperplasia and extension of the epithelial layer into the substantia propria in the form of cysts and gland-like structures. The exam presented a discontinued conjunctival epithelium, having in some areas all cellular levels, in other areas 1–2 levels, or no epithelium. In different zones, we revealed deep epithelial lacunas with goblet cells. In the level of conjunctival tissue, it is diffuse inflammatory infiltration, with round cells, especially near vessels. The vessels are numerous, with thin diameter and thin walls. Inside the conjunctival tissue, big hyaline areas with rare cellularity are detected. Amorphous deposits containing fibrillar materials are also present (Figures 2 and 3).

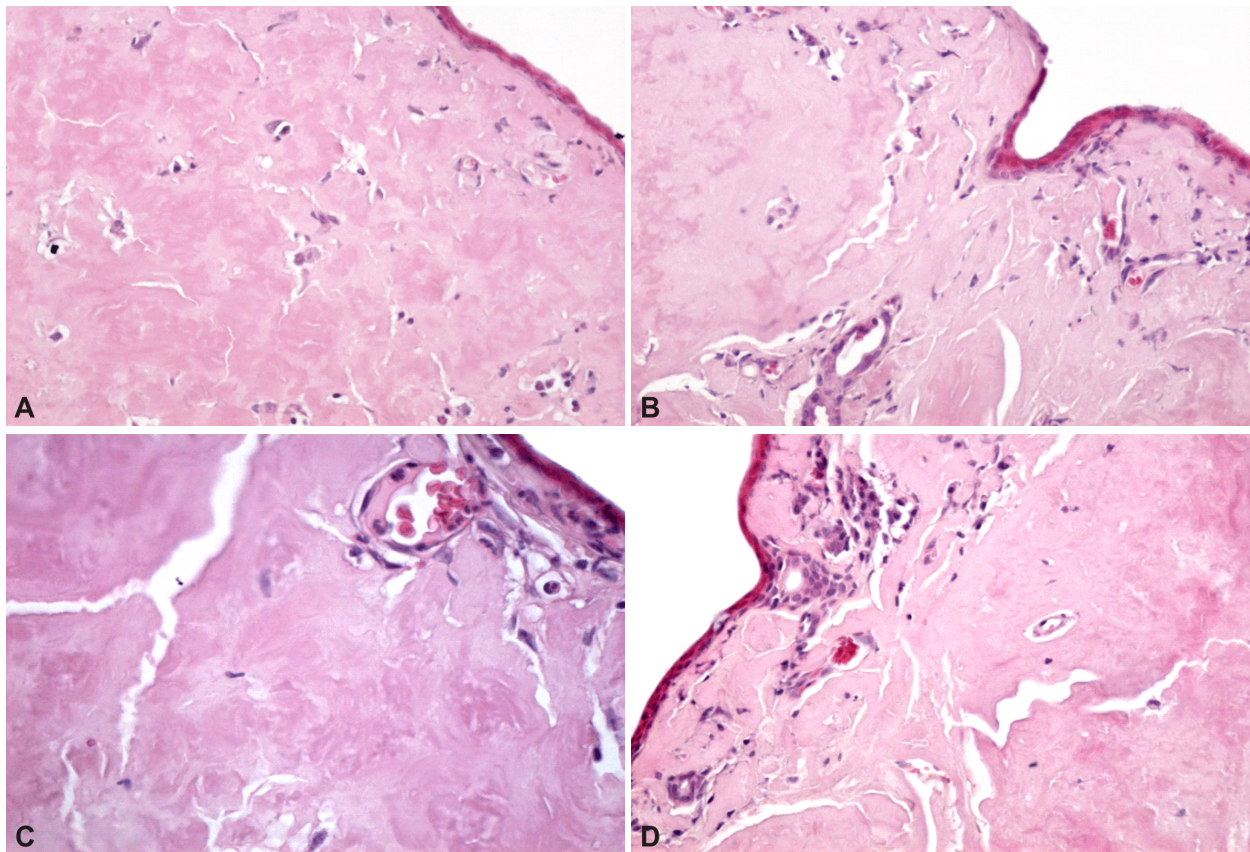


Figure 2 – Patient I.M., ligneous conjunctivitis: areas containing eosinophilic, hyaline material (A–D); diffuse inflammatory infiltration, with round cells, especially near vessels (B–D) and epithelial layer extended into the lamina propria in the form of gland-like structures (B and C). HE staining, $\times 100$.

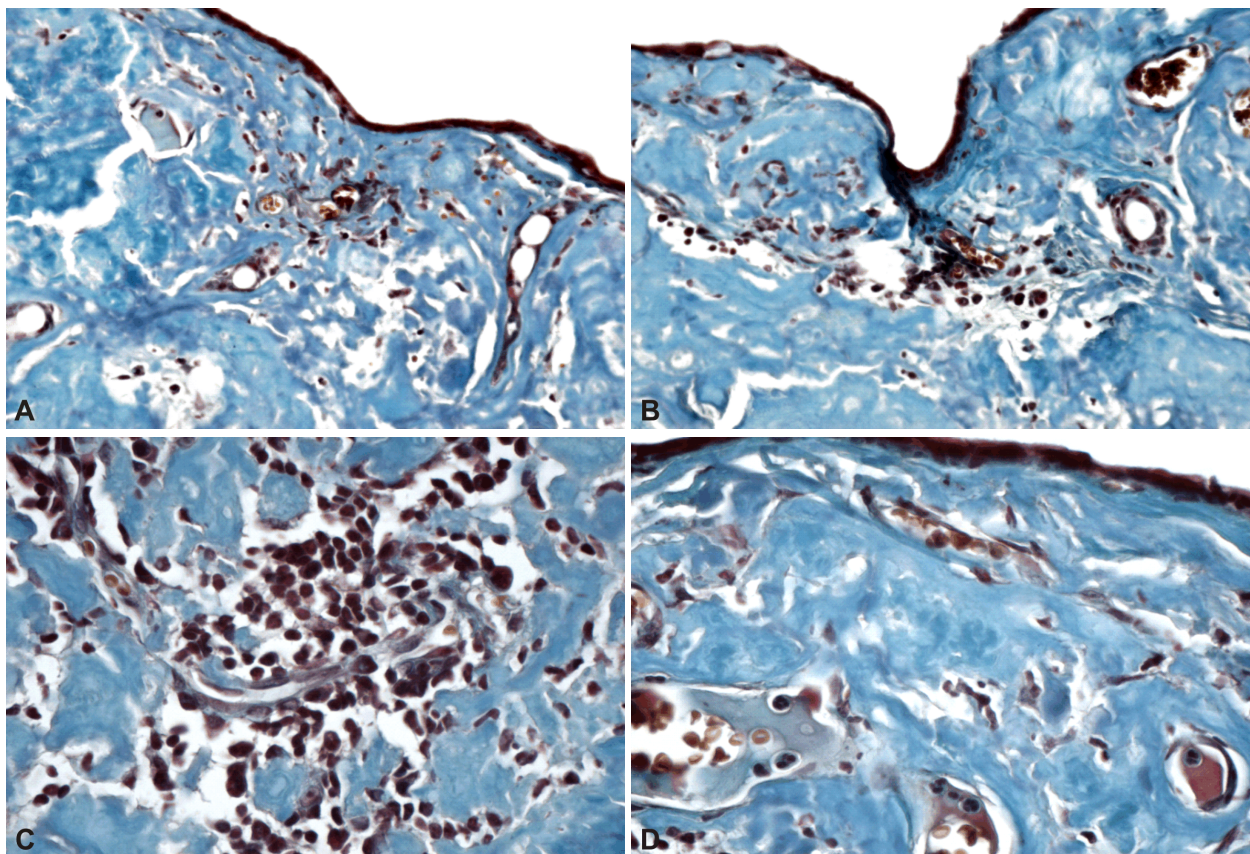


Figure 3 – Patient I.M., ligneous conjunctivitis: (A–D) Areas containing eosinophilic, hyaline material; perivascular inflammatory infiltrate. Goldner–Szekely (GS) trichrome staining: (A and B) $\times 100$; (C and D) $\times 200$.

Discussion

Ligneous conjunctivitis is a rare disease characterized by acute or chronic recurrent conjunctivitis in which the conjunctival membranes acquire a “wood-like” consistency, due primarily to deposits of fibrin [4].

The first report of ligneous conjunctivitis in a 46-year-old man with bilateral pseudomembranous conjunctivitis was published in 1847 by Bouisson [5], but the term of “conjunctivitis lignosa” was introduced by Borel, in 1933, after more than 85 years [6]. Less than 200 cases have been reported in the literature; related of this extremely reduced number of cases, the etiology is still unknown and no satisfactory treatment has been found. Most cases involve infants and children. Less than 20% of cases appear in 4th and 5th decades of life.

Usually, the other mucous membranes, like the mouth, nasopharynx, trachea, and genital tract are involved, so the disease is frequently associated with nasopharyngitis, tracheobronchial obstruction, otitis media, vulvovaginitis, and defective wound healing [7].

The etiology is unclear, but several mutations were detected in the plasminogen gene on chromosome 6 as well as a number a pseudogene and plasminogene-like gene located on chromosome 2. In patients with ligneous conjunctivitis, the plasmin, the active form of enzyme that degrades fibrin, does not function and fibrin deposits accumulate.

It is most frequently reported as a clinical manifestation of severe homozygous or compound-heterozygous hypoplasminogenemia. Prevalence in the general population is unknown but estimates range between 0.13% and 0.42% in healthy subjects with heterozygous hypoplasminogenemia [8].

Conjunctivitis is characterized typically by “woody” induration of the upper tarsal conjunctiva, covered by whitish pseudomembrane. Corneal involvement and chronic obstruction of the eye may lead to blindness [9].

The condition is characterized by initial chronic tearing and redness of the conjunctiva with the subsequent formation of fibrin-rich pseudomembranes. These pseudomembranes form mostly on the upper tarsal conjunctiva but involvement of the lower eyelid and bulbar conjunctiva were reported. The lesions progress to form white, yellow-white, or red thick masses with a “wood-like” consistency that replaces normal mucosa. The disease is bilateral in around half of cases and corneal involvement is present in around a third of cases. Corneal involvement may lead to blindness due to scarring, vascularization, keratomalacia and perforation [10]. In patients with ligneous conjunctivitis, wound healing in mucous membranes is markedly impaired; it seems it remains at the stage of granulation tissue formation [11].

In our both cases, we have noticed that the membranes reappeared almost spontaneously after ablation, determining the eyelid induration; it appears like a post-membranous recidivate granuloma of palpebral conjunctiva with ligneous induration of eyelids.

Hery *et al.* showed that typical histopathological aspects could be identified at the level of false membrane, epithelium, and conjunctival stroma [12].

The false membrane is constituted by fibrin disposed

in network, where the fibers are disposed parallel with the epithelium surface. When the false membrane becomes old, the structure is invaded by connective tissue; the conjunctiva takes a lamellar arrangement, where altered cellules and cellular debris can be identified.

In both our observations, the epithelial surface was affected, normal multilevel dispositions being replaced on large area with abnormal epithelium with 1–2 cellular levels.

The cells were intense altered, with pyknotic nucleus, and intracellular and intercellular edema. Some area were characterized by superficial level keratinization, with epithelial crypts who enter very deep to the conjunctive layer, in the sections having the aspect of isolated epithelial islands, or pseudo-cystic aspect with goblet cell.

Connective tissue presents an important inflammatory infiltration, with large hyaline deposits. Vessels present constricted and dilated areas with extremely thin walls surrounded by inflammatory cells. The vascular wall is imperfect, exuding fibrin, that is present on large areas inside the connective tissue. Mucopolysaccharide exudate frequently overlies large areas of ulceration [13]. Lesions contain large, sparsely cellular deposits of eosinophilic, Periodic Acid–Schiff-positive (PAS+) amorphous material with adjacent acute and/or chronic inflammatory cell infiltrates composed of neutrophils, T-cells, macrophages, B-cells, and mast cells [14]. Neovascularization and deposition of plasma proteins such as immunoglobulin and albumin are frequently present, whereas lipid, amyloid, and keratin are generally not detectable [15]. The amorphous deposits contain fibrillar material, consistent with fibrin, and stain intensely for fibrin by immunohistochemistry.

Experimental studies on animals revealed that after immunization appear in time histological phenomena like ligneous conjunctivitis in predispose persons [16]. Because amorphous deposits present in pseudomembranes also contain other plasma proteins such as albumin and immunoglobulins, it has been suggested that permeability of blood vessels in these lesions may be increased [17]. Electron microscopic studies of pseudomembranous lesions showed abnormal blood vessels with wide gaps between lining endothelial cells that were degenerated and surrounded by a thick and multi-laminar basement membrane [18]. Impaired healing of skin wounds of patients with ligneous conjunctivitis has not been reported in the literature. These apparently contradictory findings may be, at least in part, explained by the fact that the conjunctivae (and other mucous membranes) represent a “locus minoris resistentiae” when compared with normal intact skin [19]. The treatment is extremely difficult and it is not standardized. The results of therapy with hyaluronidase eye drops, corticosteroids, cyclosporine, and antiviral agents are generally disappointing. Repeated surgical excisions of conjunctival pseudo-membranes and topical administration of steroids, cyclosporine, hyaluronidase, and cromolyn (disodium chromoglycate) resulted in only transient and short-term improvement. Surgical excision of pseudomembranes is frequently followed by rapid regrowth of the membranes and is believed to be by itself a trigger for recurrences [20]. Other treatment approaches include topical and sub-conjunctival fresh frozen plasma (FFP), administration

of standard heparin in combination with topical corticosteroids or alpha-chymotrypsin, and topical (or systemic) application of immunosuppressive drugs (cyclosporine A, azathioprine) [21]. In our cases, the local and general anti-inflammatory treatment was indicated for two months. Long-term topical treatment with sodium cromoglycate as an inhibitor of mediator release from mast-cell granules had a moderate favorable effect that supports the theory that mast cells are also involved in the pathogenesis of ligneous conjunctivitis. In time, both cases developed severe recurrences, despite the medical and surgical treatment.

✉ Conclusions

Histological abnormalities of pseudomembranous lesions of ligneous conjunctivitis and its associated complications have been studied in two cases, one of them being previously diagnosed with Lyell's syndrome. In one patient similar lesions have been detected in other mucous membranes of the body indicating that these manifestations are part of a systemic disease. Pseudomembranous lesions of the eyes and other mucosal tissue mainly contain clotted fibrin, histopathological findings revealing markedly decreased extracellular fibrinolysis. Long-term topical treatment with sodium cromoglycate as an inhibitor of mediator release from mast-cell granules had a moderate favorable effect that supports the theory that mast cells are also involved in the pathogenesis of ligneous conjunctivitis.

Conflict of interests

The authors declare that they have no conflict of interests.

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