Delayed-onset ligneous conjunctivitis as a rare association with congenital hydrocephalus: a case report and review of the literature

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Published October 28, 2022.

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doi: 10.5693/djo.02.2022.08.005

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Summary

Ligneous conjunctivitis is an uncommon form of chronic and recurrent conjunctivitis characterized by a thick, “woody,” yellowish pseudomembranous lesion on the tarsal conjunctiva. Plasminogen deficiency plays an important role in this disease, which affects the mucous membranes, including the conjunctiva as well as other systemic organs. In rare cases, congenital hydrocephalus is associated with this disease. We present the case of a 21-year-old woman with delayed-onset bilateral ligneous conjunctivitis and a history of congenital hydrocephalus in infancy. She was treated with topical ophthalmic medication and surgical excision.

Introduction

Ligneous conjunctivitis is a rare, chronic, membranous conjunctivitis that occurs most commonly in females, in infancy, and in children.1 It is characterized by the formation of a yellow-white pseudomembranous lesion on the conjunctiva that progresses to a thick, woodlike membrane mainly on the tarsal conjunctiva.2 It occurs bilaterally in more than 50% of patients. It may be triggered by ocular trauma after local surgeries. Classically, it presents with chronic lacrimation, discomfort, and conjunctival injection.2

Although ocular involvement is most common, some patients present with the pseudomembranous lesion in the extraocular mucosa, such as the mouth and gingiva, nasopharynx, trachea, respiratory tract, ear, vagina, and cervix.3-4 Association with congenital hydrocephalus has also been reported.1,4,5 Type 1 plasminogen deficiency explains pathologies in ligneous conjunctivitis that associate with ligneous lesions in other mucous membranes.1,5 Treatment is challenging, and different therapeutic strategies have been used to treat this disease.2 We report the case of a 21-year-old Iranian woman with a history of controlled
hydrocephalus in infancy who had delayed-onset ligneous conjunctivitis.

Case Report

A 21-year-old woman presented for the first time at the Cornea and External Eye Disease Clinic, Farabi Eye Hospital. Her chief complaints were visual impairment, discomfort, tearing, redness, difficultly blinking, and increased discharge, which had begun 2 years prior to presentation, when she was 19 years of age, and had progressed recently. Medical and family history was obtained from the patient and her parents. The patient had been previously diagnosed with vernal keratoconjunctivitis at another eye clinic and had been treated with topical betamethasone 0.1%, antiallergic drugs, including naphazoline 0.1%, olopatadine 0.1%, and artificial tears for 1 year; however, her symptoms did not respond to treatment.

Her family members had no systemic disease, ocular abnormalities, or ligneous lesions in their eyes or other mucous membranes. The patient informed us that when she was 10 months of age, she had a high fever with seizure and was evaluated for meningitis at a pediatric hospital. She was diagnosed with congenital hydrocephalus, based on clinical presentation, computed tomography, and magnetic resonance imaging. Dandy-Walker syndrome was suspected. Because of persistent symptoms and progressive hydrocephalus signs, ventriculoperitoneal shunt was implanted at this time. By 10 years of age, she had no evidence of seizure and progressive hydrocephalus, which remained controlled in all subsequent examinations (Figure 1). When she was 13 years of age, she had unilateral hearing loss with ear discharge and otorrhea. She was surgically managed with tympanomastoidectomy for cholesteatoma in her left ear.

On examination at our clinic, best-corrected visual acuity was logMAR 0.3 in the right eye and logMAR 0.2 in the left eye. On slit lamp examination, fine diffuse punctate epithelial erosions were present, there was mild right bulbar conjunctival injection, and mild right upper
eyelid erythema and swelling were detected (Figure 2). Anterior and posterior segment examinations were otherwise unremarkable. A yellowish-white membrane with an asymmetric appearance was found under both upper eyelids that adhered to the underlying right tarsal conjunctiva. It was more prominent and thicker in the right eye, and at the left tarsal conjunctiva a small size (4 × 3 mm), thin yellow-white pseudomembrane was detected that peeled off easily. Diffuse hyperemia and follicular reaction were evident near the upper-right fornix (Figure 3). Hematologic studies, including total blood count and serum biochemical markers, were normal.

The patient was diagnosed with ligneous conjunctivitis based on history, clinical examination, and histopathological features. She underwent total excisional biopsies of the right tarsal pseudomembranous lesion. The ligneous lesion was peeled off completely, and surgical diathermy at the right upper palpebral conjunctiva was performed using a bipolar electrosurgical cautery device.

Microscopic sections of a tissue specimen were stained with hematoxylin and eosin. Histopathologic examination showed a thin conjunctival epithelium with thick pink eosinophilic amorphous material in the stroma, admixed with lymphoplasmacytic infiltrative cells that were covered by fibrinoleukocytic exudate in some foci (Figures 4-6). There was no evidence of fungal or bacterial growth. Testing for amyloidosis was not performed.

For maintenance therapy, the patient received intensive topical treatment with betamethasone 0.1% every 4 hours, which was tapered within 3 months, chloramphenicol 0.5% (chlobiotic 0.5%) 4 times a day for 2 weeks, tacrolimus 0.01% twice a day, autologous serum 20% ocular solution every 4 hours, fresh frozen plasma (FFP) every 4 hours, and artificial tears 6 times daily. The patient continued to instill lubricant and autologous serum, FFP eye drops, and tacrolimus 0.01% twice daily for 9 months. We could not evaluate plasma plasminogen activity,
because this laboratory test was not then available in our country.

The patient improved after local surgical excision and the topical regimen. Signs and symptoms completely disappeared within 3 months of surgery. At 10 months after initiation of the postoperative treatment, however, the patient returned with symptoms even more severe than before. We noted recurrence of the ligneous pseudomembranous lesion, which was larger and thicker in size and formed on both upper tarsal conjunctivae (Figure 7). Visual acuity was undiminished in both eyes (logMAR 0.3 in the right eye and logMAR 0.2 in the left eye). The patient again underwent surgical excision with surgical diathermy. The topical medication, including autologous serum 20% ocular solution and FFP eye drops in combination with topical cyclosporine 2% and lubricating drops were continued.

**Discussion**

Ligneous conjunctivitis is an unusual type of chronic conjunctivitis that occurs more frequently in infants and young children than in older patients. It is characterized by a yellowish-white fibrin-rich pseudomembranous lesion or red hard masses that usually present on the tarsal conjunctiva. Many patients have mucoid discharge from their affected eyes. Corneal involvement is a common complication in this disease and may lead to corneal scarring, vascularization, perforation, and poor visual acuity. Ligneous conjunctivitis is often bilateral, with involvement of the palpebral conjunctiva.

Our patient had bilateral tarsal lesions with an asymmetric appearance. In the right eye, there was a thick, dense, hard yellowish lesion attached to the tarsal conjunctiva. However, in the left tarsal conjunctiva, a thinner pink-white membrane was detected, and in the cornea only fine punctuate epithelial erosions were noted. The diagnosis was based on the clinical manifestations and histopathological findings.
Histopathological evaluation showed a fibrinous membrane with inflammatory cells. It should be noted that infectious causes must be ruled out before finalizing a diagnosis of ligneous conjunctivitis. Diagnosis based on histology can be problematic, because there may some disparity in histopathological findings in previously reported cases.

The relationship between hypoplasminogenemia, or decreased plasma plasminogen activity, and ligneous conjunctivitis has been established. Wound healing is a regulated tissue remodeling that entails inflammation, cell proliferation, migration, and extracellular matrix production. In ligneous conjunctivitis, this process in mucous membranes is noticeably impaired or arrested at the stage of granulation tissue formation, and the main content of the pseudomembranes is fibrinogen. This material shows a major deficiency of plasma plasminogen activity due to recessive mutations in the PLG gene, which encodes plasminogen. Therefore, severe type I plasminogen deficiency may explain pathologies found in ligneous conjunctivitis.

We diagnosed ligneous conjunctivitis in our patient solely on the basis of clinical examination and histopathological results, because plasma plasminogen activity measurement was not previously available in our country.

Although the conjunctiva is the most affected membrane in because of its exposure to external irritants, other mucosal tissues have been involved. Also, systemic organs, including the month and gingiva, ear, nasopharynx, trachea, respiratory tract, urinary or female genital tract, and kidney, can show disease involvement, especially during the acute phase of ligneous conjunctivitis. Congenital hydrocephalus is a life-threatening event that is also associated with ligneous conjunctivitis.

The pathogenesis of this condition is still unknown. It may be similar to the mechanism in occlusive hydrocephalus, because of fibrin deposition in the cerebral ventricular system.
damaging circulation of the cerebrospinal fluid in the aqueduct and results in fluid retention.\textsuperscript{1} Children with comorbid ligneous conjunctivitis and congenital occlusive hydrocephalus have been reported in the literature.\textsuperscript{1,4-5,8} Our case highlights the connection between congenital hydrocephalus and ligneous conjunctivitis, but our patient, unlike previously reported cases, had hydrocephalus in infancy, treated with a cerebral shunt, and no contemporaneous evidence of ligneous conjunctivitis; rather, onset of ligneous conjunctivitis in our patient was delayed until she was 19 years of age, when she presented with no symptoms of hydrocephalous.

There is no standard treatment strategy for ligneous conjunctivitis. In our patient, we performed surgical debridement of conjunctival membranes and surgical diathermy to cauterize the bleeding area on the palpebral conjunctiva. Surgical excision is frequently performed, but it may be followed by recurrence of the membranes, requiring reoperation. Recently, combining surgical removal with amniotic membrane transplantation has been shown to decrease the recurrence rate of ligneous pseudomembranes.\textsuperscript{9} On the other hand, local medication and topical treatment with intensive topical heparin, FFP, corticosteroid eye drops, alpha-chymotrypsin, hyaluronidase, and cyclosporine A 2\% have been recommended.\textsuperscript{5,7,10-12} Hyaluronidase alone or in combination with alpha-chymotrypsin is useful for the enzymatic digestion of the mucopolysaccharides that exist on the pseudomembranes. Also, topical corticosteroids and cyclosporine A 2\% may reduce the recurrence of pseudomembranes after surgical excision. Heparin stimulates the activity of antithrombin III, which inhibits thrombin formation, blocks the change of fibrinogen to fibrin, also prevents the transformation of thrombin into prothrombin.\textsuperscript{10} Topical plasminogen drops and intravenous infusions of plasminogen are now available in some parts of the world and should be considered, if available.

Our patient responded well to the second surgery and has not, on continued medical
treatment, experienced recurrence as of the most recent follow-up, 6 months after the second surgery. Ligneous conjunctivitis is a serious though uncommon eye disease. Diagnosis is based on clinical and histopathological examination, but testing of plasminogen levels is helpful for early and precise diagnosis. Timely initiation of medical therapy is necessary for relieving symptoms.

**Literature Search**

A PubMed search on congenital hydrocephalous associated with ligneous conjunctivitis was performed, for English-language publications, with fewer than 130 relevant articles. Case reports on ligneous conjunctivitis associated with hydrocephalous were also searched, with fewer than 30 results. The earliest onset of hydrocephalous found was in infancy. The first presentation of ligneous conjunctivitis was coincidental with hydrocephalous in infancy or childhood, with a short period between presentation of both conditions.\textsuperscript{1,4,13-20} We found no other report of delayed-onset ligneous conjunctivitis associated with congenital hydrocephalus.
References


Figure 1. Cranial computed tomography scan showing dilated cerebral ventricles (A) and dilated cerebral ventricles with cerebral shunt (B).
Figure 2. A, Unilateral mild erythema and swelling in the right upper lid. B, Fibrinous membrane deposits affecting the right eye. C, Superior corneal punctuate epithelial erosions of the right eye.
Figure 3. A, Ligneous conjunctivitis, right eye. B, Fine thin yellow-white pseudomembrane (arrow), left eye, at presentation.

Figure 4. Histopathological examination of conjunctival tissue with hematoxylin-eosin (H&E) stain
(original magnification ×100) showing fibrinoleukocytic exudate (four-point star) on the conjunctival surface; subepithelial tissue shows fibrinoid material (five-point star) surrounded by inflammatory cells (arrow).

**Figure 5.** Histopathological examinations of conjunctival tissue with H&E staining (×400) showing conjunctival tissue covered by epithelium (arrow) and goblet cells (four-point star). The subepithelial area shows fibrinoid material (five-point star) admixed with inflammatory cells.

**Figure 6.** Histopathological examinations of conjunctival tissue with H&E staining (×400) showing thin superficial conjunctival epithelium (arrow) containing polymorphnuclear cells (PMN), stroma with fibrinoid material (five-point star), and chronic inflammatory cells and PMNs (four-point star).
Figure 7. A, Recurrent ligneous conjunctivitis with thick membranous lesion, right eye. B, Pink-white pseudomembrane lesion, left eye.