

Grand Rounds

A 6-week-old baby boy with discharge

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History

A 6-week-old non-Hispanic white boy presented to the Neonatal Intensive Care team of Tulane University Medical Center with a 3-week history of yellow-grey discharge from both eyes; he was otherwise in no distress. He was born by normal vaginal delivery at 37 weeks gestational age after an uneventful pregnancy. He was in the care of foster parents, and the medical history of his biological parents was unknown. There was no other ocular history. He had no known allergies, and his immunizations were up-to-date. He had pulmonary hypertension, a patent ductus arteriosus, and had undergone repair of a diaphragmatic hernia at 1 week of age. For 4 days prior to presentation, he had been administered erythromycin elixir, 400 mg orally four times daily, without improvement in ocular discharge.

Examination

On examination, the pupils were round and reactive to light, the globes were soft by palpation, and extraocular movements were full in both eyes. On pen-light examination, both upper and lower eyelids appeared mildly erythematous with minimal swelling, and a large amount of woody-appearing, thick, mucoid discharge overlying all conjunctival surfaces was present (Figure 1). The underlying conjunctiva appeared white and quiet, and the corneas appeared clear. Dilated fundus examination revealed a cup-to-disc ratio of 0.2 in both eyes. Both discs were pink with sharp edges. The maculae, vessels, and retinal periphery were also normal bilaterally.

Ancillary Testing

A conjunctival scraping was negative for microorganisms (Gram stain) and chlamydia (Giemsa stain); there was no culture growth. Plasminogen enzyme activity was depressed (12%; normal, 75%–125%). A membrane



Figure 1. Thick, woody discharge overlying conjunctiva in both eyes.

peel was performed (see below), and histopathology demonstrated a plaque-like, laminated fibro-inflammatory pseudomembrane with scattered neutrophils and other inflammatory cells (Figure 2). The low plasminogen enzyme activity and the appearance of the palpebral conjunctival epithelium with organizing neovascular ingrowth was consistent with ligneous conjunctivitis.

Treatment

The pseudomembranes in both eyes were surgically removed (Figure 3). Immediately after removal, the patient was placed on prednisolone acetate (1%), 1 drop instilled hourly in both eyes; moxifloxacin (0.5%), 1 drop every 4 hours in both eyes; and heparin 1000 U/ml, 1 drop hourly in both eyes. By 1 month after the procedure, the prednisolone acetate and moxifloxacin had been tapered off completely, and the heparin was reduced to 1 drop every 3 hours. There was no membrane recurrence, but epiphora was present.

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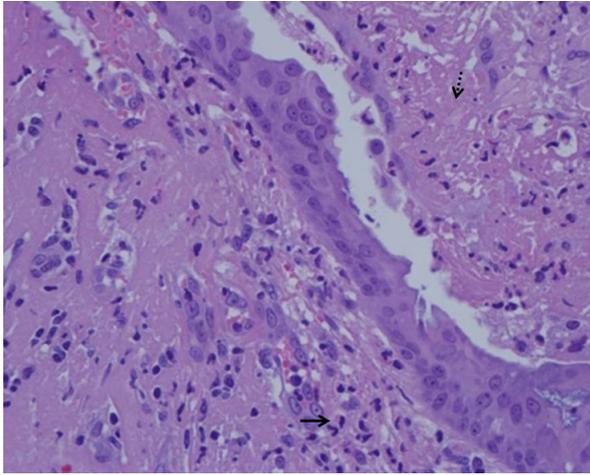


Figure 2. Amorphous fibrinous material (broken arrow) and infiltrating inflammatory cells (straight arrow) in pseudomembrane tissue (hematoxylin-eosin, original magnification $\times 40$).

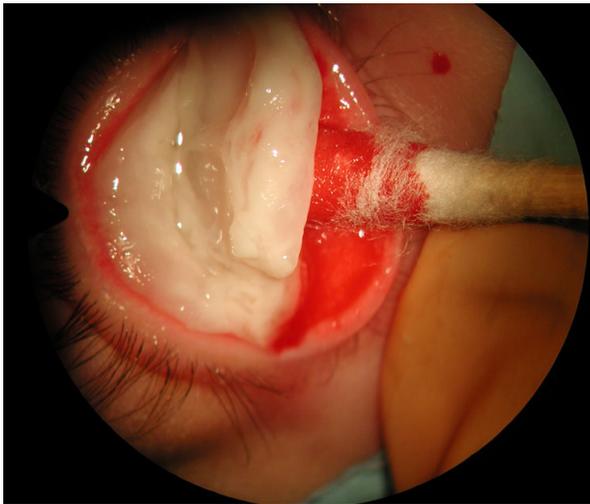


Figure 3. Removal of pseudomembrane.

By 2 months after surgery, the heparin dosage remained unchanged and a small membrane had recurred along both lower lids. The new membrane was removed, and the patient subsequently started on Maxitrol (Neomycin sulfate 3.5mg, polymyxin B sulfate 10,000 units, dexamethasone 0.1%) and heparin 1000 U/ml, 1 drop hourly in both eyes. The Maxitrol was tapered off by 2 months after surgery, and the heparin continued 1 drop every 3 hours; there was no recurrence at this time, but epiphora persisted and a mild entropion of the left lower eyelid was noted.

By 4 months after surgery the membrane had recurred along both lower eyelids and the left lower eyelid entropion persisted, as did the epiphora. A third membrane peel was performed. This time an amniotic membrane graft was placed along the palpebral conjunctiva of both lower lids. Postoperatively, prednisolone acetate, 1 drop hourly, moxifloxacin 4 times daily and heparin, 1 drop hourly, were started. The moxifloxacin was discontinued after 2 weeks and the prednisolone acetate tapered off over 2 months. At last follow-up, 7 months following the second membrane removal, there was no recurrence of membrane formation, the entropion and epiphora were improved, and the heparin (after a slow taper) was discontinued.

Differential Diagnosis

The differential diagnosis for pseudomembranes or membranes most commonly includes severe viral or bacterial conjunctivitis, Stevens Johnson syndrome, and chemical burns. Less common are ligneous conjunctivitis, ocular cicatricial pemphigoid, and superior limbic keratoconjunctivitis. Ligneous conjunctivitis can be distinguished from other causes of pseudomembranes because of its thicker, more homogenous appearance, and by patient history as it is more common in infants than are other causes of membranes such as ocular cicatricial pemphigoid. Pseudomembranes can be differentiated from membranes on peeling: the presence of blood after peeling favors the diagnosis of a true membrane.

Diagnosis

Histopathology of ligneous lesions typically shows fibrin deposition, mixed inflammatory infiltrate, and amorphous, hyaline-like eosinophilic material resembling amyloid but found to be negative with Congo red stain. The inflammatory component in ligneous conjunctivitis is a result of the pseudomembrane, unlike in other etiologies, where the inflammatory component is the cause of pseudomembrane. Our patient's characteristic histopathologic findings in conjunction with his severely decreased level of plasminogen activity and classic woody pseudomembranes confirmed the diagnosis of ligneous conjunctivitis. Whereas the other etiologies of pseudomembrane are primarily inflammatory or infectious in origin, the origin of ligneous conjunctivitis is genetic.

Pseudomembranes covering both eyes were first described by Bouisson in 1847. By 1933 the term *ligneous conjunctivitis* was proposed because the pseudomembrane had a woody appearance. Plasminogen deficiency was genetically linked with ligneous conjunctivitis in

1997.¹ A missense mutation at location K19E on the plasminogen gene (*PLG*) was found to be the most common mutation found in 34% of patients.⁵ At this time there appears to be no racial predisposition in this genetic disorder, although there is a slightly higher incidence in females, and it has been suggested that there may be a higher incidence in areas where consanguinity is more common.^{4,5}

The pathophysiology proposed for ligneous conjunctivitis is that a deficiency in plasminogen leads to deficient extravascular fibrin clearance, with wound-healing arrested at the granulation stage: minor insults to the conjunctiva may lead to an accumulation of the characteristic woody material.^{4,5} The median age of clinical manifestation for plasminogen deficiency is 9.54 months, with ligneous conjunctivitis being the most frequently observed association, in 80% of cases, followed by ligneous gingivitis (34%), respiratory involvement (16%), and ligneous vaginitis (8%). Congenital occlusive hydrocephalus has been associated with plasminogen deficiency in up to 8% of cases.⁵ The clinical course of plasminogen deficiency depends on the site of involvement. When considering ligneous conjunctivitis, erythema of the lid margin precedes epiphora, followed by development of woody conjunctival membranes. The condition is bilateral in roughly 50% of patients. Vision loss occurs in 20–30% of cases, primarily due to corneal involvement. Although most patients present as children, there are case reports of ligneous conjunctivitis in patients over age 55.

The natural history of these lesions is variable. Some resolve without treatment over months, whereas others may last many years. Patients with plasminogen deficiency may have a reduced life expectancy, but this is most particular to the groups manifesting respiratory or cerebral involvement. Pseudomembranes involving the larynx or tracheobronchial tree can lead to recurrent pneumonia and airway obstruction. Pseudomembranes can also lead to a congenital occlusive hydrocephalus, which has a particularly poor outcome.^{4,5}

Surgical excision often results in regrowth, as in our case, and many therapies have been attempted to prevent this, including amniotic membrane transplantation (AMT), local heparin, corticosteroids, cyclosporine, azathioprine, hyaluronidase, oral contraceptives, topical plasminogen, systemic plasminogen, fresh frozen plasma, and allogeneic serum drops. The AMT used in our patient prevented recurrence for 7 months. Barabino and Rolando⁵ first used AMT in the treatment of ligneous conjunctivitis; they reported no membrane recurrence 36 months postoperatively. Recently, Lee and Himmel¹ reported success combining allogeneic serum with topical heparin every two hours plus prednisolone acetate 1% drops 4 times daily. Resolution of a ligneous membrane occurred without surgical intervention over a 2-month period, at which time all drops were discontinued. At 2 year's follow-up there was no membrane recurrence. Many case reports describe good success with plasminogen drops; however this therapy is not available in the US.^{1,2,4,5}

Acknowledgments

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References

1. Lee WB, Himmel K. Fresh frozen plasma treatment of ligneous conjunctivitis: use of heparin and allogeneic serum. *Cornea* 2009;28:122-3.
2. El-Darouti M, Zayed AA, El-Kamah GY, Mostafa MI. Ligneous conjunctivitis with oral mucous membrane involvement and decreased plasminogen level. *Pediatr Dermatol* 2009;26:448-51.
3. Mehta R, Shapiro AD. Plasminogen deficiency. *Haemophilia* 2008;14:1261-8.
4. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. *J Thromb Haemost* 2007;5:2315-22.
5. Barabino S, Rolando M. Amniotic membrane transplantation in a case of ligneous conjunctivitis. *Am J Ophthalmol* 2004;37:752-3.