Case Report

Fresh frozen plasma as a source of plasminogen for ligneous conjunctivitis: Case report and a review of the literature

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Clinical presentation

A 6–year–old Caucasian girl was referred to our clinic by a local ophthalmologist for management of a left, pseudomembranous conjunctivitis. A diagnosis had been given of adenoviral conjunctivitis and the patient had been using moxifloxacin drops for 10 days. The parents noted that neither time, nor the antibiotics drops were helping. Additionally, the parents noted that the thick white membranes had been increasing until the father manually removed exposed membranes that were described as "removing a contact lens made out of cooked shell pasta".

The patient is the youngest of three otherwise healthy children. She was born by cesarean section at term with APGARs of 9 / 9. Her peri–natal history was complicated by an arrest in her developmental milestones after the age of six months, at which time she was diagnosed with infantile spasms, even after seeing multiple specialists. The etiology of her spasms was never diagnosed. She was started on felbamate and a
ketogenic diet involving carnitine, by a pediatric neurologist. There was a decrease of the number of seizures, from approximately four hundred per day, to fifty per day. Her past medical history was also significant for a hypotonic episode requiring airway intubation for eight days and subsequent tracheomalacia, which was not repaired. Her past surgical history was remarkable for placement of a feeding tube. The patient had a medical diagnosis of cerebral palsy. When she was seen at the clinic, the patient was wheelchair bound and communicated by cooing.

Visual exam

The patient was noted to fix and follow poorly in each eye, but no nystagmus was present. The pupils were equal, round, and reactive to light, with no relative afferent pupillary defect noted. Slit lamp examination revealed swelling and an erythematosus slit area limited to the left upper and lower lids, with fine telangiectasias seen along the eye lid margins. No follicles were present on the bulbar or tarsal conjunctiva. A thick, white, avascular pseudo-membrane was noted on the left, inferior lateral palpebral conjunctiva extending over the lateral one third of the lower lid. All other areas of the conjunctiva for both eyes were clear. There was no intraocular inflammation, auricular lymphadenopathy, or oral mucosal lesions. There was no vaginal or anular mucous membrane pathology.

Diagnosis and management

Very minimal bleeding was noted when the pseudomembrane was gently debrided with a cotton swab under topical anesthesia. The clinical picture and history suggested a diagnosis of ligneous conjunctivitis. The father had saved the original membrane that he had removed; we sent our sample and the membrane that the father had removed to pathology. The pathology evaluation revealed strips of epithelium making up the membrane, with resultant pseudomembrane formation [8].

After discussion with the hematologist about plasminogen levels in Fresh Frozen Plasma (FFP), we decided to try treating the patient with her father’s FFP. Since he was found to have adequate plasminogen activity levels, we felt that his FFP might have enough plasminogen to be effective. Plasminogen drops were concentrated from the FFP, and we had the patient use these drops every hour while awake. The cyclosporine A drops were continued, and the topical steroids were tapered over one month.

Clinical improvement was first evident at two weeks after starting the plasminogen drops. Significant improvement was noted at five weeks, and the conjunctivitis and pseudomembranes were totally resolved by seven weeks. The patient also received a few courses of intravenous FFP and the parents subjectively noted that the patient seemed to have fewer seizures after receiving these infusions.

The patient was followed over the next 8 years, during which she had four more flares. These flares were managed each time with the plasminogen drops derived from her father’s FFP. The longest interval the patient went between flares was 32 months.

Discussion

Ligneous conjunctivitis is rare, painful, chronic, fibrinous inflammation of the bulbar and/or tarsal conjunctiva. Systemic associations include other mucosal involvement (gingival, cervical, and vagina), juvenile colloid milium, hydrocephalus and potentially life-threatening laryngeal and tracheobronchial membranes [7]. Known ocular complications of this disease include eye lid scarring, corneal ulceration, corneal perforation and possible deprivation amblyopia [8]. Ample evidence, points to systemic Type I plasminogen deficiency as the etiology of ligneous conjunctivitis [1–6]. Plasminogen appears to be an important factor mediating tissue remodeling in the conjunctiva, an exposed mucosal surface vulnerable to environmental irritants and micro-trauma. This remodeling is a balance between the deposition of extracellular matrix proteins and their removal by fibrinolysis. Plasminogen deficiency skews this delicate balance in favor of the former with resultant pseudomembrane formation [8].

Treatment modalities aimed at restoring local fibrinolysis have included topical hyaluronidase, 6 α–chemotrypsine [1,6,9], and cyclosporin A [10,11] all with varying success. In addition, surgical debridement of these lesions often leads to their recurrence within days to weeks [8]. Amniotic membrane grafts have been used to facilitate epithelization and reduce inflammation [12,13]. Heparin has been used as a cost-effective option to prevent recurrences [9,13–15]. Many interventional case reports and series have shown that topical therapy with plasminogen containing drops is an effective treatment for ligneous conjunctivitis. These cases are summarized in Table 1.

When used as an adjuvant to surgical debridement, topical plasminogen has been shown to be effective at managing ligneous conjunctivitis for over 5 years [25]. Interestingly, plasminogen acts as a necessary precursor, as plasmin is readily inactivated and rendered ineffective when given topically [1]. The difficulty in treatment comes from issues of availability and cost of plasminogen. The facts that the condition is rare, plasminogen is difficult to isolate, and it does not have other large scale uses, results in it not being readily available to clinicians in the treatment of ligneous conjunctivitis.

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Given that ligneous conjunctivitis appears to be a local manifestation of a systemic disease, some groups have attempted to correct the plasminogen deficiency with donor intravenous FFP in addition to topical drops or subconjunctival injections. We chose to use it concurrently because we were unsure of how it would be most efficacious. Further research needs to be conducted to determine the optimal delivery route for plasminogen.

In our case, we were able to test the parents and use intravenous and topical donor FFP from the father. FFP is an FDA approved blood product known to contain plasminogen. Although we could not be sure of the exact amount available plasminogen being delivered hourly, topical application of donor FFP from the father resulted in clinical improvement of the patient conjunctivitis. Because the father was the donor, it provided a level of confidence in the safety of the drops against

### Table 1: Review of the Literature.

| Authors and Year | Age and Presentation | Type of Plasminogen Use | Additional Interventions | Outcome* |
|------------------|----------------------|-------------------------|--------------------------|----------|
| Schott, et al. 1998 [5] | 6-month-old Turkish male with recurrent, bilateral pseudomembranous conjunctivitis | Systemic lys-plasminogen obtained from Immuno | - | 7 months |
| Kraft, et al. 2000 [3] | 9-month-old Turkish female with bilateral pseudomembranes | Systemic lys-plasminogen | Pseudomembrane excision, topical heparin, topical antibiotics | 6 months |
| Watts, et al. 2002 [6] | 5-year old Caucasian female with recurrent, bilateral membranous conjunctivitis | Topical FFP | Pseudomembrane excision | 12 months |
| Watts, et al. 2002 [6] | 5-year-old female with unilateral membranous conjunctivitis | Topical FFP | Pseudomembrane excision | 12 months |
| Watts, et al. 2002 [6] | 18-month-old Libyan male with recurrent bilateral membranous conjunctivitis | Topical FFP | Pseudomembrane excision | 12 months |
| Heidemann, et al. 2003 [1] | 7-year-old male with recurrent, unilateral membranous conjunctivitis | Topical plasmin | Pseudomembrane excision, subconjunctival steroid injection | No improvement |
| Tabarra, et al. 2004 [16] | 18-year-old female with recurrent membranous conjunctivitis | Subconjunctival injections of FFP and topical FFP | Pseudomembrane excision | 6 months |
| Gürlü, et al. 2008 [17] | 17-day-old Turkish male with bilateral conjunctival membranes | Systemic and topical FFP, and topical physiologic serum | Pseudomembrane excision, systemic antibiotics, topical antibiotics | 1 year |
| Lee, et al. 2009 [18] | 32-year-old male with recurrent pseudomembranous lesions | Topical allogenic serum | Topical heparin, systemic antibiotics | 2 years |
| Suzuki, et al. 2009 [19] | 71-year-old Japanese female with recurrent membranous lesions | Topical FFP | Topical steroids, topical cyclosporine A, topical Argatroban | 12 months |
| Suzuki, et al. 2009 [19] | 73-year-old Japanese female with recurrent membranous lesions | Topical FFP | Topical steroids, topical heparin | 12 months |
| Pergantou, et al. 2011 [20] | 4-year old female with recurrent pseudomembranes | Systemic and topical FFP | Pseudomembrane excision | 10 months |
| Ku et al. 2012 [21] | 73-year-old Caucasian female with recurrent, unilateral ligneous conjunctivitis | Topical FFP | Pseudomembrane excision, topical heparin | 6 months |
| Karadag-Oncel, et al. 2015 [22] | 6-month-old female with bilateral pseudomembranes | Systemic and topical FFP | Pseudomembrane excision | 2 months |
| Conforti, et al. 2016 [23] | 4-year-old female with unilateral pseudomembranes | Topical plasminogen, provided by Kedrion (Barga, Italy) | - | 3 years |
| Conforti, et al. 2016 [23] | 4-year-old female with unilateral pseudomembranes | Topical plasminogen, novel formulation | - | 30 days |
| Ang, et al. 2017 [24] | 32-year-old white female with bilateral ligneous conjunctivitis | Topical plasminogen, purchased from DiaPharma (West Chester, Ohio, U.S.A.) | Pseudomembrane excision | 5 months |
| Tu, et al. 2016 [25] | 45-year-old Caucasian female with pseudomembranous conjunctivitis | Topical 60% FFP | - | 5 years with 3 mild flare-ups |
| Kizloca, et al. 2018 [26] | 13 patients with ligneous conjunctivitis, 8 females and 5 males, ages from 15 days to 9 months | Systemic FFP, and/or topical FFP | Pseudomembrane excision | Clinical response in 8 out of 11 patients, FFP was stopped in 2 patients with allergic reactions |
| Watts, et al. 2019 [12] | 6-year-old Arab female with recurrent, bilateral conjunctival lesions | Systemic FFP | Pseudomembrane excision with synthetic amniotic membrane graft, topical heparin, topical cyclosporine A, topical steroids, topical antibiotics | 2 months |
| Watts, et al. 2019 [12] | 18-month-old white male with recurrent, pedunculated, vascular masses on the left upper tarsal conjunctiva | Systemic FFP | Excision of masses, topical heparin, topical antibiotics, topical steroids | 1 year |
| Martins, et al. 2019 [27] | 55-year-old female with recurrent pseudomembranous conjunctivitis | Topical 50% heterologous serum | - | 1 year |
| Ocak, et al. 2020 [28] | Twin 4-month-old Arab males with conjunctivitis with membranes | Systemic and topical FFP | Topical heparin, topical cyclosporin A | 1 year |

*Outcome reflects no recurrence at last follow-up, time to recurrence, or clinical response

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possible immune reactions. Additionally, the patient had a readily available source of plasminogen for future recurrences.

Treatment with plasminogen drops derived from FFP for ligneous conjunctivitis appears to be safe and effective in the long term. However, this method is costly, so these authors recommend first using topical heparin as it may prevent recurrence, is much cheaper, and is more readily available. Should heparin fail, we recommend treatment with plasminogen. Whether topical therapy with FFP alone is as effective as combined topical and parenteral therapy remains to be elucidated. In the future, gene therapy may play a role in reversing this enzymatic defect.

Method of literature search

Literature was researched on PubMed. Pertinent keywords were searched, including “ligneous conjunctivitis” “plasminogen deficiency” “fresh frozen plasma” “plasminogen”. Articles in English relevant to the discussion were selected from these search results.

Off-label use/unapproved drugs or products

Fresh Frozen Plasma is not labeled by the FDA for the use under discussion.

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