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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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Abstract

Purpose: To describe management of a patient with ligneous conjunctivitis secondary to plasminogen deficiency and review the literature on treatment with plasminogen.

Design: Interventional case report.

Methods: A 6-year-old Caucasian girl developed ligneous conjunctivitis recalcitrant to debridement and treatment with topical cyclosporin A and steroids. The literature was reviewed regarding treatment of ligneous conjunctivitis with plasminogen.

Results: The patient was treated with plasminogen containing drops derived from her father's fresh frozen plasma. The ligneous conjunctivitis resolved, and the patient was managed on these drops for the following 8 years, initiating treatment for flares and tapering according to clinical response.

Conclusions: Plasminogen drops concentrated from fresh frozen plasma are a safe and effective option for long-term treatment of ligneous conjunctivitis.

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

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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 erythematous 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 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 anal 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 pseudomembranes, composed of fibrin and eosinophilic dense material infiltrated by neutrophils and lymphocytes, consistent with the diagnosis of ligneous conjunctivitis. In an initial effort to suppress inflammation and further pseudomembrane production, the patient was placed on cyclosporin A drops and topical steroids as frequently as every hour without improvement. Although it was known that plasminogen has completely resolved some cases of ligneous conjunctivitis, there was difficulty in quickly finding a preparation for our patient.

Consultation was sought with a hematologist for work up of possible plasminogen deficiency as has been described in the literature [1-6]. The reference levels of plasminogen activity are 70% to 113%. The hematologic evaluation revealed plasminogen activity levels for the parents as follows: father 105% (normal) and mother 100% (normal). The patient's plasminogen activity was 11% (low).

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, cervix, and vagina), juvenile colloid milium, hydrocephalus and potentially life-threatening laryngeal and trachea-bronchial 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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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
	5-year-old female with unilateral membranous conjunctivitis	Topical FFP	Pseudomembrane excision	12 months
	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
		Topical plasminogen	-	3 months
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, topical steroids	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
	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
		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
Kızılocak, 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
	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

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 sub-conjunctival 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 our patient conjunctivitis. Because the father was the donor, it provided a level of confidence in the safety of the drops against

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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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