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Case Report

Ligneous Conjunctivitis with Plasminogen Deficiency Treated with Topical Allogeneic Serum Drops: A Case Report

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Abstract

To report a case of refractory ligneous conjunctivitis (LC) in which topical allogeneic serum eye drops from a relative with proven serum plasminogen activity were effective.

A 12-year-old male complained of intractable swelling and hardness of all eyelids, with woody discharge. He had been followed up with similar complaints since he was 1 year old. Until his teenage years, his membranes were relatively mild and non-progressive with topical cyclosporine (0.05%), artificial tears (single dose), antihistamines, antibiotics, and prednisolone acetate during active periods. His symptoms have been aggravated by impending corneal epithelial erosions due to thick ligneous membranes under the upper eyelids for the last year. Since commercial plasminogen eye drops were unavailable, allogeneic serum eye drops were prepared from a plasminogen-rich relative of the patient after obtaining informed consent.

The patient's and his 1st° relatives' plasma plasminogen activities were determined by chromogenic assay, and only his mother's brother had a plasma plasminogen activity of 98%. Therefore, allogeneic serum eye drops were prepared from his plasma and given qid in addition to topical cyclosporine bid and artificial tears qid. Inflammatory pseudomembranes regressed with a dramatic resolution of the swelling and redness of the upper eyelids. No new conjunctivitis attacks were encountered during the last year.

Plasminogen-rich allogeneic serum seems reasonable when there is no access to commercially available plasminogen eye drops for patients with intractable LC.

Keywords: Allogeneic serum eye drops, ligneous conjunctivitis, plasminogen deficiency

Introduction

Ligneous conjunctivitis (LC) is a rare chronic disease characterized by the formation of chronic and recurrent pseudomembranes of the conjunctiva, which are firm, fibrin-rich, and often localized in the tarsal conjunctiva (1). LC is the most common complication of severe plasminogen deficiency type 1 (PLGD-1) (2). There is no standardized treatment for LC. Pseudomembranes characteristically tend to recur shortly after surgical excision and may cause vision-threaten-

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ing complications (3,4). Treatment alternatives include topical antibiotics, corticosteroids, immunosuppressants (mostly cyclosporine), heparin, plasminogen, fresh frozen plasma (FFP), and amniotic membrane transplantation in selected cases (3,4). Many countries need help accessing commercially available plasminogen eye drops.

Herein, we present a 12-year-old boy for whom treatment with topical allogeneic serum eye drops from a relative with proven serum plasminogen activity successfully resolved pseudomembranes and effectively prevented recurrence. The patient and his parent consented to this experimental treatment method and publication of the results.

Case Report

An otherwise healthy male patient, born in 2006, had been admitted to Pediatric Ophthalmology and Cornea Divisions at the Department of Ophthalmology, Dokuz Eylul University Hospital, initially in August 2007, with complaints of redness and discharge in both eyes. His ambulatory examination revealed membranous discharge in both eyes. He was re-examined under general anesthesia; tarsal conjunctival membranes were peeled, and samples were taken for smears, cultures, and pathological examinations with the suspicion of LC. Smears showed rare leukocytes with no bacteria or other microorganisms. The patient was discharged and scheduled for follow-up with topical steroids and antibiotic eye ointments.

Histopathological examination with hematoxylin and eosin staining revealed infiltration of inflammatory cells over the membranous lesions, defined as "inflammatory pseudomembranes." The cultures revealed no microbiological growth. As expected in the case of LC, he presented with a rapid recurrence of the membranes in subsequent controls. The membranes were relatively milder with maintenance therapy with topical cyclosporine, artificial tears, and antihistamines. Attacks could be controlled with short courses of topical prednisolone acetate for almost 1 year, but then, he was lost to follow-up.

Eight years later, in 2015, he presented with similar but mild ocular surface findings. A similar regimen kept his symptoms under control. However, in 2021, he presented with aggravation of the clinical picture. Thick tarsal membranes were abundant under the upper lids that were difficult to flip (Fig. 1a and b). He had difficulty opening his eyes due to corneal epithelial defects triggered by ligneous membranes. Pediatric Allergy Department consultation ruled out systemic involvement, including hydrocephalus and pseudomembranes on the laryngeal mucosa, vocal cords, gingiva, trachea, nasopharynx, or eardrums. He was prescribed systemic antihistamine therapy.

Since commercial plasminogen eyedrops are not commercially available in our country, we planned to prepare autologous or allogeneic eye drops with adequate plasminogen activity for more definitive treatment. At this point, the patient's and his 1st° relatives' plasma plasminogen activities (PPA) were determined by chromogenic assay for the 1st time. The PPA was severely decreased in our patient and his only parent (i.e., <30%). His father's brother also lacked adequate PPA (63%), but his mother's brother had a PPA of 98%.

Allogeneic serum eye drops were prepared from his uncle's plasma. According to the protocols published by Geerling and Liu (5,6), the blood drawn in a standard tube without endotoxin and anticoagulant (about 450 mL) was left to coagulate at room temperature (18–25°) for 2 h. It was then centrifuged at 3500 Hz for 6–7 min. A total of 200 mL was taken from the upper separated serum and then diluted with physiological saline to obtain 20% serum drops to simulate the tears' contents. Studies have shown that autologous and allogeneic serums prepared with this method contain epidermal growth factor, transforming growth factor-beta, and Vitamin A, similar to those in tears, and the pH value is the same (~7.4) (7-10).

Allogeneic serum drops were given qid in addition to topical cyclosporine bid and artificial tears qid. Pseudomembranes were thinner, with a dramatic resolution of the swelling and redness of the upper eyelids at the 2-week follow-up.

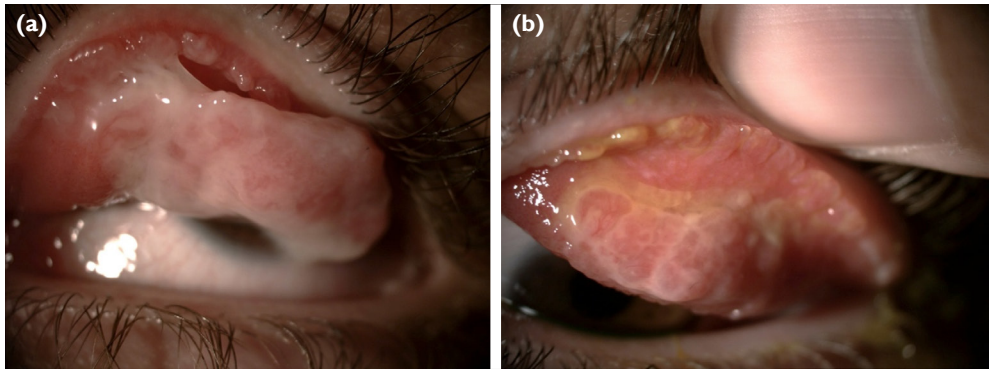

Figure 1. (a, b) Biomicroscopic anterior segment photographs of a recent attack with severe inflammatory pseudomembranes in both eyes (2021 OD-OS).

Giant papillary reaction in the upper tarsal conjunctiva continued with reduced severity (Fig. 2a and b). As the patient had fewer symptoms and could easily open his eyes, his compliance with topical allogeneic serum eye drops increased. Corneal epithelial defects resolved.

We tested post-treatment anti-plasminogen antibodies to see if the patient developed antibodies against allogeneic serum eye drops containing plasminogen after a full year of maintenance therapy. The enzyme-linked immunosorbent assay method examined the anti-plasminogen antibodies in the serum obtained by centrifugation of the blood drawn from our patient and his father as the control group. The patient and his father's tests revealed no difference after 1 year of topical treatment (Fig. 3). Both the patient, who had topical plasminogen treatment for 1 year and his father, both of whom had PPA <30%, did not reveal antibodies against plasminogen. Therefore, the proposed treatment did not induce an immune reaction in the patient.

No recurrences of the ligneous exudates were noted within 1 year. His treatment continues as topical cyclosporine bid and artificial tears qid.

Discussion

LC is a rare chronic disease characterized by the formation of pseudomembranes in the conjunctiva. This rare disease was first reported in 1847 in a 46-year-old male patient. The definition of LC was first used by Borel in 1933 (11). Although ocular lesions are the most common, many patients have similar pseudomembranous lesions on the larynx mucosa, vocal cords, gingiva, trachea, nasopharynx, eardrum, vagina, and cervix (12,13). Histopathological examination of pseudomembranous lesions reveals a disrupted epithelium accompanied by inflammatory cellular infiltration, replaced by superficial or subepithelial deposits of amorphous hyaline-like eosinophilic material (11). Although the incidence of LC is unknown, it often affects newborns or children; it can recur at any age (14).

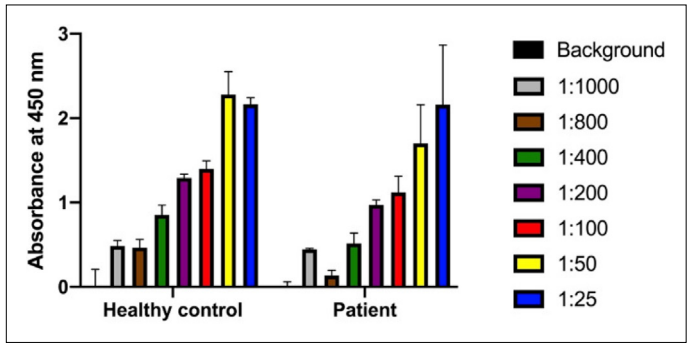

Figure 3. Anti-plasminogen antibody enzyme-linked immunosorbent assay signals from serum samples of the healthy control and the patient. Serum dilutions were done from 1:25 to 1:1000.

Severe hypo-plasminogenemia is usually caused by homozygous or compound heterozygous mutations in the plasminogen gene (PLG), which causes a decrease in functional plasminogen activity (13,15). Several studies have shown a relationship between PLG mutations and human LC (12,15,16). Meanwhile, Drew et al. (17) showed that plasminogen-deficient (Plg-/-) mice develop conjunctival lesions indistinguishable from human LC in appearance and histology, resulting in a possible link between plasminogen and disease.

There is no consensus on the curative treatment of LC (18). Multiple therapy regimens have been followed. Most case reports have shown reduced relapse with a combination of medical and surgical treatment. On the other hand, pseudomembranes that characteristically tend to recur shortly after surgical excision can cause vision-threatening complications (3,4).

Schuster and Seregard (11) reviewed the literature on the treatment of LC between 1966 and 2002. They recommended using a topical fibrinolytic agent such as plasminogen or plasminogen activator (tPA), followed by surgical excision and a prolonged, intensive topical heparin course. This may be supplemented with topical corticosteroids with or without topical cyclosporine to reduce inflammation (11). It has

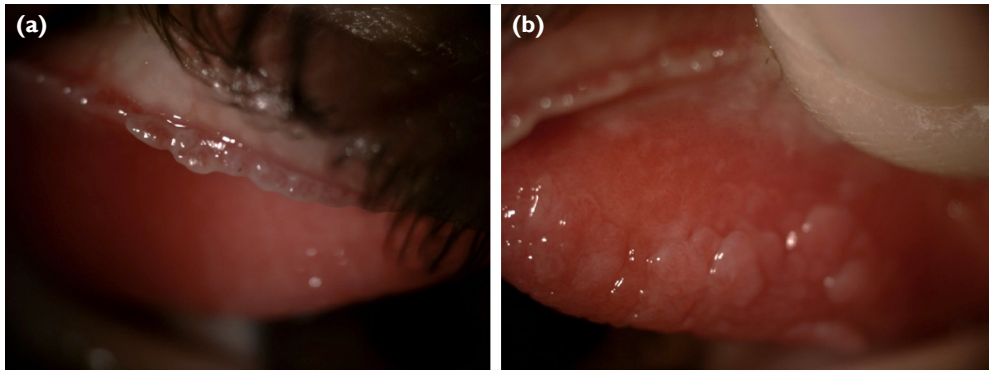

Figure 2. (a, b) Biomicroscopic anterior segment photographs at the last follow-up show thinner pseudomembranes and regression of the swelling and redness of upper eyelids where the patient could open his eyes easily (2022 OD-OS).

been extensively reported that pseudomembranes associated with LC do not respond fully to antibiotic and steroid therapy (4,19-21). Later, other treatment forms were developed, including immunosuppressants (cyclosporine), heparin, plasminogen, FFP, and amniotic membrane transplantation in selected cases (3,4).

Although systemic treatment can replace the deficiency in the blood, the rationale for using topical plasminogen seems sound, as eye involvement is at the forefront. Topical application of FFP has been used to eliminate the possibility of adverse outcomes such as anaphylaxis, transfusion-related acute lung injury, and hemolysis with systemic administration, as well as the need for hospitalization, intravenous access, and the short half-life of intravenous FFP (21,22). It has been shown that the concomitant use of topical and systemic FFP (21,23) treatment can help rapid rehabilitation and prevent recurrences after conjunctival membrane excision (21). According to other reports, Only topical FFP may be a viable option for treating exacerbations and preventing recurrences (4,19-21). Although FFP seems beneficial in reducing the size of existing pseudomembranes, controversially, it was reported to prevent the recurrence of pseudomembrane formation only after surgical excision (4,19). Successful results were seen in the case series where topical FFP and heparin were combined (19,24). Topical heparin (19,25,26) alone or combined with corticosteroids or alpha chemotrypsin (11) has been shown to prevent recurrence.

Plasminogen treatments have also been studied for LC for a long time. Plasminogen drops are converted to plasmin, which is required to break down fibrin membranes. Systemic low-dose Lys-plasminogen (11,18) replacement effectively prevents relapses, but the need for repeated infusions limits its use (21,24). Topical plasminogen therapy allows for easy administration and has shown efficacy in several case studies (11,27-30). In 2002, effective treatment of LC was initially reported by Watts, who successfully treated three cases (two 5-year-olds and one 18-month-old kid) of LC with topical plasminogen concentrate (approximately 1 mg/mL) (27). Then, Hiedemann et al. (29) described a 7-year-old boy with severe unilateral LC treated with topical plasmin after several surgical excisions and failure to respond to conventional topical therapy. The patient, however, did not respond to plasmin drops, and membranes rapidly recurred, so therapy with plasminogen eye drops was started. The response to plasminogen treatment was prompt and dramatic, resulting in complete resolution of the membranes within 1 month.

In July 2006, Kedrion, S.p.A. manufactured a commercially available topical plasminogen product according to the protocol published in 2002 (27) following a request from the Italian Medicines Agency (AIFA). Plasminogen posology was defined as either a high dose (2 drops/eye, 8 times/day) or a low dose (2 drops/eye, 4 times/day) by examining studies in the literature. In the clinical trial KB046, 15 subjects with LC-linked plasminogen type I deficiency have been treated with Kedrion human plasminogen under compassionate use in six different hospitals in Europe and the US from 2006 to date. Kedrion S.p.A. has been granted Orphan Drug Designation for human plasminogen in the treatment of LC by both the European Medicines Agency (2007) and the US Food and Drug Administration (FDA) (2010). The product is currently not licensed in the US or any other country. In 2016, the FDA granted Kedrion's request to designate human plasminogen for treating LC as a drug for a "rare pediatric disease," as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act. The production procedures, results of safety studies conducted in animal models, and available data on their use in humans support the safety and tolerability of the product outside of clinical trials (Phase II/III study).

The Canadian subsidiary of the company, Prometic Biotherapeutics Inc., then developed Ryplazim®, plasma-derived human plasminogen, the first FDA-approved therapy PLGD-1. Between 2017 and 2021, Study 2002C011G enrolled 15 subjects, including six pediatric subjects (4–16 years). All subjects received Ryplazim® at a 6.6 mg/kg dose administered every 2–4 days for 48 weeks or longer. Ten subjects, including three pediatric subjects, had ligneous lesions at baseline. At week 48, all subjects with any ligneous lesion at baseline had at least 50% improvement in the number or size of their lesions.

In addition, one subject with pulmonary lesions and abnormal spirometry at baseline was normalized after 12 weeks of treatment. Three subjects had a total of four serious adverse events in Study 2002C011G. Fortunately, none of the subjects had recurrent or new external lesions during week 48.

Another controversial treatment approach was surgical excision, which tends to result in rapid recurrence of pseudomembranes when performed alone due to the surgical trauma induced in these patients with poor wound healing (11). Therefore, treatment should constantly be enriched with topical and systemic FFP, topical plasminogen, steroids, cyclosporine, or heparin before and after the operation to maximize the chance of relapse-free recovery. In one study in which two 8-month-old and 5-year-old cases were presented, complete resolution of the membranes without recurrence was demonstrated after amniotic membrane transplantation after membrane excision and topical cyclosporine application at 40- and 28-month follow-up, respectively (31).

In this case, we used serum instead of plasma. Serum is the liquid that remains after the blood has clotted and is

obtained after clotting by centrifugation, which allows the removal of fibrin clots, blood cells, and related coagulation factors. In contrast, plasma is the liquid that remains when clotting is prevented by adding an anticoagulant, and plasma samples are obtained by adding anticoagulants (i.e., ethylenediaminetetraacetic acid, citrate) before the removal of blood cells by centrifugation. When blood was allowed to clot for 15 h at 49°C, the concentrations of functional plasminogen were shown to be reduced in serum by 38% (32). However, to test the efficacy of plasminogen in the relative's blood, we did not want to introduce a potentially toxic substance to the eye drops. Despite the differences in the method of preparation, it has been shown that the plasminogen activity in serum and plasma does not differ significantly (33). Although FFP would also be theoretically more helpful in reducing the size of existing pseudomembranes, studies are reporting that it prevents the recurrence of pseudomembrane formation only after surgical excision (4,19). Allogeneic serum eye drops were straightforward for our ophthalmic nurse, who is used to prepare autologous serum eye drops for treating other corneal disorders. The reduced concentration of functional plasminogen in serum proved to be adequate. Our case showed that recurrence can be modified with serum eye drops prepared from a relative with proven PPA, and disease exacerbations can also be treated.

Although the level of plasminogen activity of the donor was evaluated as reported in the case report, the limitations of our case report include the inability to directly measure the plasminogen level in the serum eye drops and perform a genetic test to detect the specific mutation in our patient. When we have the opportunity to measure the plasminogen activity in the serum, we can answer whether this activity is caused by plasminogen or is only beneficial to the ocular surface. However, the dramatic disappearance of the ligneous exudates by the treatment cannot be explained by the beneficial effects of other ingredients of serum eye drops on the ocular surface. These tests could not be performed due to the family's financial issues. However, this is the first case report with retractable LC that successfully resolved pseudomembranes and prevented their recurrence by allogeneic serum eyedrops from relatives with proven PPA. The development of anti-plasminogen antibodies, which could potentially reduce the effectiveness of treatment over time, was also investigated when using allogeneic serum eye drops. After 1 year of topical therapy, the patient tested negative for anti-plasminogen activity. Although not tested before treatment, we believe that the patient did not have remarkable levels of antibodies from the beginning, as he responded well to the treatment, and even after the treatment, he did not display the production of anti-plasminogen antibodies.

Conclusion

Although there is no standardized treatment for LC, topical plasminogen administration is well-known to yield successful patient rehabilitation. Preparation of allogeneic serum eye drops from a relative proven to have adequate PPA seems an easy alternative in countries without access to commercially available plasminogen and where private blood donation from a particular donor is permitted. Further studies with a higher number of patients are warranted.

This case report was submitted as an oral presentation at The International Society of Cornea, Stem Cells and Ocular Surface SICSSO Congress, June 29-30th and July 1st, 2023.

Disclosures

Informed Consent: The patient and his parent consented to this experimental treatment method and publication of the results.
Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – O.O., C.A.U.; Design – O.O., C.A.U.; Supervision – O.O., C.A.U.; Resource – O.O., C.A.U.; Materials – O.O., C.A.U., Z.O., A.Y.; Data Collection and/or Processing – O.O., C.A.U., Z.O., I.D.; Analysis and/or Interpretation – O.O., C.A.U., A.T.B.; Literature Search – O.O., C.A.U.; Writing – O.O., C.A.U., Z.O., I.D.; Critical Reviews – A.Y., A.T.B., O.O., C.A.U.

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