Ligneous Conjunctivitis Treated Successfully with Cryo-Depleted Plasma Infusions and Topical Ciclosporin

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Received: 13 Aug 2023
Accepted: 02 Oct 2023
Published: 10 Oct 2023
J Short Name: AJSCCR

Keywords:
Histological; Pseudomembranes; Infections

1. Abstract
1.1. Purpose: To present the clinical, histological, and genetic characteristics of a patient with ligneous conjunctivitis and to present long-term treatment with cryo-depleted plasma infusions in combination with short-term use of topical ciclosporin as a successful therapeutic option.

1.2. Methods: A 12-year-old Turkish girl presented with ocular itching, irritation and increased light sensitivity, which had been going on for several years. Initial clinical examination revealed the presence of pseudomembranes and giant papillae on the tarsal conjunctiva of both eyes. A biopsy of a membrane from the left eye was taken and sent to histological examination. Because of systemic symptoms including complicated congenital hydrocephalus, asthma, recurrent respiratory infections and impaired wound healing started at the age of 6 months, the patient was subsequently referred for genetic investigation.

1.3. Results: The pseudomembranes were composed of fibrin, granulation tissue, and inflammatory cells persistent with the diagnosis of ligneous conjunctivitis. The genetic analysis revealed that the patient was homozygote for a pathogen missense variant in PLG, causing the plasminogen deficiency. Due to severe systemic complications, the patient was successfully treated with cryo-depleted plasma infusions and ciclosporin eye-drops leading to the complete regression of ligneous conjunctivitis.

1.4. Conclusion: This case report highlights the importance of considering plasminogen deficiency in patients with recurrent chronic conjunctivitis. Long-term treatment with cryo-depleted plasma infusions in combination with short-term use of topical ciclosporin may provide a good therapeutic option for ligneous conjunctivitis in patients with plasminogen deficiency.

2. Introduction
Ligneous conjunctivitis is a rare and severe type of chronic conjunctivitis characterized by the painful wood-like, fibrinous pseudomembranes in the conjunctiva that may result in visual impairment [1, 2]. It is possible to have ligneous conjunctivitis only affecting the eye as an isolated disease entity. The disease is poorly understood, risking delayed diagnosis and treatment. There is no standard cure for ligneous conjunctivitis, and treatment strategies mainly rely on small case studies, reporting different therapeutic approaches with varying success. In this report we present the case of a 12-year-old Turkish girl with ligneous conjunctivitis which ultimately led to the diagnosis of her underlying plasminogen deficiency and the successful treatment with cryo-depleted plasma infusions and topical ciclosporin.

Plasminogen deficiency presents in two forms: fulminant congenital plasminogen deficiency (type I, hypoplasminogenia) and plasminogen deficiency (type II, dysplasminogenia). Congenital plasminogen (congenital PLGD) deficiency is an autosomal, recessive disorder resulting in an accumulation of fibrin that forms pseudomembranes in mucosal tissue, predominantly affecting the conjunctiva as ligneous conjunctivitis. Other sites of manifestations may include the respiratory tract, urinary tract, female reproducti-
tive tract, and gingiva. Rare manifestations including renal failure and occlusive hydrocephalus have been reported [3]. Unlike congenital plasminogen deficiency, plasminogen deficiency (type II) is likely a polymorphic variation in the general population without any direct association with specific clinical manifestations.

3. Case Report

3.1. Clinical History

A 12-year-old Turkish girl was referred to our ophthalmology department in March 2020 due to chronic conjunctivitis, which had been going on for several years.

Her past medical history was notable. She was born with complicated congenital hydrocephalus, requiring drainage since birth, starting with ventricular peritoneal shunt (VP-shunt). Due to multiple episodes of shunt dysfunction a ventricular atrial shunt (VA-shunt) was chosen when she was 2 years of age. Even this shunt needed several revisions due to occlusion. She also had atypical asthma, recurrent respiratory infections, and impaired wound healing, which had been treated by the family doctor.

Upon presentation to our department, the patient reported ocular itching, irritation, and increased light sensitivity. Initial clinical examination revealed the presence of pseudomembranes and giant papillae in the tarsal conjunctiva of both eyes (Figure 1AB). The visual acuity was 0.4 of the right eye and 0.8 of the left eye. Further examination using a slit lamp biomicroscope, revealed a normal ophthalmological investigation.

The findings were initially interpreted as severe atopic vernal keratoconjunctivitis, but as treatment with dexamethasone, ketotifen and lubricating eye drops failed to show any improvement, the membranes were peeled off and sent for a histological examination.

The histological examination showed fibrinoid necrosis in minor fragments of tissue, covered by a normal epithelium. The tissue displayed scattered acute and chronic inflammatory cells, comprising plasma cells and eosinophils. The stroma was identified with PAS-positive materials. The fibrinogen was red using the Martius Scarlet Blue staining. The findings were consistent with the diagnosis of ligneous conjunctivitis (Figure 1DE).

Given the patient’s past medical history together with the histological diagnosis, a plasminogen deficiency was suspected, and the patient was referred for genetic investigation.

In June 2020, one month after being diagnosed with ligneous conjunctivitis due to plasminogen deficiency, the patient was hospitalized with an infection and concomitant acute renal failure necessitating dialysis. Suspecting the origin of the infection to be the VA shunt, a transesophageal echocardiography was performed, surprisingly revealing a thrombus measuring 4x4x3 cm in the right atrial corresponding to the tip of the shunt. Acute surgical excision was performed but left the patient with an insufficient tricuspid valve. Multiorgan dysfunction and sepsis ensued due to the presence of infection, shunt malfunction, and thromboses in the heart valves, resulted in prolonged hospitalization and intermittent admission to the intensive care unit. Remarkably, the patient’s cardiovascular function was restored; but the patient subsequently developed chronic renal failure requiring a renal transplant. A genetic investigation was conducted during hospitalization, and the patient was ultimately diagnosed with congenital plasminogen deficiency (type I, hypoplasminogenia) in July 2020. The blood plasminogen values were close to zero (>10% of normal activity) and between 0.1-0.13 units/L (0.71-1.35 units/L). In 2021 her left ovarian was removed and both uterine tubes were resected due to hematoma and adherences.
3.2. Genetic Analysis

The analysis of the PLG-gene was performed as a targeted NGS analysis covering >99% of all coding regions including flanking intron sequences via the Twist Human Core Exome Kit, followed by sequencing on the NovaSeq platform to an average depth of 100X. The analysis revealed that the patient was homozygote for a pathogen missense variant in PLG (NM_000301.3:c.2287C>T, p.(Pro763Ser)), causing the plasminogen deficiency in the patient. Further investigation including an NGS analysis of the complement factor H (CFH) gene, revealed a normal sequence, excluding almost all pathogen variants in the CFH gene.

3.3. Treatment

Discovering that the patient had a plasminogen deficiency, several ophthalmological treatments were considered. Due to her severe systemic condition, intravenous cryo-depleted plasma infusions were initiated along with topical ciclosporin.

Fresh frozen plasma (FFP) has a close to normal content of fibrinogen, but can be fractionated into cryo-depleted plasma and the cryoprecipitate. The cryoprecipitate comprises concentrated pro-coagulation factors such as fibrinogen, Von Willebrand Factor, and factor VIII among others. Conversely, cryo-depleted plasma lacks these procoagulants resulting in a hypo-coagulant state but still retains normal levels of plasminogen after fractionation.

600mL cryo-depleted plasma was administered intravenously 2-3 times a week increasing the plasminogen plasma levels to above 10% of normal activity. After a few weeks, the fibrinous pseudomembranes had disappeared, and the patient was able to open her eyes again. Despite the positive response on the ligneous conjunctivitis, there were still systemic symptoms from the plasminogen deficiency including shunt dysfunction, renal failure, and impaired wound healing. Considering this, treatment with cryo-depleted plasma infusions was continued, and ciclosporin eyedrops were prescribed, to maintain the improvements achieved thus far.

After one year of treatment in March 2021, the patient no longer experienced any eye symptoms. The final clinical examination revealed no pseudomembranes or papillas in the conjunctiva and the topical ciclosporin was terminated. The patient is currently without any topical treatment. The multiple shunt complications had resulted in visual field defects with a left homonym hemianopsia along with a sparse degeneration of the optic nerves bilaterally. The patient was discharged from the hospital in March 2021. In June 2022 she underwent a successful living related kidney transplant. The hydrocephalus is treated with a ventriculo-vesical shunt. Despite her severe course of disease the patient was able to continue her every day including returning part time to school.

To date, the patient still requires treatment due to plasminogen deficiency to achieve levels above 10% of normal activity as prophylaxis and above 20% during phases of surgery, inflammatory activation and illness. The infusions are continuously monitored and dosed based on the blood levels of plasminogen aiming for higher levels prior to surgery.

4. Discussion

Ligneous conjunctivitis is a rare subtype of chronic conjunctivitis, with approximately 250 reported cases worldwide (16). Typically, it results from a congenital plasminogen deficiency, although a few previous case studies have reported infectious agents as the cause (16).

Congenital PLGD deficiency is an autosomal recessive hereditary disease. Plasminogen is involved in several biological processes including angiogenesis, tissue formation, cell migration, and fibrin degradation. Its absence disrupts the maintenance of mucosal tissue, leading to fibrin accumulation forming pseudomembranes [5-7]. The accumulation of fibrin and the growth of pseudomembranes causes systemic symptoms, with ligneous conjunctivitis being the most common [3]. Other sites of manifestations may include the respiratory tract, female reproductive tract, kidneys, gingiva, and brain ventricular system. These manifestations except ligneous gingivitis were present in our patient, who had a past medical history of congenital hydrocephalus, asthma, respiratory tract infections, and non-healing wounds. The symptoms had lasted for several years, with inadequate treatment and without clinical suspecting either ligneous conjunctivitis or plasminogen deficiency. Following her ligneous conjunctivitis diagnosis in 2020, she experienced cardiac thromboses, valve dysfunction, shunt malfunctions and concurrent renal failure.

With an estimated prevalence of 1.6 per million population [3], congenital PLGD is considered extremely rare. However, because not all individuals with congenital PLGD exhibit symptoms, the condition may be underreported. In our patient, the parents were consanguineous for several generations. Multiple family members experienced symptoms potentially related to congenital PLGD including two maternal cousins, one aunt, and one uncle who had similar eye symptoms. One cousin was also born with hydrocephalus, and the patient’s father and maternal grandfather had impaired wound healing. According to Schuster et al. [10], Kizilocak et al. [8] and Klammt et al. [9], ligneous conjunctivitis appears more frequently in Middle Eastern populations. This pattern could be due to genetic similarities or a higher prevalence of consanguineous marriages in countries where congenital PLGD is more common [3, 10].

Treating and monitoring ligneous conjunctivitis remains challenging (Table 1). Currently, no specific cure exists, and neither the U.S. Food and Drug Administration or European Medicines Agency have approved any treatment for this condition yet. Despite this, several therapeutic options have been suggested in the literature, why the understanding and treatment strategies for ligneous conjunctivitis due to plasminogen deficiency largely rely on case reports and only one international observational study [3].
Surgical excision of the membranes is a common therapeutic option, but it provides only temporary symptom relief and could potentially exacerbate the condition, as factors such as traumas, injuries, foreign bodies, and surgery to the conjunctiva can trigger the occurrence of ligneous conjunctivitis [2, 3, 5, 6, 10, 11]. (One study, however, showed promising results using FFP peri- and postoperatively, suggesting that FFP might enable surgery [21]).

Multiple case studies report the use of various combinations of topical eye drops, including heparin, ciclosporin, antibiotics, azathioprine, alfa-chymotrypsin, and corticosteroids [11, 12, 17-20]. However, the success of these treatments varies, leaving their efficacy in question. The most severe manifestations tend to occur in infants and teenagers, and ligneous conjunctivitis may spontaneously resolve [10].

Schuster and Seregard [10] proposed in a major review, that the most effective treatment for ligneous conjunctivitis involves the administration of fibrinolytic eye drops, followed by surgical excision of the membranes and application of topical heparin thereafter. However, Shapiro et al. [3] noted inconsistent success with this approach when reviewing subsequent studies.

Mingers et al. [13] described the short-term use of low-dose Lys-plasminogen infusions to treat ligneous conjunctivitis, but the treatment did not sufficiently alleviate the patient’s symptoms. In contrast, Schott et Al. [14] reported favorable results using high-dose Lys-plasminogen over a long-term period, which led to complete regression of the membranes and further stabilizing the systemic symptoms. This suggests that Lys-plasminogen infusions could be a therapeutic option if administered at high doses over a prolonged period. However, using Lys-Plasminogen is currently not an option, as medically manufactured Lys-plasminogen is not available. Further, it has an extremely short half-time and requires a central venous catheter to administrate [10].

Another therapeutic option is the use of FFP which has shown success when administered topically and intravenously. However, Shapiro et Al. [3] questioned the effectiveness of FFP due to its low plasminogen concentration. This would require the administration of large volumes to reach improvement, increasing the administration time, risk of volume overload, antibody and transfusion-related complications, and need for repeated infusions.

Watts et al. [15] reported promising results using plasminogen eye drops, but this treatment is probably only suitable for patients without systemic manifestations. Additionally, medically manufactured plasminogen eye drops are currently not available. In our patient, systemic manifestations were present in the kidneys, brain ventricular system, and respiratory tract, thereby excluding topical plasminogen as a treatment option. A previous study (4) based on 14 patients with congenital PLGD demonstrated success with intravenously administered FFP-derived plasminogen every two to four days, improving or resolving all symptoms.

Our patient was successfully treated with a combination of ciclosporin eye drops and cryo-depleted plasma infusions. The success is probably attributed to the advantageous properties of cryo-depleted plasma, which lacks pro-coagulants but retains normal plasminogen levels [23]. Consequently, cryo-depleted plasma allows the transfusion of higher plasminogen levels into the patient, partially restoring the plasminogen deficiency [24]. FFP also contains normal plasminogen levels but a normo to procoagulant profile with the potential to increase the risk of thromboses. Due to the lack of pro-coagulants, cryo-depleted plasma stimulates the fibrinolytic system and minimizes the accumulation of fibrin, why it probably offers advantages over FFP. In our patient, this therapeutic approach led to the complete regression of ligneous conjunctivitis and significantly improved the systemic manifestations. However, the patient still requires 2-3 weekly infusions of cryo-depleted plasma to manage the systemic manifestations of congenital PLGD.

### Table 1: Summary of therapeutical approaches

<table>
<thead>
<tr>
<th>Therapy</th>
<th>References</th>
<th>Total No. of patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasminogen concentrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>(4), (13), (14)</td>
<td>11</td>
<td>Not commercially available, expensive, short half-time, requires CVC*</td>
</tr>
<tr>
<td>Topical</td>
<td>(15)</td>
<td>3</td>
<td>Not sufficient in patients with systemic symptoms</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>(8)</td>
<td>3</td>
<td>Variable results, low plasminogen concentration risking side effects</td>
</tr>
<tr>
<td>Cryo-depleted plasma</td>
<td>(**)</td>
<td>1</td>
<td>Minimizes accumulation of fibrin, stimulates the fibrinolytic system, lowers the risk of thromboses, and allows the administration of higher volumes of plasma to obtain a higher concentration of plasminogen in the blood</td>
</tr>
<tr>
<td>Topical</td>
<td>(8)</td>
<td>1</td>
<td>Not sufficient in patients with low systemic plasminogen levels</td>
</tr>
<tr>
<td>Topical + IV</td>
<td>(8)</td>
<td>7</td>
<td>Time-consuming preparation, low plasminogen concentration, need for long-term therapy</td>
</tr>
<tr>
<td>Topical eyedrops</td>
<td>(21)</td>
<td>1</td>
<td>Risk of steroid-response with increased intraocular pressure</td>
</tr>
<tr>
<td>Immunosuppressants</td>
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5. Conclusion

This case report highlights the importance of considering congenital plasminogen deficiency in patients with recurrent chronic conjunctivitis and systemic affections including congenital hydrocephalus. Long-term treatment with cryo-depleted plasma infusions in combination with short-term use of topical ciclosporin may provide a viable therapeutic option for ligneous conjunctivitis in patients with a verified plasminogen deficiency.

References