ECRONICON OPEN ACCESS

EC PAEDIATRICS
Case Report

Fresh-Frozen Plasma Transfusion for Replacement Therapy in a Child with Hypoplasminogenemia and Ligneous Conjunctivitis: An Alternative Option to Delay Recurrence

Hanan F Nazir[1,2]*, Maha M Mameesh[3,4] and Anil V Pathare[5]

[1]*Child Health Department, Sultan Qaboos University Hospital, Muscat, Oman*

[2]*Department of Pediatrics, Alexandria Faculty of Medicine, Alexandria, Egypt*

[3]*Department of Pediatric Ophthalmology, Sultan Qaboos University Hospital, Muscat, Oman*

[4]*Department of Ophthalmology, Alexandria Faculty of Medicine, Alexandria, Egypt*

[5]*Department of Haematology, Sultan Qaboos University, Muscat, Oman*

***Corresponding Author**: Hanan Fawzy Nazir, Child Health Department, Sultan Qaboos University Hospital, Muscat, Oman.

Received: June 06, 2018; **Published:** September 14, 2018

Abstract

Ligneous conjunctivitis is a rare form of pseudomembranous conjunctivitis that develops specifically in patients with plasminogen deficiency. Lack of plasmin activity in those patients result in defective fibrinolysis and formation of fibrin-rich membranous material/masses that develops on the palpebral conjunctiva as well as other sites of the body. Surgical excision of the masses is usually complicated by multiple recurrences. Recently, use of topical plasminogen concentrates helped delaying recurrence, but currently, those concentrates are not commercially available [1].

Hereby, we report on the perioperative use of Fresh-Frozen Plasma (FFP) transfusion as an alternative replacement of plasminogen during surgical excision of ligneous conjunctivitis. Such management delayed but did not prevent recurrence of ligneous lesions.

Keywords: *Cryoprecipitate; Fresh- Frozen Plasma; Hypoplasminogenemia; Ligneous Conjunctivitis; Recurrence*

Abbreviations

FFP: Fresh-Frozen Plasma; CSA: Cyclosporine A; ED: Eye Drops

Introduction

Ligneous conjunctivitis is a rare form of pseudomembranous conjunctivitis that develops specifically in patients with type 1 plasminogen deficiency. Current management involve surgical excision of the masses that is usually complicated by multiple recurrences. Recently, the use of topical plasminogen concentrates helped delaying recurrence, but currently, those concentrates are not commercially available.

Plasminogen replacement using FFP or cryoprecipitate transfusion are thought to be alternative options to delay recurrence in such cases after surgical excision. Unfortunately, no studies addressed cryoprecipitate as an option for replacement despite of its advantage of having less risk to cause volume overload. We performed a pharmacokinetic study to evaluate plasminogen recovery after both FFP and cryoprecipitate transfusion in a child with hypoplasminogenemia and ligneous conjunctivitis.

Case Summary

AA is an 8-year-old Omani girl with hypoplasminogenemia, diagnosed at the age of 6 months. Her plasminogen level was 0.140 u/ml (reference range 0.730-1.270 u/ml), confirming congenital plasminogen deficiency. In addition to low plasminogen level, her initial assessment also revealed high levels of Alpha 2 antiplasmin of 1.300 u/ml (RR 0.890 - 1.120) and plasminogen activator inhibitor-1 of 170.0 ng/ml (RR 4.0 - 43.0), resulting in the early development and severe clinical course. The diagnosis was suspected at the age of 2 months when she developed pseudomembranous conjunctivitis (ligneous conjunctivitis). Initial laboratory assessment at the age of 6 months is shown in table 1.

Laboratory test	Patient Result	Reference Range
Plasminogen	0.140 u/ml (↓)	0.730 - 1.270 u/ml
D dimer	1.2 (↑)	0.2 - 0.7
Coagulation screening		
PT	10.9 sec	10 - 12.1 sec
INR	1	0.91 - 1.10
aPTT	28.6 sec	26.3 - 38.2 sec
Fibrinogen	3.2	1.7 - 3.6 g/L
Protein C:		
functional chromogenic assay	1.050 u/ml (N)	0.720 - 1.540
functional clotting assay	0.909 u/ml (N)	0.800 - 1.810
Protein C global	0.62 u/ml (↓)	0.75 - 1.43
Protein S	0.559 u/ml (N)	0.520 - 1.180
Anti-thrombin functional (IIa inhibition 20 sec)	1.212 u/ml (N)	0.880 - 1.220
Factor VIII: c assay	1.296 u/ml (N)	0.495 - 1.382
Alpha-2 antiplasmin	1.300 u/ml (↑)	0.890 - 1.120
Tissue plasminogen activator	4.6 ng/ml (N)	1.0 - 12.0
Plasminogen activator inhibitor-1	170.0 ng/ml (↑)	4.0 - 43.0

Table 1: *Laboratory assessment in Ligneous conjunctivitis.*

Her parents are cousins, and she has two older healthy sisters. Recently, a younger brother aged 6 weeks was reviewed in ophthalmology clinic for conjunctivitis (Figure 1), his plasminogen level proved hypoplasminogenemia. There was no other family or personal history of abnormal bleeding/thrombosis. Clinical assessment ruled out involvement of her gingiva, ears, skin, respiratory or genitourinary tracts.

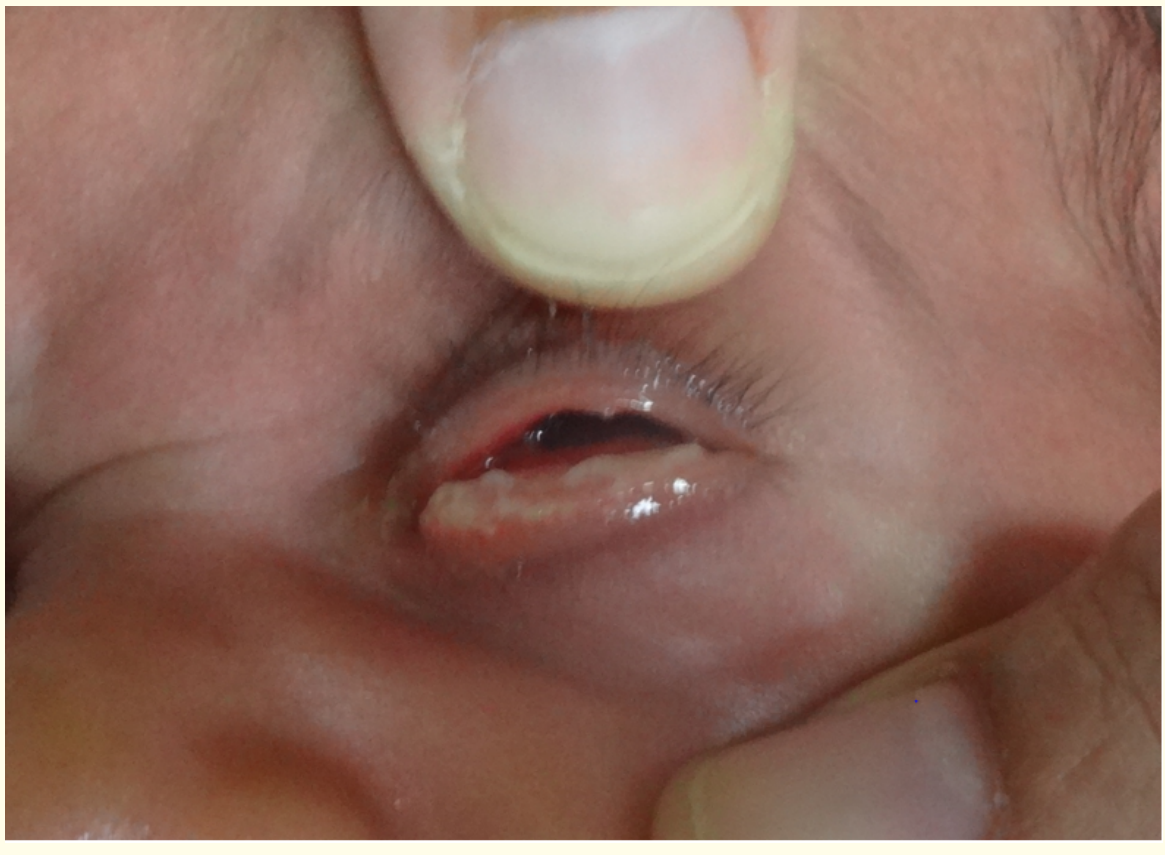

Figure 1: *Starting conjunctivitis in a 6 weeks-old sibling with hypoplasminogenemia.*

Her clinical course was marked with recurrent ligneous conjunctivitis, and she had her first left sided eye surgery when she was 3 months old. Between the age of 3 months till 3.5 years, she underwent 6 eye surgeries for excision of ligneous lesions. Topical steroids and cyclosporine eye drops (ED) were used in an attempt to prevent or delay recurrence. After each surgical procedure, recurrence was noted within days to weeks. In June 2013, at the age of 4 3/12 years, she had mechanical ptosis in both eyes with more bulky lesions that started to encroach on the limbus (Figure 2). Treatment with topical plasminogen was considered, but was not available and it was logistically difficult to prepare locally in our blood bank. Topical FFP ED were thought of as an alternative, but was technically difficult to prepare. Six months later, she was seen at ophthalmology clinic and noted to have mild exophoria, and conjunctival masses measuring 7 * 13 mm on the Rt side, 15 * 11 mm on the left side (Figure 3). She was managed conservatively with topical steroids, CSA, and lubricant ED and remained stable. In October 2015 (age 6.5 yrs.), she had worsening of bilateral ligneous lesions with left lower mechanical entropion. Surgical excision was considered of poor prognosis; because irritation secondary to surgery increases the risk of recurrence and complications like symblepharon. At the age of 7 years, she had left sided conjunctival mass excision + amniotic membrane grafting followed after 2 months by a similar procedure on the right side. Replacement therapy was needed to insure good plasminogen level around the time of eye surgery for normal healing to occur. In Oman, plasminogen concentrates are not available; the sources available for plasminogen supplementation are FFP and cryoprecipitate. Thus, to achieve optimal plasminogen level, assessment of plasminogen recovery was performed by estimating serial plasminogen levels after FFP and cryoprecipitate transfusions (Figure 4).

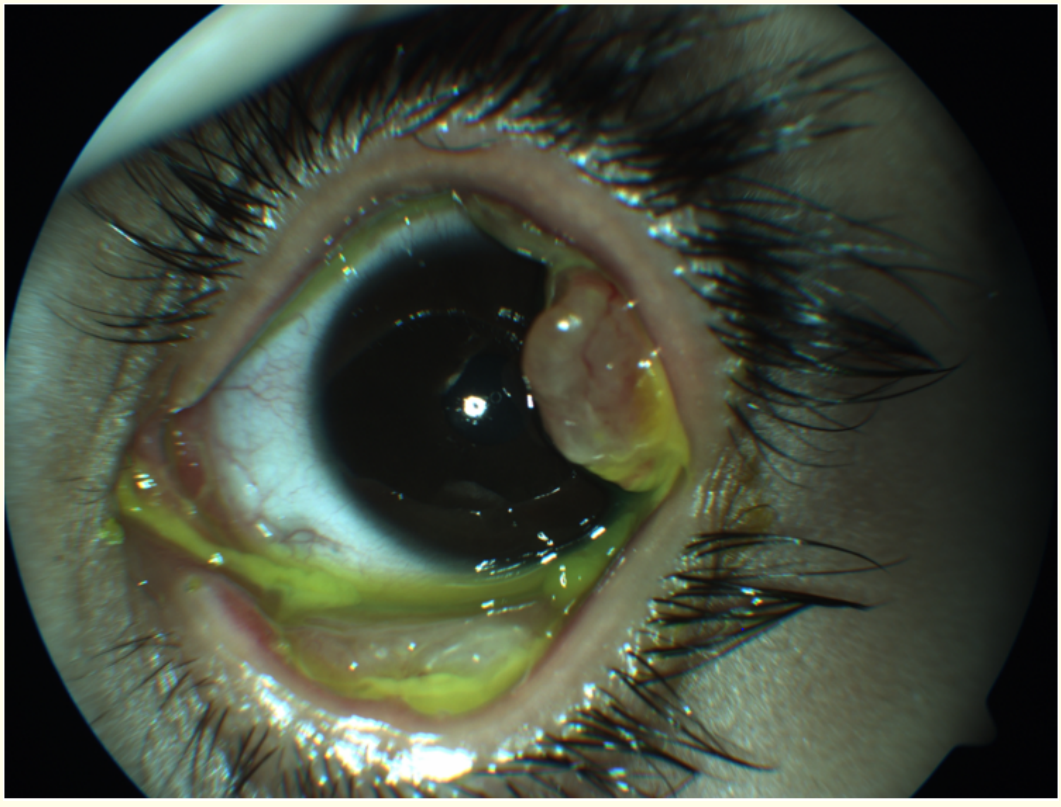

Figure 2: *Ligneous lesions encroaching on the limbus on the left eye.*

Figure 3: *Bilateral bulky ligneous lesions.*

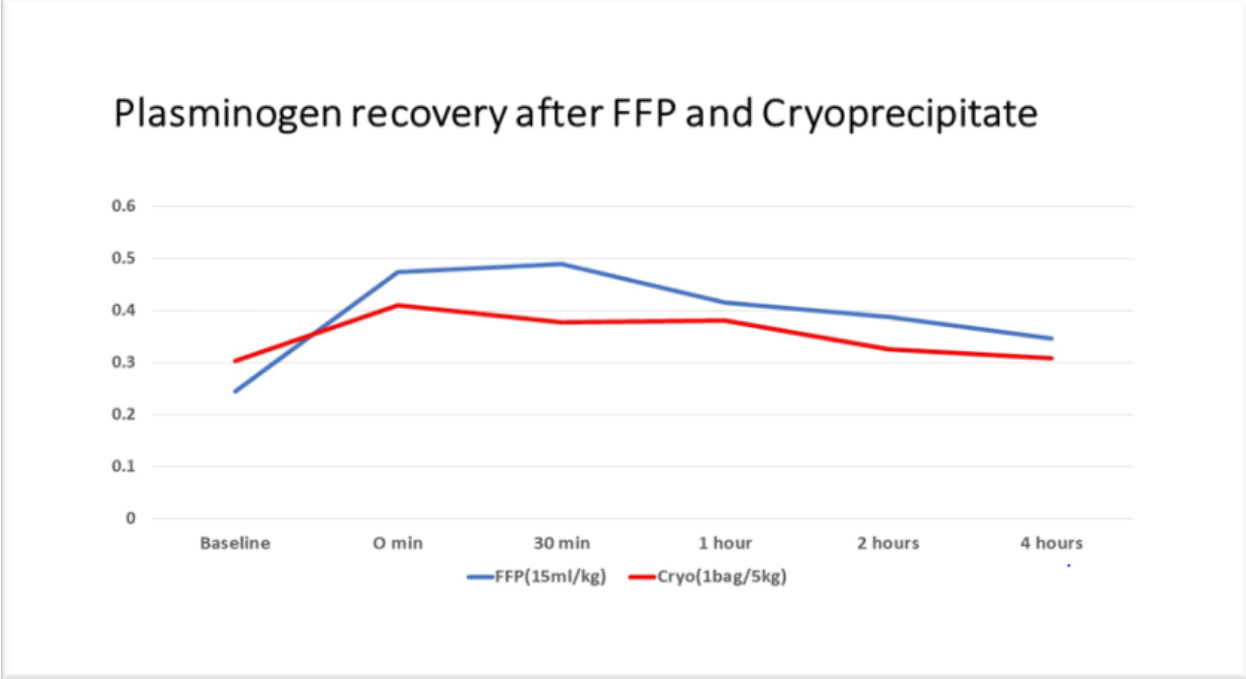

Figure 4: *Plasminogen recovery after FFP and cryoprecipitate transfusion.*

As shown in figure 4 plasminogen levels remained subnormal after either FFP or cryoprecipitate administration. With FFP, the maximum concentration reached was almost 50% of normal. Although half- life of plasminogen is known to be 2 - 2.5 days, the patient seemed to have a high catabolic rate after receiving cryoprecipitate, with plasminogen levels reaching basal levels within 4 hours. Because of the better recovery profile with FFP, we opted to give FFP before and after surgery. She remained hospitalized for 17 days after the first procedure, and 8 days after the second. Her perioperative management included FFP transfusion at 20 ml/kg/12 hours one day before and for 3 days post operatively, followed by 10 ml/kg once daily from day 4 - 6, then 20 ml/kg on 7th post- operative day. Topical treatment was initiated using antibiotic and steroids ED on the day of surgery, followed by Heparin ED on the second day. On follow up, she used topical heparin, cyclosporine, prednisolone, and topical lubricant eye drops for variable durations. Clinical picture remained stable for almost 1 year post operatively, when she started to develop recurrence of ligneous lesions again.

Histopathological examination of the excised conjunctival masses revealed focal epithelial ulceration, acute inflammation and regenerative squamous epithelial changes. The subepithelial stroma showed patchy dense inflammatory cell infiltration comprised of many plasma cells, numerous eosinophils, lymphocytes and notable neutrophils. The underlying stroma contained masses of abundant eosinophilic fibrinous material (resembling amyloid but Congo red stain was negative), consistent with ligneous conjunctivitis.

Discussion

The current report discusses the available options for replacement therapy when topical and systemic plasminogen concentrates are not available. We performed pharmacokinetics to check recovery levels of plasminogen after FFP and cryoprecipitate transfusion and opted to use FFP. The perioperative use of FFP delayed, but did not prevent recurrence of ligneous lesions.

Plasminogen plays an important role in fibrinolysis, wound healing, cell migration, tissue modeling and angiogenesis [2].

Plasminogen deficiency is a rare autosomal recessive disorder, with an incidence of 1: 10^6, most reported patients are of Turkish origin, and there was unexplained predominance of female patients [2]. Our patient had an exceptionally severe course, with early presentation and multiple rapid recurrences after surgical excision. This severe course might be partly attributed to other hemostatic abnormalities with high levels of Alpha-2 antiplasmin and plasminogen activator inhibitor-1. Histopathological examination of excised lesions confirmed the diagnosis as reported by Mocano., *et al*. [3].

Several reports stressed on the fact that surgical excision of ligneous lesions can cause irritation and inflammation that enhance recurrence. Thus, surgical excision alone is not recommended unless highly indicated; when lesions are affecting vision. Individual reports confirmed successful treatment with plasminogen concentrates. The initial preclinical trials of Pignataro., *et al.* in 2013, confirmed the beneficial effect of instillation of plasminogen concentrates into the eye of plasminogen knock-out mice with ligneous conjunctivitis [4]. Topical heparin and FFP were used successfully to control ligneous lesions in a 4 months old patient [5]. In 2016, Conforti MF., *et al.* reported on the successful use of topical formulation composed of plasminogen and hyaluronate sodium in a 9-year-old girl with ligneous conjunctivitis [6].

Besides ligneous conjunctivitis, systemic use of plasma derived plasminogen concentrates was reported to be successful as an emergency medicine in a Turkish child with plasminogen deficiency and respiratory failure [7].

In Oman as well as other countries, plasminogen concentrates or ED are not commercially available to be used for replacement therapy. In August 2017, plasminogen concentrates got triple designation of orphan drug, fast track status, combined with rare pediatric designation, underscoring significant unmet need for such a therapy. Local preparation of plasminogen eye drops and plasminogen concentrates was technically difficult. Thus, we thought to use either FFP or Cryoprecipitate transfusion as a source of plasminogen at least to cover the time of eye surgery and the immediate post-surgical period, to allow for best chances of healing with delayed recurrence. Unfortunately, there is paucity of literature addressing utility of either resource in such a situation. Few studies addressed the use of

systemic and topical FFP, but none addressed the use of cryoprecipitate that was thought of as an alternative because of its smaller volume and less risk to cause volume overload compared to FFP transfusion. That was why we opted to do pharmacokinetics to check recovery level of plasminogen in our patient.

Recently, Kizilocak H., *et al.* from Turkey reported on their experience with the combined use of topical and systemic FFP in treating patients with ligneous conjunctivitis [8]. Regular weekly FFP transfusion at 20 ml/kg/week was used for prophylaxis, but did not prevent the development of respiratory tract involvement in a Turkish child with hypoplasminogenemia. That patient developed bilateral exophytic lesions within both main bronchi. On the other hand, systemic administration of plasminogen concentrates helped clearing his airways from membranes and exophytic lesions leading to progressive improvement of his oxygenation and reversing lung atelectasis [7].

In contrast to our patient, apparently, topical use of FFP ED rather than systemic FFP transfusion was behind prolonged remission in the case reported by Pergantou., *et al.* Discontinuation of FFP eye drops in their case was followed by recurrence of ligneous lesions after 2 weeks, while prolonged remission exceeding 10 months was achieved by continued use of FFP ED [9].

In agreement with that hypothesis, topical FFP alone without systemic or subconjunctival therapy was reported to be effective in an infant with ligneous conjunctivitis [10]. Unfortunately, topical FFP ED were not available for use in our patient.

Conclusion

Until topical and plasminogen concentrates are widely available, systemic use of FFP transfusion around the time of surgical excision of ligneous conjunctivitis can delay but not totally prevent recurrence.

Essentials

- Recurrent ligneous conjunctivitis develops in patients with hypoplasminogenemia after excision.
- Replacement therapy with plasminogen concentrates is not commercially available.
- Pharmacokinetic study revealed that plasminogen recovery is better with FFP than cryoprecipitate.
- Perioperative administration of FFP resulted in delayed recurrence of almost 1 year.

Ethics Statement

An informed consent was obtained from parents to share photos of the patient as well as her infant brother's eyes.

Financial Disclosure

Authors have no financial relations relevant to this article to disclose.

Conflict of Interests

Authors have no conflict of interests relevant to this article to disclose.

Author Contribution

- HF Nazir: Dr. Nazir was directly involved in clinical care of the case, collected the data, drafted the initial manuscript, did literature review, and approved the final manuscript as submitted.
- MM Mameesh: Dr. Mameesh did the ophthalmic surgery and post-operative follow up for the child (with other colleagues) She reviewed and revised the manuscript, and approved the final manuscript as submitted.
- AV Pathare: Dr. Pathare performed and interpreted plasminogen pharmacokinetics, critically reviewed the manuscript, and approved the final manuscript as submitted.

Bibliography

1. Ang MJ., *et al*. "Topical Plasminogen as Adjunctive Treatment in Recurrent Ligneous Conjunctivitis". *Ophthalmic Plastic and Reconstructive Surgery* 33.2 (2017): e37-e39.

2. Tiraje C. "Plasminogen Deficiency". *Journal of Thrombosis and Thrombolysis* 43.1 (2017): 132-138.

3. Mocanu CL., *et al*. "Clinical and histopathological aspects in two cases of ligneous conjunctivitis". *Romanian Journal of Morphology and Embryology* 57.2 (2016): 601-605.

4. Pignataro G., *et al*. "Conjunctival instillation of plasminogen eliminates ocular lesion in B6.129P2-Plg(tm1Jld) transgenic mice, a model of ligneous conjunctivitis". *Pharmacological Research* 74 (2013): 45-48.

5. Putri SC., *et al*. "Response of Plasminogen Deficiency- Associated Ligneous Conjunctivitis To Topical Fresh- Frozen Plasma with Heparin". *Journal of Case Reports* 5.1 (2015): 132-136.

6. Conforti FM., *et al*. "Novel plasminogen and hyaluronate sodium eye drop formulation for a patient with ligneous conjunctivitis". *American Journal of Health-System Pharmacy* 73.8 (2016): 556-561.

7. Hassenpflug WA., *et al*. "First-in-Man Emergency Use of Plasminogen Replacement for Respiratory Failure Due to Congenital Hypoplasminogenemia". *Blood* 128 (2016): 3792.

8. Kızılocak H., *et al*. "Treatment of plasminogen deficiency patients with fresh frozen plasma". *Pediatric Blood and Cancer* 65.2 (2018).

9. Pergantou H., *et al*. "Management of ligneous conjunctivitis in a child with plasminogen deficiency". *European Journal of Pediatrics* 170.10 (2011): 1333-1336.

10. Tunay ZÖ., *et al*. "Successful treatment of ligneous conjunctivitis with topical fresh frozen plasma in an infant". *Arquivos Brasileiros de Oftalmologia* 78.5 (2015): 318-319.

Volume 7 Issue 10 October 2018