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Research Article

Administration of Heterologous Blood Drops in Ligneous Conjunctivitis: Case Report of a New Approach in a Young Patient

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Abstract

Background/Aims: Heterologous serum drops are the main treatment of ligneous conjunctivitis, but they are not available worldwide. This study has described a new approach to ligneous conjunctivitis treatment.

Methods: Topical heterologous blood drops were administered - 2 to 4 times a day, for one year- in the eyes of a patient with advanced ligneous conjunctivitis, with no longer access to heterologous serum and no response to conventional treatment.

Results: The patient presented partial pseudomembrane and eye secretion regression.

Conclusion: The administration of topical heterologous blood drops would be a reasonable, accessible and inexpensive treatment for ligneous conjunctivitis in places where topical or systemic plasminogen replacement therapy is unavailable.

Keywords: *Child Health (Paediatrics); Conjunctiva; Inflammation; Ocular Surface; Case Report*

Abbreviations

FFP: Fresh Frozen Plasma; LC: Ligneous Conjunctivitis

Introduction

Ligneous conjunctivitis (LC) is a rare disease that mainly consists in recurrent pseudomembrane formation in the tarsal conjunctiva [1]. It was first described by McKusick, back in 1874, and it is known to be caused by deficient plasminogen levels. This protein plays important role in fibrinolysis; therefore, its deficiency leads to the accumulation of a woody-like material rich in fibrin. The aforementioned disease can emerge at any age, although most cases emerge and become more severe in individuals' first years of live [1,2]. The eye is the most affected organ, but this disease can onset other mucosal sites, such as gum and female genital tract [1,3], in 12% of cases. Its bilateral ocular form accounts for 51% of cases.

Treating this condition has always been a challenging task; most therapies reported nowadays are somewhat disappointing due to poor results [4]. Yet, they can be somewhat inaccessible due to their high cost and regulation requirements, mainly in developing countries, such as Brazil.

It is recommended to use heterologous serum drops to treat LC, given its relatively satisfactory outcomes [3,4]. It is based on replacing the plasminogen deriving from a donor's blood, who is often a patient's close relative, if this patient does not produce it. However, it is a costly and long-term therapy, whose manipulation has not yet been approved by most regulatory agencies; therefore, it is not easily accessed.

Autologous serum has been reported as effective treatment for dry eye issues. However, because it is not easily accessible, autologous fingerprick blood emerges as alternative to treat the aforementioned issue, as shown in recent article, which also addressed serum components capable of improving dry eye symptoms [5].

This herein presented report described the use of heterologous fingerprick blood as alternative to heterologous serum to treat LC cases.

Methodology and Results

We herein describe the case of an infant patient who came to our service for LC treatment purposes.

This patient had history of fibrinous pseudomembranes in the palpebral conjunctiva of both eyes, since his birth and they progressively worsened despite several removal procedures and topical and systemic antibiotics. After low plasminogen activity was objectified, LC was confirmed and heterologous serum drops - collected from a non-relative blood donor - were administrated, with partial improved symptoms. However, 11 months after the heterologous serum drop therapy started, he discontinued the treatment due to lack of accessibility to it, evolving with recurrence of symptoms. Patient's relatives did not present any similar condition.

When the patient first came to our service, he had stopped using heterologous serum drops for 2 years due to lack of access to it. He received the serum from the government, but its production had stopped. He presented many eye secretion episodes, pseudomembrane growth on the palpebral conjunctiva and temporal ankyloblepharon caused by the aforementioned membranes in both eyes (Figures 1-3). It led to full vision blockage in the left eye, as well as to partial blockage in the right eye. Neither the cornea nor other body parts were compromised. At the time, he was treated with tacrolimus, fluorometholone and eye lubricating drops.

Figure 1: *Photograph of both eyes when the patient first came to our service.*

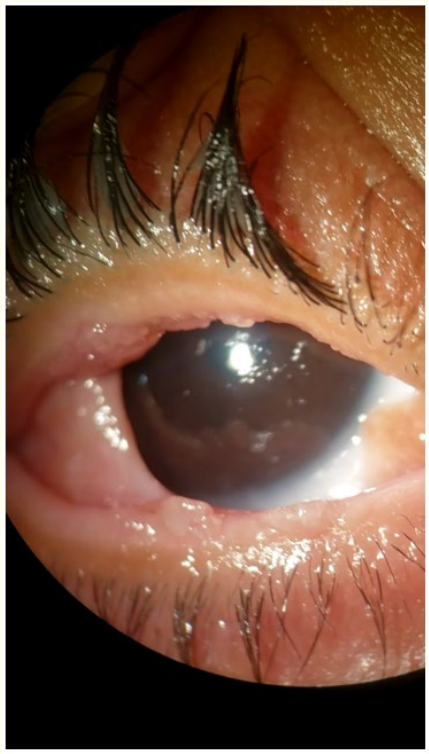

Figure 2: *Slitlamp photograph of the right eye when the patient first came to our service.*

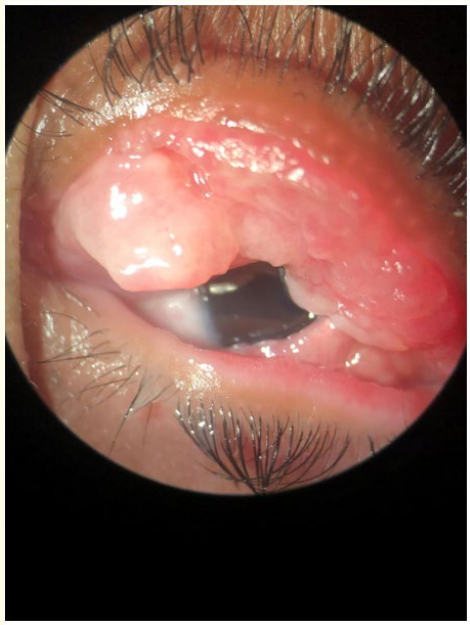

Figure 3: *Slitlamp photograph of the left eye when the patient first came to our service.*

We decided to resume the use of heterologous serum drops, but this treatment was not available due to limited government regulations and, consequently, to its high cost. Given the unavailability of serum replacement therapy and possible evolution to amblyopia in the left eye due to visual blockage, we suggested that the patient's mother should try direct blood repositioning. Upon parents' permission, we started the administration of heterologous blood drops deriving from samples provided by his mother, after the HIV, syphilis and hepatitis tests she was subjected to presented negative results. Finger hygiene concern was emphasized. In order to collect the sample, she did asepsis and antisepsis and pricked her finger with a lancet four times a day in order to draw a fresh blood drop, which was applied to the lower fornix of the patient's eyes.

Clinical improvement was already noticed one week after the treatment started; with reduction of the eye secretion. The size of the pseudomembranes progressively decreased, especially in his left eye, the most affected one. His clinical condition remained stable in the following 6 months; he no longer presented intense eye secretion, nor had a relapse growth of the lesions in both eyes. After that period, we decided to reduce heterologous fingerprick blood drops to twice a day. Eye secretion increased after one week of the reduced dose. After discussion with the mother, we decided to go back to previous dosage. Symptoms had improved over the following week. A new dose reduction attempt was tried, this time to three times a day. No further increase of the symptoms was noticed. The patient remains with the condition stable in one-year follow-up period (Figures 4-6). No adverse event was noticed.

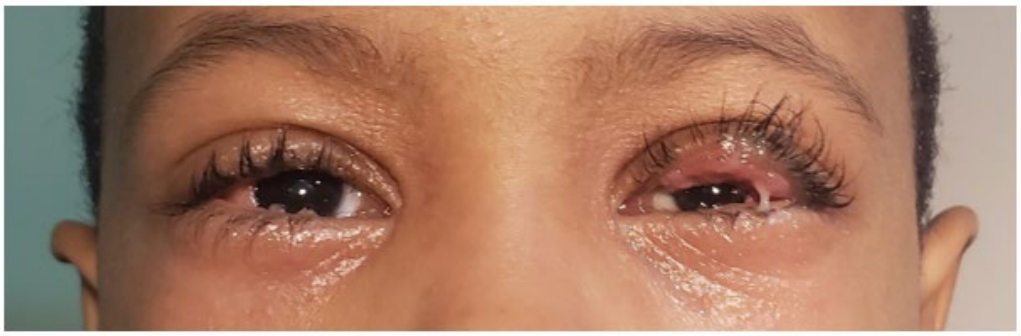

Figure 4: *Photograph of both eyes after one year of treatment.*

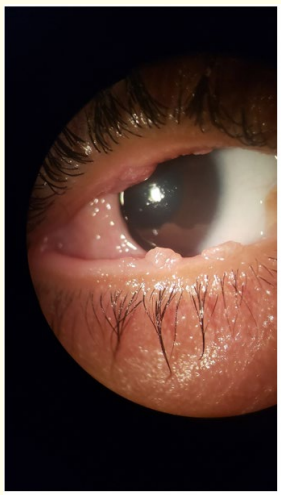

Figure 5: *Slitlamp photograph of the right eye after one year of treatment.*

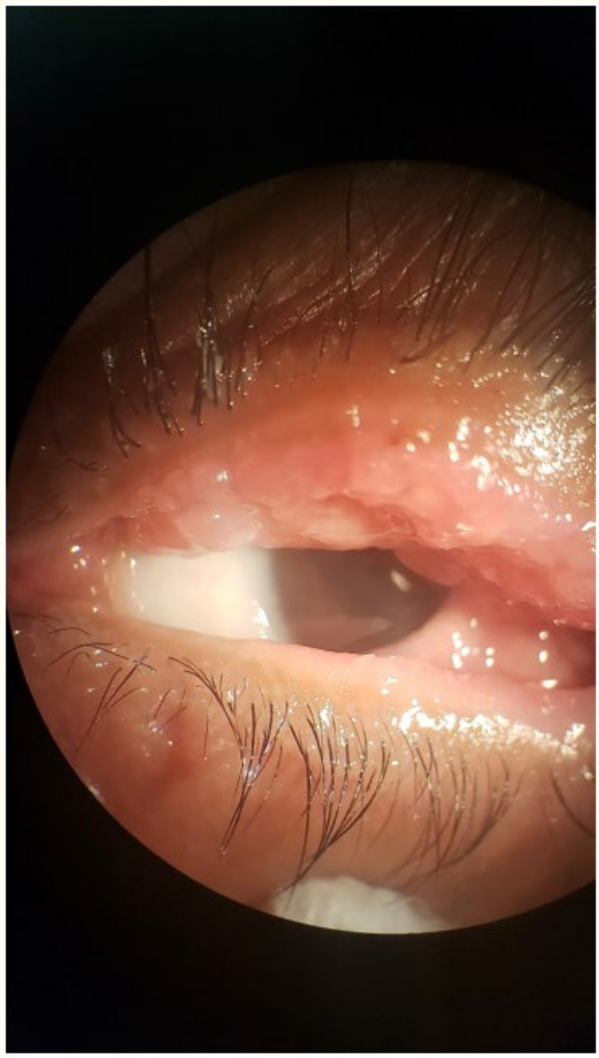

Figure 6: *Slitlamp photograph of the left eye after one year of treatment.*

Discussion

There are few options to treat LC available in the market, but none of them is optimal. First, pseudomembrane triggers, such as ocular surface inflammation and trauma, should be avoided. Furthermore, LC treatment is currently based on combining immunomodulatory therapy (corticosteroids and calcineurin inhibitors), anticoagulants (heparin), and, preferably, plasminogen replacement therapy [6]. This replacement was herein performed based on using blood derivatives, such as topical or intravenous fresh frozen plasma (FFP). Antibiotic therapy was ineffective.

Plasminogen is a precursor plasmin that inhibits fibrin cross-linking, contributes to fibrin-rich extracellular matrix migration in skin healing processes, as well as enables keratinocyte division, migration and differentiation to support skin wound closure. Plasminogen

deficiency hinders fibrin cleavage; therefore, wound healing stops at granulation stage, and it leads to grease deposits' formation [7]. The anticoagulant role played by heparin is explained by its ability to bind to antithrombin and to inhibit the coagulation cascade to stop fibrin lesions.

Fresh frozen plasma comprises growth factors, vitamin A, fibronectin, cytokines and plasminogen [4]. Nowadays, its replacement is the most effective therapy applied to LC cases, since it acts in the disease mechanism. Based on a case series of 13 patients with conjunctival disease treated with both intravenous and local FFP, two patients had allergic reactions, three did not respond to the therapy, whereas eight (72%) presented satisfactory response to it and did not require surgery [8].

Topical plasminogen drops appear to be more advantageous than intravenous infusion therapy in controlling pseudomembrane growth and in decreasing potential complications that may require hospitalization [9]. However, is important to elude that plasminogen deficiency is a systemic disease and some patients have airway, GI and genitourinary lesions which would not be addressed by ocular topical therapy.

Specific therapies based on glu-or lys-plasminogen concentrates remain under investigation [9-11]. Glu-plasminogen is the prevalent circulating native plasminogen form (> 95%), whose half-life is longer than that of Lys-plasminogens. A study conducted with 14 patients treated with human Glu-plasminogen IV at 6.6 mg/kg, every 2 - 4 days, reported more than 50% reduction of symptoms in all children and adult patients.

However, plasminogen replacement therapy has limited use, since it is not easily accessible due to its low demand, high production costs, lack of well-defined acquisition flow and small number of manufacturing centers available [3,9,12]. In addition, its topical form is not yet commercially available; only the intravenous recombinant plasminogen for LG is FDA approved and available in the United States now. Moreover, it is hard to be produced, transported and conserved, because it requires low temperatures to do so. It also requires daily preparation and transportation, even in weekends[7]. Therefore, even individuals who can afford serum therapy have a hard time maintaining it, in the long term. Therapy discontinuation leads to symptom recurrence.

Recent study has emphasized these very same difficulties experienced by patients in France [12], who were forced to wait for the aforementioned product for approximately two years. However, difficult access to it was also reported in all literature reviews, worldwide. Article 23 of Brazilian Law n. 10.205/2001 allows non-therapeutic apheresis, but only for blood products' obtainment purposes; this procedure can only be performed by the public sector. It is regulated by a specific rule, which identifies fresh frozen plasma as pharmaceutical input for blood products' production; however, this practice is not yet performed in Brazil [13-16].

Surgical intervention is an option for advanced cases, but its recommendation must be quite strict (overall, in cases presenting visual loss) [1]. High lesion relapse rates have decreased after intra- and post-operative administration of human plasminogen and heparin within a one-year follow-up period [9,17,18].

If one takes into consideration that the LC treatment is based on plasminogen replacement, is it possible saying that heterologous blood is an evident source of it. Fingerprick blood has been reported to be used for other ocular surface diseases with some level of success [19].

Recent study has used fingerprick blood drops to treat dry eye syndrome in 29 eyes of 16 patients. They were administered to the lower fornix of patients' eyes four times a day, for eight weeks. The adopted therapy led to improved clinical parameters, such as mean Oxford corneal-staining grade, tear break-up time, visual acuity and ocular comfort index score. Rates recorded for the aforementioned parameters have worsened 4 weeks after the fingerprick blood drop therapy stopped [5].

Our patient had history of presenting satisfactory results after plasminogen replacement therapy administration based on FFP. However, it was hard to acquire this blood product, and it made the long-term treatment unfeasible. Commercially available therapies (corticosteroids, calcineurin inhibitors and anticoagulants) have few satisfactory outcomes and many side effects. Patients who do not undergo plasminogen replacement therapy become steroid-dependent, even when they use other immunomodulators, such as calcineurin inhibitors. Therefore, advanced cases - such as the herein reported one - that present poor response to the available therapy, often require alternative treatments.

Our service has already received patients who used autologous blood for dry eye treatment and presented satisfactory response to it.

The biggest obstacle to patients' adherence to our therapy lies on the constant need of fingerpricking. However, our patient's mother was motivated to try new resources when this possibility was presented to her. The mother was herein selected as donor because she was the closest person to the child and the most motivated one.

Because plasminogen deficiency is inherited, with great variety of genetic mutations [20], the patient's mother may have less plasminogen than the overall population because she is possibly heterozygous. No genetic tests were available in our region. Thus, in theory, blood donors unrelated to the patient can provide greater plasminogen amounts than heterozygous donors.

The patient and his mother were satisfied with the therapy outcome, as well as eager to continue the treatment.

Concluding Thoughts

The current study presented the case of an infant patient with LC, who was treated with heterologous blood donated by his mother and presented improved clinical condition. Given the difficulty in accessing plasminogen replacement therapy based on heterologous serum, plasminogen replacement based on direct heterologous blood administration would be the cheapest and most accessible way to guarantee LC treatment to patients. We reinforce that the preferred treatment for ligneous conjunctivitis remains being fresh frozen plasma (FFP), heterologous serum or recombinant plasminogen. Blood heterologous drops are an emergency option. We expect to start FFP treatment in our patient as soon as it gets available in our region. Further studies should be conducted with larger number of patients to help validating this therapy.

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