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Case Report

Marsupialization of conjunctival inclusion cyst in Stevens-Johnson syndrome☆

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1. Background

Conjunctival inclusion cyst is formed by hyperplasia and degeneration of epithelial cells implanted in subconjunctival area, which is common after ocular trauma and eye surgery.[1] It can also be found in Stevens-Johnson syndrome (SJS), which results in extensive and severe symblepharon and the formation of cysts by encapsulating residual conjunctival epithelium on the fornix.[2] The previous treatments of conjunctival inclusion cyst include complete excision surgically, cyst aspiration, foam sclerotherapy after cyst aspiration,[3] and fornix reconstruction with cyst marsupialization,[4] which owned many advantages but a similar surgery was only presented in a few case reports. In our clinical practice, the cyst wall was used for marsupialization in four patients suffering from both large conjunctival inclusion cyst and severe symblepharon. Owing to the difficulty of the treatment of SJS, the poor therapeutic effect of the traditional method, and the small number of articles on fornix reconstruction with conjunctival inclusion cyst marsupialization, such cases are summarized in the present study to introduce the clinical application of this operation for reference.

2. Surgical techniques and results

A retrospective case series. Four conjunctival inclusion cyst patients hospitalized in PLA General Hospital for SJS from January 2012 to January 2022 were extracted from the hospital electronic medical record system. Following preoperative evaluation, fornix reconstruction with conjunctival inclusion cyst marsupialization was performed. The study adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013, and the study protocol was approved by the Ethics Committee of Chinese PLA General Hospital. And patient consent for inclusion was waived because all data were anonymized and the study was retrospective in nature.

Surgical procedures and techniques: Retrobulbar anesthesia was carried out, usually accompanied by eyelid tissue infiltration anesthesia. Penetration into the cyst should be avoided so that the cyst would remain intact and be exposed smoothly. Under the surgical microscope, the conjunctiva was cut off along the palpebral margin to separate the exposed cyst (Fig. 1A) and the cyst wall was cut open (Fig. 1B) to the bottom of the fornix in parallel. Timely removal of the fluid in the cyst and gentle flushing of the ocular surface with saline solution can reduce the probability of postoperative cyst recurrence. Then, the medial margin of the cyst wall was sutured with the bulbar conjunctiva, and the lateral margin of the cyst was sutured with the palpebral conjunctiva (Fig. 1C), with the epithelium of the inner wall of the cyst as the lining of the fornix. The cyst wall should be fixed on the scleral surface to increase adhesion. Eyelid movement should be avoided as it would induce displacement and tear of the cyst wall. Intraoperative care should also be taken to protect the epithelium of the cyst. In the case of large wound surface, incomplete coverage with the cyst wall in the process of separating symblepharon should be covered with amniotic membrane or conjunctiva.[5,6] Topical steroids and antibiotics were prescribed postoperatively. Table 1 and Table 2 show the demographics, clinical manifestation, and clinical procedures of the four cases. The grading score of ocular surface appearance before surgery according to earlier publications is shown in Tables 1.[7,8] The patients were followed up for 7 months to 3 years (an average of 19 months and the median was 14 months). There was no recurrence of cyst, and the symptoms and signs were improved after operation. Case 1 and Case 4 are described as follows, and the other two cases are described in the Supplementary materials.

☆ **Precis:** This article describes and summarizes the indications, surgical modalities and postoperative outcomes of marsupialization of conjunctival inclusion cyst in Stevens-Johnson syndrome.

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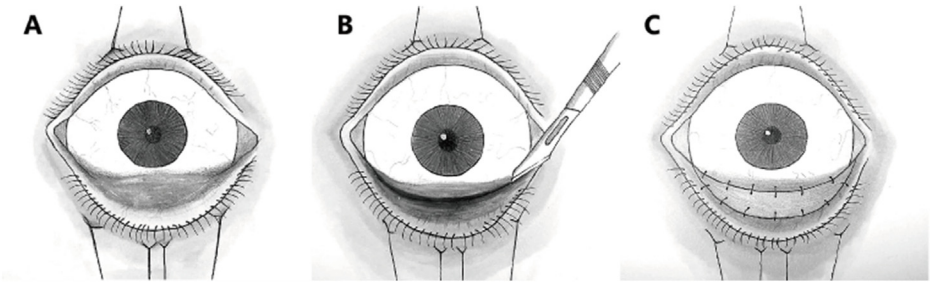

Fig. 1. (A) Ideograph of conjunctival inclusion cyst in Stevens-Johnson syndrome; (B) Ideograph of conjunctiva was cut off along the palpebral margin to separate the exposed cyst; (C) Ideograph: The medial margin of the cyst wall was sutured with the bulbar conjunctiva and the lateral margin of the cyst with the palpebral conjunctiva.

Table 1
Summary of demographic details and clinical presentation of 4 cases of Conjunctival inclusion cyst in SJS.

Case	Age (y)	Gender	Symptoms	Ocular examination	Symblepharon (grade)	Corneal neovascularization (grade)	Conjunctivalization (grade)	Corneal opacification (grade)
1	31	M	Bilateral lower eyelid mass	Translucent, clear, cystic mass, the right cyst was about 10mm × 8mm in size, and the left was about 30mm × 10mm; symblepharon	1	1	0	0
2	39	M	Superolateral eyelid mass of right eye	Soft mobile upper lid swelling, the cyst was about 25mm × 20mm in size; symblepharon; patchy turbidity in the center of the cornea	1	0	0	1
3	42	F	Superolateral eyelid mass of left eye	Cystic swelling of temporal region, the cyst was about 10mm × 10mm in size; symblepharon	1	0	1	1
4	43	F	Upper eyelid mass of left eye	Two large cysts over the upper lid with the size of about 15 mm × 15mm and 10mm × 10mm; Intraocular pressure T+2; limited ocular activity; keratinization of corneo-conjunctival epithelium on both eyes; symblepharon	3	3	3	3

Table 2
Summary of the treatment and outcome of the conjunctival inclusion cyst in SJS.

Case	Treatment of the cyst	Recurrence of the cyst	Other outcomes
1	Marsupialization of the left cyst and excision of the right cyst	No recurrence for 15 months	The depth of the left conjunctiva sac was about 4.0mm, and the right became shallow
2	Marsupialization	No recurrence for 13 months	The depth of the upper conjunctiva sac was about 6.0mm
3	Marsupialization	No recurrence for 7 months	The depth of the upper conjunctiva sac was about 6.0mm
4	Marsupialization	No recurrence for 3 years	Conjunctival sac was significantly deepened after operation accompanied by severe dry eye and repeated symblepharon in the later stage with the disappearance of conjunctival sac; choose another eye for artificial corneal implantation

3. Case presentation

Case 1: A 31-year-old male patient presented with bilateral lower eyelid masses, which had persisted for 22 years, and the left one aggravated for 3 months. The patient was diagnosed with SJS years ago due to the occurrence of fever, blisters, and mucosal erosion caused by the drug allergy. After treatment, the systematic symptoms were relieved. About a year later, the lower eyelids of both eyes became enlarged, which was diagnosed as epithelial implantation cyst by the local hospital. After repeated operations in other hospitals, the cyst recurred again. Ocular examination: the best-corrected visual acuity (BCVA) was 20/25 in both eyes, and intraocular pressure was 11 mmHg (right) and 8 mmHg (left). Examination showed translucent, clear, cystic mass in bilateral lower eyelids. The lower eyelid of the left eye was filled with a strip-like conjunctival cyst (about 30mm × 10mm) from the inner canthus to the lateral canthus. The lower conjunctival sac was quite shallow and almost disappeared, accompanied by symblepharon (Fig. 2A). The lower eyelid conjunctival cyst of the right eye was about 10mm × 8mm. Diagnosis: Conjunctival inclusion cysts in the lower eyelids of both eyes; symblepharon of both eyes; and SJS. Fornix reconstruction with conjunctival inclusion cyst marsupialization was performed on the left eye with a larger cyst, and the right eye with a smaller cyst was treated with cystectomy. The images of the left eye after surgery are shown in Fig. 2B.

Case 4: A 43-year-old female patient presented with para-orbital mass in the left eye, which had persisted for over 20 years. More than 20 years ago the patient developed erythema and blisters after taking sulfonamides. About one month later, she developed red eyes with blood secretions, gradually blurred vision in both eyes, and a para-orbital mass in the upper left eyelid, which had never been treated and gradually became enlarged. Ocular examination: the vision was hand motion/10cm in the right eye and light perception with inaccurate optical positioning in the left eye. Intraocular pressure was Tn (right) and T+2 (left). Two globular masses were palpable on the upper eyelid of the left eye, about 15mm × 15mm and 10mm × 10mm, which occupying the conjunctival sac caused it to almost disappear. There was symblepharon, limited eye movement,

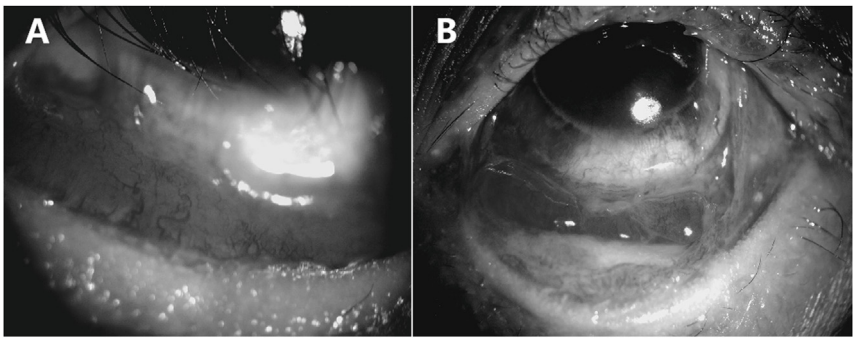

Fig. 2. (A) The cyst of the left eye in Case 1, with a strip-like appearance accompanied by symblepharon, the cyst was about 30mm × 10mm in size; (B) The left eye of Case 1 a week after surgery.

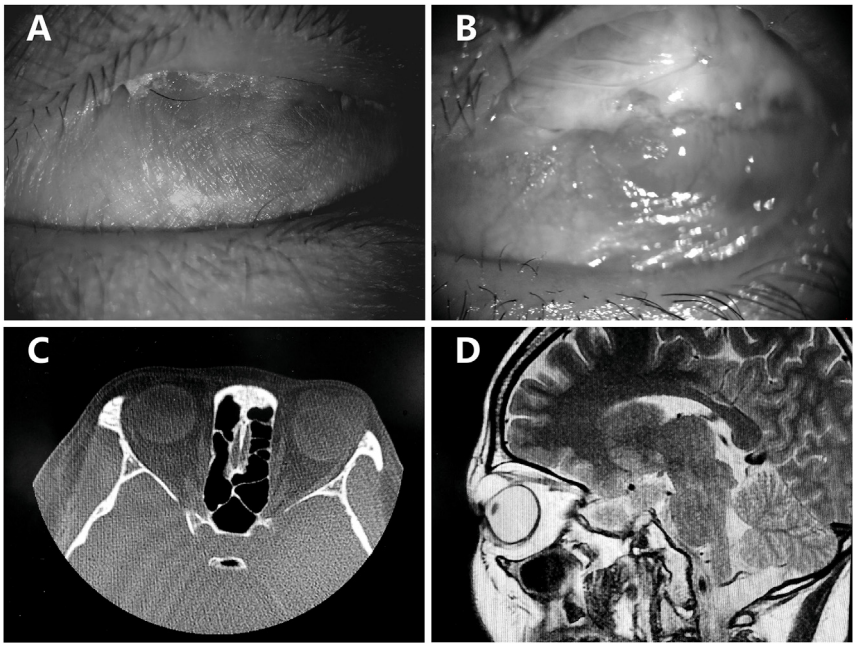

Fig. 3. (A) The left eye of Case 4 with symblepharon and keratinization of corneo-conjunctival epithelium; (B) The left eye of case 4 a week after surgery; (C/D) CT showed two spherical occupying lesions above the left eyeball with a lower density.

and keratinization of corneo-conjunctival epithelium in both eyes (Fig. 3A). CT and MRI examinations revealed two globular occupying lesions above the left eye (Fig. 3CD). B-mode ultrasonography showed the depressed optic disc in the left eye. FVEP revealed the delayed P2 peak in both eyes, which was more significant in the left one. And the amplitude of the left eye was lower than that of the right. Diagnosis: Conjunctival inclusion cysts in the upper eyelid of the left eye; secondary glaucoma in the left eye; symblepharon of both eyes; and SJS. The smaller cyst was removed completely and the larger cyst was treated with conjunctival inclusion cyst marsupialization. The postoperative image is shown in Fig. 3B.

In all four cases, BCVA remained the same as before surgery, and conjunctival sacs deepened without recurrence of cyst during the follow-ups. Pathological results: In Case 1, the cystic wall was double-layer columnar epithelium with infiltration of inflammatory cells (Additional Fig. 3A). The pathological result of Case 2 was empty. In Case 3, the cyst was covered by a single layer of flat epithelium (Additional Fig. 3B). In Case 4, the cyst was covered by squamous epithelium (Additional Fig. 3C). In some clinical cases, pathological analysis is not available because the cystic wall tissue is needed for fornix reconstruction, which may be one of the limitations. In Case 1, Case 2, and Case 3, the conjunctival sac was significantly deepened, with no constriction or obvious adhesion. In Case 4, the conjunctival sac remained well reconstructed in the early postoperative phase, yet accompanied with repeated symblepharon in the later phase owing to exacerbation of protopathy. Artificial corneal implantation was adopted for the other eye with better optic nerve function.

4. Discussion

4.1. Mechanism of severe symblepharon and conjunctival inclusion cyst in SJS

In the present study, all 4 cases were diagnosed as SJS, with the presence of chronic ocular sequelae, such as visual deterioration, symblepharon, entropion and trichiasis, severe dry eye, and epiphora. SJS is an autoimmune-mediated disease that typically involves the eye, skin, and mucous membrane, belonging to type IV delayed hypersensitivity reaction.[9,10] SJS can be caused by multiple factors, and more than 90% of cases are induced by drugs, mainly antibiotics (sulfonamides and β-lactams, etc.), nonsteroidal anti-inflammatory drugs, antipyretics, analgesics, and antiepileptic drugs (mainly phenytoin sodium and

carbamazepine).[11] Furthermore, acute eye involvement can be found in 77% of the patients with SJS.[12] It may cause severe keratoconjunctival cutinization and scarring, cornea conjunctivization or neovascularization, symblepharon, entropion, and trichiasis in the late stage and eventually lead to loss of vision.[13]

Conjunctival inclusion cysts can be caused by encapsulating of conjunctival cells adjacent to scars after penetrating trauma, surgeries involving conjunctival and Tenon's fascia manipulations such as strabismus surgery, or even after sub-Tenon's injection of anesthetic agents.[1] Cicatricial ocular inflammations are another common source of conjunctival inclusion cysts. Extensive surface inflammation with adhesions can cause encapsulating of epithelium with the formation of cysts in ocular surface inflammatory conditions. In SJS, extensive surface denudation and inflammation in the acute phase can lead to such adhesions between the healing conjunctival surfaces. Even in the late cicatricial phase, ongoing epithelial hyperproliferation with inflammatory cell infiltration has been demonstrated in the conjunctiva. The proliferation of sequestrated epithelial cells can lead to the formation of cyst as in our cases. This inclusion can be further aided by practices like breaking conjunctival adhesions with glass rods during the acute phase.

4.2. Necessity and superiority of fornix reconstruction with conjunctival inclusion cyst marsupialization

Severe acute ocular surface inflammation, such as SJS, can commonly result in severe symblepharon, where the cyst walls are usually tightly adherent to scar tissue that is difficult to separate. Traditional cystectomy often results in recurrence due to incomplete excision of the cyst wall. In Case 1, the cyst recurred after repeated cystectomy but not after marsupialization. Furthermore, in the traditional treatment of symblepharon, the wound surface is covered by amniotic membrane, autologous conjunctiva or cultivated oral mucosal epithelial after the loosening of adhesion.[14] However, SJS often develops in both eyes and results in deficiency of corneal and conjunctival stem cells, keratinization of all conjunctival epithelium, absence of epithelium on the ocular surface, severe dry eye, deficiency of autologous conjunctiva, and failure to regenerate normal conjunctival epithelium after amniotic membrane transplantation. And cultivated oral mucosal epithelial transplantation usually applies to persistent epithelial defect at an acute inflammatory stage, the culture cycle takes time and is complicated, and transplanted epithelium easily detaches due to severe dryness of the eye.[15,16] Accordingly, the traditional way of operation is not effective as it is followed by recurrent symblepharon. The above four cases showed that it is feasible to adopt conjunctival inclusion cyst marsupialization in combination with fornix reconstruction by making full use of the epithelium of the cyst wall. Meanwhile, the pathological results indicated that the cyst wall was similar to the conjunctival epithelium and could secrete fluid to moisten the ocular surface.

Considering the rareness of cases and the poor effect of the repeated treatments of the primary disease, conjunctival inclusion cyst marsupialization exhibits multiple advantages over the traditional surgery of cyst excision. By making use of the cystic wall, it turns waste into treasure, reduces the bare area of fornix, deepens the conjunctival sac, reduces symblepharon, relieves eyeball compression, improves appearance, and avoids recurrence caused by incomplete cyst excision.

4.3. Indications for fornix reconstruction with conjunctival inclusion cyst marsupialization

Small cysts that affect eye appearance and occasionally cause foreign body sensation generally require no special treatment. Enlarged cysts may lead to space-occupying lesion, restriction of eye movement, and incomplete eyelid closure, which would seriously affect eye appearance. Meanwhile, the occupying effect caused by enlarged cysts may induce prolonged compression of the eyeball, resulting in elevated intraocular pressure and irreversible damage to optic nerves. Furthermore, owing to the growing tendency of cysts, the symptom of compression will gradually aggravate and may lead to irreversible damage to optic nerve if there is no prompt surgical treatment. In our opinion, conjunctival cysts should be treated promptly, and the large single cyst in line with eyelid margin with a diameter greater than 1.0cm is recommended to be treated with conjunctival inclusion cyst marsupialization. Small cysts may be removed completely or left alone temporarily.

4.4. Analysis of factors influencing the efficacy of fornix reconstruction with conjunctival inclusion cyst marsupialization in the treatment of symblepharon

The four cases all suffered from severe symblepharon. In Case 1, 2, and 3 the cysts were enlarged and their locations conformed to the shape of the conjunctival sac. After marsupialization, no obvious constriction of the conjunctival sac has been found in the follow-up period. Case 4 had a poor prognostic outcome due to severe symptoms, long duration of illness, keratinization of corneo-conjunctival epithelium, and poor ocular surface condition. Therefore, for large single cyst in the fornix caused by SJS, early treatment of marsupialization brings a better effect to conjunctival sac reconstruction. Due to the gradual alleviation of SJS, the condition tends to be stable and the cyst epithelium can survive for a long time as its living environment is improved. However, for severe symblepharon, it means absence of ocular surface epithelium, serious dry eyes, and long-term stimulation of chronic inflammation. The use of cyst wall alone as fornix lining brings unsatisfactory outcomes and was usually followed by gradual constriction of the conjunctival sac with recurrence of symblepharon. Therefore, the crucial factors for the prognosis of conjunctival inclusion cyst marsupialization are the condition of the primary disease and the degree of preoperative symblepharon.

5. Conclusions

In conclusion, SJS often results in severe symblepharon and is often associated with conjunctival inclusion cysts that cannot be well treated by traditional surgical excision. Fornix reconstruction with conjunctival inclusion cyst marsupialization turns waste into treasure by making use of the cystic wall to reduce the bare area of fornix, and exhibits superior surgical effects.

Study approval

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Chinese PLA General Hospital. And patient consent for inclusion was waived because all data were anonymized and the study was retrospective in nature.

Author contributions

The authors confirm their contribution to the paper as follows: Conception and design of the study: Yifei Huang. Data collection and drafting the manuscript: Jinglan Li. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2022.10.004.

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