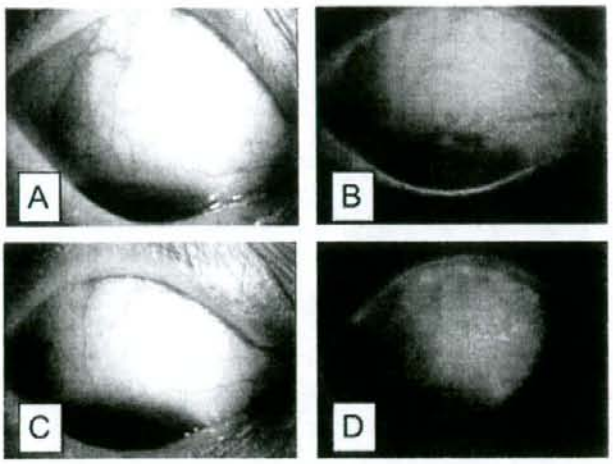
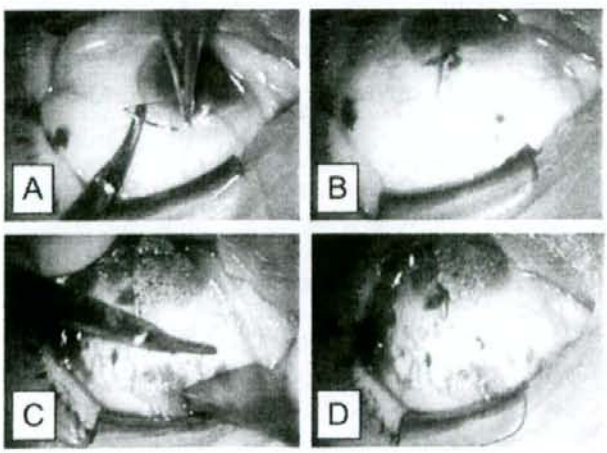
Questions:

1. What is the pathophysiology of SLK?

2. What medical treatment options exist for SLK?

3. What surgical options exist for SLK?





Answers

1 **What is the pathophysiology of SLK?**

Since Theodore published the first clinical description of SLK in 1963 [1], numerous etiologies have been proposed for this specific keratoconjunctivitis. [2] Although the etiology of SLK has not been definitively established, the authors hold the mechanical friction theory to be most plausible.

The mechanical friction theory originally advocated by Wright [3] is based on a characteristic feature of SLK, redundancy and loosening of the superior bulbar conjunctiva. The mechanical theory suggests that the superior bulbar conjunctiva is continually rubbed by the upper tarsus during blinking, resulting in chronic inflammation. This theory is supported by the clinical observations that SLK tends to be associated with thyroid dysfunction, and with the use of hydrophilic contact lenses. [4][5] SLK may also be present in eyes with essential blepharospasm, and eyes with previous upper lid blepharoplasty. [6] Thus, the pathophysiology of SLK appears to involve abnormal dynamics, or an abnormal interface load between the eyelid and the globe, resulting in friction on blinking that leads to chronic irritation and the development of keratoconjunctivitis. [7]

2. **What medical treatment options exist for SLK?**

A number of medical treatment modalities have been proposed for SLK. [2] The local application of silver nitrate, originally recommended by Theodore [1], appears to facilitate scarring and remodeling of the subconjunctival tissue, which in turn is proposed to decrease friction between the bulbar and palpebral conjunctiva. Bandage contact lenses, which are particularly effective in treating eyes with filamentary keratitis, are thought to exert a therapeutic effect by isolating the globe mechanically from the motion of the tarsus. [8]

Preexisting dry eye is linked to SLK [1][4], indicating that the loss of lubricity may contribute to the development of SLK. Lubricating eyedrops including artificial tears, sodium hyaluronate, and autologous serum, therefore, may of value to some degree. [9] Occlusion of the upper and/or lower puncta may be effective by increasing the amounts of tears that facilitate lubrication of the ocular surface. [10] Pharmacologic therapies intended to lesson ocular surface inflammation may also be considered. Corticosteroid, cyclosporine A, and cromolyn sodium have been used for this purpose. [6][11] In general, however, the effects of medical treatments are limited, and when they fail, surgical treatments become necessary.

3. **What surgical options exist for SLK?**

Thermocautery [10], simple resection [2][12], and recession of the abnormal conjunctiva [13] have been reported as effective surgical treatments for SLK. New surgical methods such as a crescent resection of the superior unaffected bulbar conjunctiva [14] and amniotic membrane transplantation [6] have recently been proposed. Additionally, in this case report, we describe the use of conjunctival fixation sutures, which, to our knowledge, is a novel approach for the treatment of SLK.

Surgical options for the treatment of SLK can be divided into two categories based on mechanism of action, procedures that seek to reinforce the adhesion of the conjunctiva to the sclera, and those that seek to correct the redundancy of the superior bulbar conjunctiva. Procedures in the first category include thermocautery, recession of the abnormal conjunctiva, and amniotic membrane transplantation. Procedures in the latter category include resection of the abnormal conjunctiva, or resection of the unaffected superior bulbar conjunctiva, as well as the conjunctival fixation suture method described in this case report.

Discussion

SLK, an inflammatory disease involving the region of the limbus and the superior bulbar conjunctiva, may result in conditions such as filamentary keratitis, superficial punctate keratopathy, and hyperemia of the limbus and superior bulbar conjunctiva. [2][4] There is prominent laxness of the superior bulbar conjunctiva when the upper lid was squeezed in patients with SLK. Recently, Yokoi et al. [14] and Kheirkhah et al. [6] independently reported that a redundant, loosened superior bulbar conjunctiva plays a significant role in the pathogenesis of SLK. These authors advocated categorizing SLK as a type of conjunctivochalasis, or recognizing SLK as superior conjunctivochalasis. [6][14]

Based in part on our successful experience using fixation sutures for the treatment of conjunctivochalasis, a method which was originally reported by Otaka and Kyu [15], we accordingly chose a similar technique for the treatment of refractory SLK. Though many surgical procedures to treat SLK have been investigated, fixation sutures offer the unique benefit of simple, quick, and minimally invasive application. Additionally, a large area of the superior bulbar conjunctiva remains unaffected by this procedure, which may be beneficial in the event of future ocular surgery, such as cataract or glaucoma surgery. We have now successfully treated a total of three patients with refractory SLK with the procedure described in this case report.

References

1. Theodore FH. Superior limbic keratoconjunctivitis. *Eye, Ear, Nose Throat Monthly.* 1963;42:25-8.

2. Driebe WT. Superior limbic keratoconjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea, Cornea and external disease: clinical diagnosis and management; Vol. . St. Louis: Mosby-Year Book, Inc.; 1997:857-62.

3. Wright P. Superior limbic keratoconjunctivitis. *Trans Ophthalmol Soc UK.* 1972;92:555-60.

4. Nelson JD. Superior limbic keratoconjunctivitis (SLK). *Eye.* 1989;3:180-9.

5. Stenson S. Superior limbic keratoconjunctivitis associated with soft contact lens wear. *Arch Ophthalmol.* 1983;101:402-4.

6. Kheirkhah A, Casas V, Esquenazi S, Blanco G, Li W, Raju V-K, Tseng SCG. New surgical approach for superior conjunctivochalasis. *Cornea.* 2007;26:685-91.

7. Cher I. Blink-related microtrauma: when the ocular surface harms itself. *Clin Experiment Ophthalmol.* 2003;31:183-90.

8. Mondino BJ, Zaidman GW, Salamon SW. Use of pressure patching and soft contact lenses in superior limbic keratoconjunctivitis. *Arch Ophthalmol.* 1982;100:1932-4.

9. Goto E, Shimmura S, Shimazaki J, Tsubota K. Treatment of superior limbic keratoconjunctivitis by application of autologous serum. *Cornea.* 2001;20:807-10.

10. Udell IJ, Kenyon KR, Sawa M, Dohlman CH. Treatment of superior limbic keratoconjunctivitis by thermocauterization of the superior bulbar conjunctiva. *Ophthalmology.* 1986;93:162-6.

11. Confino J, Brown SI. Treatment of superior limbic keratoconjunctivitis with topical cromolyn sodium. *Ann Ophthalmol.* 1987;19:129-31.

12. Passons GA, Wood TO. Conjunctival resection for superior limbic keratoconjunctivitis. *Ophthalmology.* 1984;91:966-8.

13. Tenzel RR. Resistant superior limbic keratoconjunctivitis. *Arch Ophthalmol.* 1973;89:429

14. Yokoi N, Komuro A, Maruyama K, Tsuzuki M, Miyajima S, Kinoshita S. New surgical treatment for superior limbic keratoconjunctivitis and its association with conjunctivochalasis. *Am J Ophthalmol.* 2003;135:303-8.

15. Otaka I, Kyu N. A new surgical technique for management of conjunctivochalasis. *Am J Ophthalmol.* 2000;129:385-7.

Figure Legends

Figure 1. Before surgery, hyperemia and hypertrophic changes are seen in the superior bulbar conjunctiva (A). The affected area is intensively stained with fluorescein sodium (B). Two weeks after the operation, marked improvements in hyperemia and fluorescein staining are apparent (C, D).

Figure 2. . A traction suture is made by placing a 6-0 silk suture at the limbus at the 12 o'clock position in order to rotate the eye down ward (A, B). Stretching the redundant superior bulbar conjunctiva with a spatula, anchoring sutures were used by placing 10-0 nylon sutures at 10-12 mm from the limbus to fixate the conjunctiva to the sclera (C). Two stitches were placed nasally from the superior rectus muscle, and three stitches were placed temporally (D).

あたらしい眼科 25(11)：1557～1560，2008©

結膜弛緩症に対する結膜縫着術

永井正子[*1,2]　羽藤　晋[*1,2]　大野建治[*1]　望月弘嗣[*1]　山田昌和[*1]

[*1]国立病院機構東京医療センター感覚器センター　[*2]慶應義塾大学医学部眼科学教室

Surgical Repair of Conjunctivochalasis with Anchoring Sutures

Masako Nagai[1,2], Shin Hatou[1,2], Kenji Ohno[1], Hiroshi Mochizuki[1] and Masakazu Yamada[1]

[1] *National Institute of Sensory Organs, National Tokyo Medical Center,* [2] *Department of Ophthalmology, Keio University School of Medicine*

結膜弛緩症に対するanchoring sutureによる結膜縫着術の治療成績について検討した．対象は東京医療センターで結膜縫着術を施行した結膜弛緩症症例21例38眼で，手術時年齢は平均74.0±6.9歳，性別は男性3例，女性18例であった．本術式により89.5%の例で涙液メニスカスを完全に再建できたが，自覚症状の著明な改善を得ることができたのは63.2%であった．自覚症状の改善率を自覚症状別に比較すると，流涙型では87.5%（16眼中14眼）で高かったが，ドライアイ型では50%（8眼中4眼），炎症型では50%（8眼中4眼）と流涙型以外では低い傾向にあった．また対象には，capsulopalpebral fascia（CPF）の弛緩を伴う円蓋部挙上型5眼が含まれていたが，同じ術式で対応することができた．本方法は，手術手技が比較的容易で短時間に行えること，術後の炎症所見，異物感が少ないこと，CPFの弛緩を伴う円蓋部挙上型にも同じ術式で対応できることなどが利点と考えられた．

Surgical results of conjunctivochalasis repair with anchoring sutures were reviewed in 38 eyes of 21 patients (mean age：74.0±6.9 yrs；3 males, 18 females) who were treated with anchoring sutures at National Tokyo Medical Center. Of these patients, 89.5% achieved the resolution of conjunctivochalasis, resulting in complete reconstruction of the tear meniscus. Subjective symptoms, however, were completely resolved in only 63.2% of cases. When the patients were divided into subgroups according to the subjective symptoms, the success rate of lacrimation type was excellent (87.5%), whereas the success rates of the dry-eye and inflammation types were 50% and 50%, respectively. Five cases that had accompanying relaxation of the capsulopalpebral fascia (CPF) were treated by the same procedure, without problems. This surgical technique appears to be easy, safe and less time-consuming. The minimization of postoperative inflammation and foreign-body sensation is advantageous over other techniques. Surgical repair of conjunctivochalasis with anchoring sutures appears to be effective for treating the condition.

〔Atarashii Ganka (Journal of the Eye) **25**(11)：1557～1560, 2008〕

Key words：結膜弛緩症，手術，ドライアイ，流涙，conjunctivochalasis, surgery, dry eye, epiphora.

はじめに

結膜弛緩症は，おもに下方球結膜が弛緩する状態を指し，加齢性変化によって生じるとされている[1]．また近年capsulopalpebral fascia（CPF）の弛緩により結膜円蓋部が挙上し，結果として結膜が下眼瞼縁を占拠する機序の結膜弛緩症が存在することが報告されている[2]．結膜弛緩症は決して新しい疾患概念ではなく，高齢者における有病率が高い疾患であるが，長い間，過小評価されてきた疾患の一つである[1]．しかし米国で1990年代から流涙あるいはドライアイの原因疾患の一つとして再認識され，わが国でも多彩な自覚症状を呈する高齢者の不定愁訴の原因疾患として注目されるようになってきている[3]．

結膜弛緩症の治療として手術が有用であることが知られており，その術式も横井らの結膜切除術[3,4]，Mellerらの羊膜移植を併用した結膜切除術[5]，Otakaらの結膜縫着術[6]などさまざまな術式が報告されている．筆者らはOtakaらの結

〔別刷請求先〕永井正子：〒160-8582 東京都新宿区信濃町35　慶應義塾大学病院眼科

Reprint requests：*Masako Nagai, M.D., Department of Ophthalmology, Keio University Hospital, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, JAPAN*

0910-1810/08/¥100/頁/JCLS

膜縫着術を modify して，より簡便で侵襲の少ない術式として 10-0 ナイロン® 糸を用いた anchoring suture による結膜縫着術を行っている．今回，その治療成績について検討したので報告する．

I 対象および方法

対象は東京医療センター眼科において，2005 年 4 月から 2006 年 12 月に結膜縫着術を施行した結膜弛緩症 21 例 38 眼である．対象の手術時年齢は 61～86 歳（74.0±6.9 歳，平均±標準偏差），性別は男性 3 例，女性 18 例であった．

国立病院機構東京医療センター感覚器センター（以下，当科）では，結膜弛緩症の治療の第一選択を手術とはせずに，まず点眼治療を試みている．点眼治療として人工涙液，ヒアルロン酸製剤，ステロイド薬，非ステロイド系消炎薬などを症例に応じていくつか試み，自覚症状の軽快がみられないものを手術適応とした．

手術は点眼麻酔の後に 2%リドカイン（キシロカイン®）を少量，結膜下に注射して行い，6-0 シルク糸で 6 時に制御糸をかけて上転させた状態で眼球を固定した（図 1）．輪部から結膜円蓋部に向けてスパーテルか鑷子の背の部分を用いて結膜を伸展させた状態を保ちながら，輪部から約 8 mm の部分に 10-0 ナイロン® 糸で結膜から強膜をすくって縫合した．結膜を伸展させると下直筋の位置が同定できるので，下直筋は避けるようにし，下直筋の耳側に 2 針，鼻側に 3 針縫合をかけるようにした．

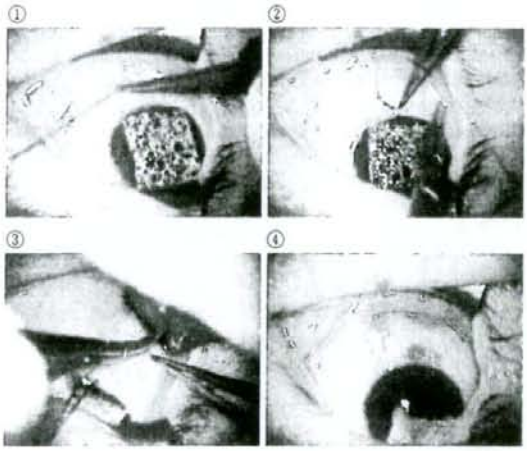


図 1 手術方法
①結膜下注射で局所麻酔を行い，②6 時方向に 6-0 シルク糸で制御糸をかける．③上転させた状態で結膜を伸展し，輪部から約 8 mm のところに 10-0 ナイロン® 糸で結膜と強膜を縫着する．下直筋を避け，その鼻側と耳側に 2～3 針ずつ縫着する．④結膜が伸展し，弛緩が解除されていることを確認して終了．

術後は，抗菌薬とステロイド薬（0.1%フルオロメトロンあるいは 0.1%リン酸ベタメタゾン）の点眼 1 日 3～4 回を術後 2～3 週間行い，原則として抜糸は行わなかった．

診療録をもとに結膜弛緩症手術症例の術後の自他覚所見の改善度，合併症，再発について retrospective に検討した．また症例を術前の臨床症状別，もしくは CPF 弛緩の有無に基づいて分類し，術後の改善度を比較検討した．CPF には下瞼板枝，円蓋部枝があり，結膜弛緩症は円蓋部枝の弛緩で起こりやすく，ここでいう CPF の弛緩とは円蓋部枝の弛緩である．臨床症状については流涙型，ドライアイ型，炎症型の 3 型に分けた[7]．流涙型は角結膜の生体染色所見や刺激症状はあまりみられず，間欠的流涙を主症状とする型，ドライアイ型は眼乾燥症状や異物感があり，弛緩結膜上方の角膜に生体染色がみられる型，炎症型は刺激症状や充血が強く，結膜炎症所見が主体の型とした．ただし，いずれか 1 つに分類できない症例に関しては，混合型としたものもある．

II 結 果

今回の対象である結膜弛緩症手術症例 21 例 38 眼を臨床所見別に分類した結果を図 2 に示す．流涙型 10 例 16 眼が最も多く，ドライアイ型 4 例 8 眼，炎症型 4 例 8 眼で，1 つに分類できなかった混合型は炎症型＋ドライアイ型 2 例 4 眼，流涙型＋ドライアイ型 1 例 2 眼であった．また，CPF 弛緩の有無では，CPF 弛緩を伴う円蓋部挙上型が 3 例 5 眼，CPF 弛緩を伴わないものが 18 例 33 眼であった．

典型的な症例の術前後の所見を図 3 に示す．弛緩した結膜が下方の涙液メニスカスを占拠しているが，CPF の弛緩は伴っていない例である．術後 1 週目には涙液メニスカスは完全に再建されており，下方球結膜の炎症所見は軽度であることがわかる．図 4 は CPF の弛緩を伴い，結膜嚢が浅くなっている例であるが，術後は結膜嚢が深く保たれていることがわかる．

38 眼のうち，涙液メニスカスを完全に再建できたものは 89.5%（34 眼）であったが，自覚症状の著明な改善を得られ

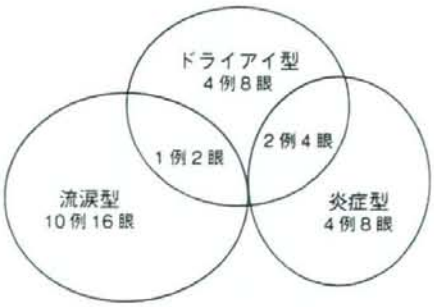


図 2 臨床所見別の症例の内訳

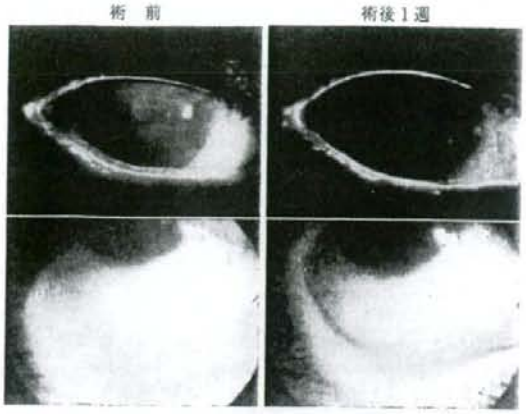


図3 典型的な症例の術前後の所見
弛緩した結膜が下方の涙液メニスカスを占拠しているが，結膜嚢短縮は伴っていない例．術後1週目には涙液メニスカスは完全に再建されており，下方球結膜の炎症所見は軽度である．

たのは63.2%（24眼）にとどまった．

臨床所見別の分類では，涙液メニスカスの再建率は流涙型で93.8%（16眼中15眼），炎症型で100%（8眼中8眼）と良好であったが，ドライアイ型では62.5%（8眼中5眼）と低い結果になった．一方，自覚症状の改善率は流涙型87.5%（16眼中14眼）で高かったが，ドライアイ型では50%（8眼中4眼），炎症型では50%（8眼中4眼）と流涙型以外では低い傾向にあった．

CPF弛緩の有無では，涙液メニスカス再建率はCPF弛緩による円蓋部挙上型では100%（5眼中5眼），CPF弛緩を伴わない型では87.8%（33眼中29眼）であったが，自覚症状の改善率は円蓋部挙上型においては20%（5眼中1眼），CPF弛緩を伴わない型では69.7%（33眼中23眼）となり，他覚的な涙液メニスカス再建率と自覚症状改善率はあまり一致しなかった．

術後の合併症として，異物感と充血・結膜下出血がみられたが，眼球運動障害，感染などの重篤な合併症はみられなかった．異物感は，術後1週間では50%（19眼）にみられたが，術後1カ月では28.9%（11眼）に減少した．術後1カ月を超えて異物感が持続した症例は6眼あったが，2例4眼でマイボーム腺機能不全，1例2眼で眼瞼外反を合併しており，持続する異物感には結膜弛緩症以外の要因が考えられた．充血・結膜下出血は，術後1週間で18.4%（7眼），術後1カ月で7.9%（3眼）の症例で生じたが，これ以上遷延する例はなかった．

術後経過観察期間中，10.5%（4眼）に再発がみられた．その内訳は炎症型2例3眼，流涙型1例1眼であり，再発の時期は術後1年後以降であった．このうち，炎症型1例1眼では再手術を施行し，症状，所見ともに改善している．

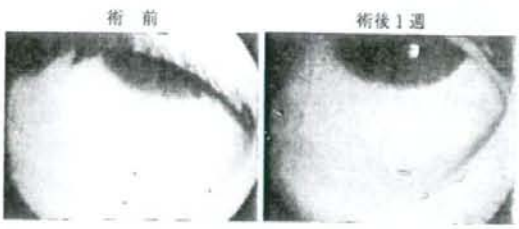


図4 円蓋部挙上型の術前後の所見
術前に比べて，術後は結膜嚢はむしろ深くなっており，円蓋部挙上型にも同じ術式で対応できる．

III 考 按

結膜弛緩症に対して施行した10-0ナイロン糸を用いたanchoring sutureによる結膜縫着術の治療成績について検討した．本術式により89.5%の例で涙液メニスカスを完全に再建できたが，自覚症状の著明な改善を得ることができたのは63.2%であった．他覚的な結膜弛緩の改善率と自覚症状の改善率の間には差があり，手術によって自覚症状の著明な改善を得られなかった症例が1/3以上あったことは，結膜弛緩症以外にマイボーム腺機能不全，眼瞼外反など他の眼表面疾患を合併している症例が含まれていたことが影響していると思われる．当科では手術の適応を点眼治療で症状が改善しない例としているが，愁訴が結膜弛緩症によるものかどうか術前にはさらに慎重な検討を要するものと考えられた．

臨床所見，自覚症状により病型を分類した場合，流涙型では自他覚所見の改善率が87.5%と良好であったが，ドライアイ型，炎症型では自覚症状の改善率がいずれも50%と低い傾向にあった．また，CPFの弛緩を伴う円蓋部挙上型においては，5眼全例で涙液メニスカスを完全に再建することができたが，自覚症状が改善したのは1眼にとどまった．これらの結果は，臨床所見や解剖学的な所見によって，手術の予後をある程度推測できることを示しているのかもしれない．ただし，病型別の奏効率に関しては，今回の症例数が十分でない面があり，今後，症例数を増やして検討する必要があるものと考えられた．

本手術は10～15分程度と短時間で行うことができ，術後の合併症は重篤なものはなかった．また，術後の異物感，充血が軽く，ほとんどの症例で術後1カ月以内に消失することも利点と考えられた．また，新たな円蓋部を作製することで，CPFの弛緩による円蓋部挙上型にも同じ術式で対応できる点で有用と考えられた．ただし，経過観察期間中に10.5%に弛緩症の再発がみられた．結膜切除による結膜弛緩症手術と異なり，球結膜と強膜に癒着が生じる範囲が狭く，結膜嚢に近い部分に限られることが原因と推測される．この

点は，術後の炎症所見が軽いという利点と表裏の関係にあるものと思われるが，再発しにくい術式の改良の余地があるものと考えられた．

本論文の要旨は第31回角膜カンファランスで発表した．

文　献

1) Meller D, Tseng SC : Conjunctivochalasis, literature review and possible pathophysiology. *Surv Ophthalmol* **43** : 225-232, 1998
2) 三戸秀哲，井出　醇：結膜弛緩症を合併した加齢性下眼瞼内反症．眼紀 **52** : 1025-1027, 2001
3) 山崎太三，井出　醇，三戸秀哲ほか：結膜弛緩症．眼科 **47** : 1536-1542, 2005
4) 横井則彦，西井正和：結膜弛緩症，結膜弛緩症関連疾患に対する手術．眼科手術 **18** : 7-14, 2005
5) Meller D, Maskin SL, Pires RT et al : Amniotic membrane transplantation for symptomatic conjunctivochalasis refractory to medical treatments. *Cornea* **19** : 796-803, 2000
6) Otaka I, Kyu N : A new surgical technique for management of conjunctivochalasis. *Am J Ophthalmol* **129** : 385-387, 2000
7) 山田昌和：結膜弛緩症の考え方．東京都眼科医会報 **194** : 2-5, 2006

*　　*　　*

Journal of Medical Case Reports

BioMed Central

Case report

Open Access

Presumed stromal graft rejection after automated lamellar therapeutic keratoplasty: case report

Motoko Kawashima*[1,2], Hiroshi Mochizuki[2], Tetsuya Kawakita[1], Shin Hatoh[2], Jun Shimazaki[1] and Masakazu Yamada[2]

Address: [1]Department of Ophthalmology, Tokyo Dental College, Chiba, Japan and [2]Division for Vision Research, National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo, Japan

Email: Motoko Kawashima* - motokok@tdc.ac.jp; Hiroshi Mochizuki - mochizukih@s08.itscom.net; Tetsuya Kawakita - kawatetsu@gmail.com; Shin Hatoh - hatoushin@kankakuki.go.jp; Jun Shimazaki - juns@eyebank.or.jp; Masakazu Yamada - yamadamasakazu@kankakuki.go.jp

* Corresponding author

Published: 1 April 2007

Journal of Medical Case Reports 2007, 1:10 doi:10.1186/1752-1947-1-10

Received: 6 January 2007
Accepted: 1 April 2007

This article is available from: http://www.jmedicalcasereports.com/content/1/1/10

Abstract

Purpose: To describe the development of presumed immune-mediated stromal rejection after automated lamellar therapeutic keratoplasty (ALTK) and its reversal after initiation of intensive topical corticosteroid therapy.

Methods: Observational case report.

Results: Stromal edema localized in the graft developed 42 days after ALTK for Avellino corneal dystrophy in a 65-year-old man. After one week of intensive topical corticosteroids, complete reversal of graft edema occurred, with full recovery of visual function.

Conclusion: The clinical appearance and response to therapy in this case supported the diagnosis of immune-mediated stromal rejection. Ophthalmologists should be aware that stromal rejection may occur in lamellar corneal grafts.

Background

Lamellar keratoplasty was the first form of corneal transplantation ever attempted, and now has a history of over a century. Occasionally, it is employed in the rehabilitation of thinned corneas or those with anterior opacification[1]. However, the use of lamellar keratoplasty has been limited by difficulties such as irregularity and scarring of tissue interfaces, leading to poor visual outcomes compared with penetrating keratoplasty, as well as technical difficulties and prolonged operating time[1]. The thickness and contour of the transplanted tissue are difficult to control, which causes problems with optical clarity.

Automated lamellar therapeutic keratoplasty (ALTK) is a new approach to lamellar keratoplasty which avoids some of these problems[2]. In ALTK, an automated keratome is used to cut partial-thickness sections through the anterior surfaces of both the donor and host corneas. These sections are very similar to the flaps cut in LASIK surgery, and allow a very precise surface to be obtained. Thus, ALTK offers advantages over traditional lamellar keratoplasty, as it reduces astigmatism, thereby resulting in better potential visual outcomes and shorter operation time.

Lamellar grafting offers several advantages over penetrating keratoplasty, including elimination of allograft rejec-

tion and avoidance of intraocular complications. Although there is still the possibility of rejection at either the donor epithelium or stroma, the avoidance of endothelial rejection is an exceptional advantage. Irreversible loss of vision after lamellar keratoplasty due to presumed stromal rejection has occurred in only 1.4%–1.9% of patients according to previous reports[3,4]. This lower rate of stromal rejection may due to the small number of lamellar keratoplasties performed compared to penetrating keratoplasties, and an increased number of lamellar keratoplasties may, therefore, result in an increased number of stromal rejection. Here, we report a case of presumed immune-mediated stromal rejection after ALTK that was completely reversed with prompt initiation of intensive steroid therapy.

Case presentation

A 65-year-old Japanese man was referred to the National Tokyo Medical Center because of blurred vision in both eyes. The patient was diagnosed with Avellino corneal dystrophy, and had a history of keratectomy in both eyes at the age of 60. Corrected visual acuity was 20/100 in the right eye, and 20/50 in the left eye. Examination by slit-lamp microscopy revealed gray-white granular opacities in the anterior stroma of both eyes, which was compatible with the diagnosis of Avellino corneal dystrophy. The patient's medical history was otherwise unremarkable. His daughter also had Avellino corneal dystrophy.

Additional PTK was ruled out because of insufficient corneal thickness due to previous keratectomy, and ALTK was performed in the right eye to remove anterior stromal deposit in October, 2004. Using the "Moria LSK Evo-II MircoKeratome Evo II Micro Keratome (Moria Japan, Tokyo, Japan), a 9.5-mm-diameter, 200 μm-depth flap was cut out from the recipient cornea. In same way, a 9.5-mm-diameter, 300 μm flap was obtained from a donor cornea maintained in an artificial chamber (Moria Japan). The donor cornea was transported from an eye bank in the United States, and met the criteria of the Eye Bank Association of America for donor quality. Fresh, full-thickness graft material preserved in Optisol GS (Bausch & Lomb, Rochester, NY) for 7 days was used for the lamellar keratoplasty. The lamellar graft was sutured in place with 9 interrupted 10-0 nylon sutures. Topical betamethasone phosphate 0.1% (Shionogi Pharmateutical Co., Osaka, Japan) and levofloxacin 0.5% (Santen Pharmateutical Co., Osaka, Japan) were applied three times daily in the postoperative periods. Visual acuity improved to 20/40 with correction at 4 weeks after the operation.

Forty-two days postoperatively, the patient returned to our clinic with the sensation of a foreign body and blurred vision in the right eye. Slit-lamp examination revealed a diffuse stromal edema limited to the graft (Fig. 1). The posterior half of the corneal stroma, which was the recipient bed, remained clear. There were no epithelial defects, and no keratic precipitates or inflammation were seen in the anterior chamber. Intraocular pressure was 12 mmHg. A diagnosis of presumed immune-mediated stromal rejection was made based on these findings. On an hourly regimen of betamethasone phosphate 0.1%, the stromal edema began to improve immediately, completely clearing within 1 week (Fig. 2). Corrected visual acuity in the right eye improved to 20/25 at 10 days after treatment. Topical corticosteroids were tapered and discontinued over 3 months, and the graft remained clear at the last follow-up.

Discussion

The patient developed stromal edema localized in the graft 42 days after ALTK. Differential diagnoses might have included diffuse lamellar keratitis (DLK) and herpetic keratitis, as well as allograft rejection. DLK is usually a postoperative complication of LASIK in early phase (within 1–6 days after surgery), and is defined as an inflammatory condition in which white blood cells migrate along the stromal interface[5]. The etiology of DLK remains to be clarified, and it is generally thought that the cause of this inflammatory reaction may be multifactorial [6].

In this case, DLK could be excluded due to the lateness of onset (42 days after the operation) and involvement of the entire graft, not just the interface. Herpetic infection

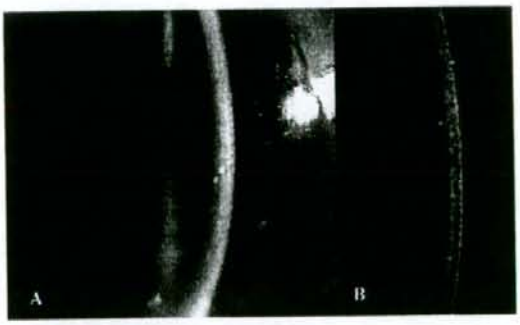


Figure 1
Day 42 after surgery. A. Diffuse edema of lamellar graft was apparent, whereas there were no epithelial defects, keratic precipitates, or inflammation in anterior chamber. Gray-white granular opacities were observed in the graft bed, which were residual deposits of Avellino corneal dystrophy. B. High-magnification slit-lamp photograph demonstrated marked anterior stromal thickening (graft edema). In contrast, posterior half of corneal stroma, which was recipient bed, remained clear.

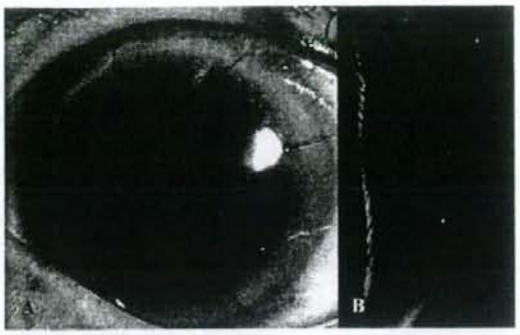


Figure 2
One week after treatment with topical corticosteroids. Corneal stroma cleared completely.

could also be excluded due to the localization of the stromal edema in the graft and negative history of herpetic eye infection. Although stromal edema has been reported to sometimes occur following LASIK, such as in eyes with uveitis and elevated intraocular pressure[7], this possibility was also excluded due to the maintenance of normal range (around 12 mmHg) throughout the follow-up period. The absence of associated ocular abnormalities and the prompt response to intensive corticosteroid therapy indicated a diagnosis of stromal allograft rejection after ALTK. Stromal rejection involves infiltration rather than edema of the stroma[8], and recently Watson et al reported that the stroma became opaque and edematous in 2 stromal rejection cases after deep lamellar keratoplasty[4], which also supported our diagnosis. In our case, one contributing factor to stromal rejection could be the large graft size in ALTK

Three different types of allograft rejection have been identified after penetrating keratoplasty: endothelial rejection, epithelial rejection, and subepithelial infiltrates [9]. Theoretically, lamellar grafts are free from endothelial rejection, but not from other types of rejection. Alldredge and Krachmer[9] reported that frequencies of epithelial rejection and subepithelial infiltrates after penetrating keratoplasty were 10% and 15%, respectively. However, the true frequencies of these two types of rejection are hard to determine because they can easily take place without symptoms between examinations. In our case, the patient developed a diffuse stromal edema localized in the graft, with no epithelial involvement, which ruled out epithelial rejection or subepithelial infiltrates.

Our case appears to resemble the case of stromal rejection after deep lamellar keratoplasty described by Al-Torbak and associates[10]. In their case, diffuse stromal edema of the entire graft developed 16 months after surgery for keratoconus. Although such stromal rejection is not included in reported criteria of allograft rejection after penetrating keratoplasty[9], it might be overshadowed by endothelial rejection in penetrating keratoplasty.

Conclusion

In this case, the clinical appearance and response to therapy supported the diagnosis of immune-mediated stromal rejection. This case suggests that stromal rejection can occur after lamellar keratoplasty and that it usually goes unrecognized. We propose that ophthalmologists should be aware of stromal rejection as a potential complication of lamellar corneal grafts.

Abbreviations

ALTK; automated lamellar therapeutic keratoplasty, PTK; phototherapeutic keratectomy, DLK; diffuse lamellar keratitis, LASIK; Laser in situ keratomileusis.

Authors' contributions

MK drafted the manuscript. TK and JS helped to draft the manuscript. SH and HM participated in the data collection and treat this case. MY performed surgery and treat this case. All authors read and approved the final manuscript.

Acknowledgements

That patient consent was received for this case report to be published.

The author has no proprietary interest in any of the materials described in this manuscript.

References

1. Terry MA: **The evolution of lamellar grafting techniques over twenty-five years.** *Cornea* 2000, **19**:611-6.
2. Jimenez-Alfaro I, Perez-Santonja JJ, Gomez Telleria G, Bueno Palacin JL, Puy P: **Therapeutic lamellar keratoplasty with an automated microkeratome.** *J Cataract Refract Surg* 2001, **27**:1161-5.
3. Saini JS, Jain AK, Sukhija J, Saroha V: **Indications and outcome of optical partial thickness lamellar keratoplasty.** *Cornea* 2003, **22**:111-3.
4. Watson SL, Tuft SJ, Dart JK: **Patterns of rejection after deep lamellar keratoplasty.** *Ophthalmology* 2006, **113**:556-60.
5. Smith RJ, Maloney RK: **Diffuse lamellar keratitis; a new syndrome in lamellar refractive surgery.** *Ophthalmology* 1998, **105**:1721-6.
6. Herrin S: **What causes interface inflammation?** *Rev Ophthalmol* 1998, **59**:71-4. lamellar interface fluid collection after LASIK Am J Ophthalmol. 2005;139:1137-9
7. Lyle WA, Jin GJ, Jin Y: **Interface fluid after laser in situ keratomileusis.** *J Refract Surg* 2003, **19**:455-9.
8. Khodadoust AA, Silverstein AM: **Transplantation and rejection of individual cell layers of the cornea.** *Invest Ophthalmol* 1969, **8**:180-95.
9. Alldredge OC, Krachmer JH: **Clinical types of corneal transplant rejection. Their manifestations, frequency, preoperative correlates, and treatment.** *Arch Ophthalmol* 1981, **99**:599-604.
10. Al-Torbak A, Malak M, Teichmann KD, Wagoner MD: **Presumed stromal graft rejection after deep anterior lamellar keratoplasty.** *Cornea* 2005, **24**:241-3.

Quantitative Evaluation of Tear Meniscus Height From Fluorescein Photographs

Masataka Kawai, MD, Masakazu Yamada, MD,† Motoko Kawashima, MD,* Makoto Inoue, MD,* Eiki Goto, MD,* Yukihiko Mashima, MD,* and Kazuo Tsubota, MD**

Purpose: To describe a method of quantifying the tear meniscus height (TMH) and using these values to diagnose patients with dry eye.

Methods: Thirty-eight eyes of 19 healthy subjects and 14 patients diagnosed with dry eye were studied. Each eye received 2 μL of 1% fluorescein-sodium solution in the conjunctival sac, and digital photographs were taken of the external surface of the eye with a fundus camera. The tear meniscus was extracted from the digitalized image and used to measure the TMH with NIH image software. The correlation between the mean TMH and Schirmer test values or cotton-thread test values was evaluated.

Results: The means of the upper and lower TMH in healthy subjects were 0.22 ± 0.06 and 0.24 ± 0.08 mm, respectively. The comparable values in patients with dry eye were 0.17 ± 0.04 and 0.17 ± 0.07 mm (upper TMS, $P = 0.01$; lower TMH, $P = 0.04$; unpaired t test). A significant correlation was found between the TMH and Schirmer test values ($r = 0.72$, $P = 0.01$) but not with cotton-thread test values.

Conclusions: Fluorescein photographs of the eye can be used to quantify the upper and lower TMH separately and simultaneously without specialized equipment. This technique can be used for the diagnosis of dry eye.

Key Words: dry eye, fluorescein, fundus camera, tear meniscus

(*Cornea* 2007;26:403–406)

An adequate volume of tears is essential to prevent desiccation of the exposed ocular surface. The tear meniscus is a part of the precorneal tear film and results from the reservoir of tears.[1] The clinical importance of measuring the tear meniscus has not been stated clearly,[2,3] although it has been suggested that quantifying the size of the tear meniscus may be useful for the diagnosis of dry eye.[4,5]

The tear meniscus height (TMH) has been measured by slit-lamp examination with a scale attached to the objective lens,[1] a digital photographic system with a slit-lamp equipped with a digital camera,[6] and a meniscometer that measures the radius of curvature of the tear meniscus.[7–9] The measurement of the radius of curvature of the tear meniscus might be a useful method, but the instrument to do this is not available commercially.

We hypothesized that TMH is correlated with the degree of dry eye. To test this hypothesis, we calculated the coefficient of correlation between TMH and other more conventional measures of dry eye.

MATERIALS AND METHODS

Healthy Subjects and Patients With Dry Eye

The upper and lower TMH of 38 eyes of 19 healthy subjects (8 men and 11 women; age range, 18–79 years) with no abnormalities of the cornea, conjunctiva, lacrimal system, or meibomian glands were studied. Fourteen right eyes of 14 patients with dry eye (3 men and 11 women; age range, 28–74 years), who had a Schirmer test value of <5 mm (Schirmer I test with anesthesia) or a value of a cotton-thread wetting test of <10 mm, were compared with the 19 right eyes of healthy subjects. The principles of the World Medical Association Declaration of Helsinki were followed. Each subject received a full explanation of the study and all procedures involved in the study, and they provided written informed consent before enrollment. Approval for this study was granted by the Committee for the Protection of Human Subjects at the Keio University School of Medicine.

Meniscus Photographs and TMH Analyses

A 10 × 2-mm paper strip that had been stained with sodium fluorescein was placed on the inferior eyelid as a calibration marker (Fig. 1A). Then, 2 μL of 1% fluorescein sodium solution was dropped into the lower conjunctival sac with a micropipette. After 3 minutes, the anterior segment of the eye was photographed with a fundus camera (TRC-50LX; Topcon, Tokyo, Japan) equipped with blue light for excitation and a fluorescence filter for detection of the tear meniscus. Only the tear meniscus and paper strip were highlighted under these conditions (Fig. 1B). These images were uploaded to the IMAGENET system (IMAGE NET 2000;

Received for publication July 22, 2005; revision received January 1, 2006; accepted November 11, 2006.

From the *Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan; and the †Division for Vision Research, National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo, Japan.

Supported in part by a grant from Santen Pharmaceutical Co. Ltd., Osaka, Japan.

The authors state that they have no proprietary interest in the products named in this article.

Reprints: Masataka Kawai, Kawai Eye Clinic, 1-1-8 Kugenumatachibana, Fujisawa, Kanagawa 251-0024, Japan (e-mail: eye@fujisawamv.jp).

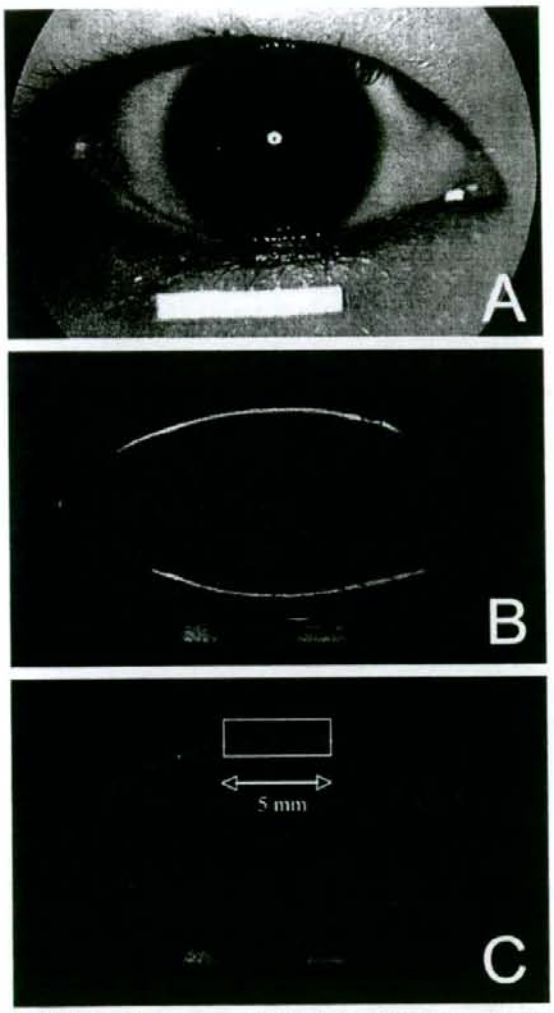


FIGURE 1. Photographs of anterior segment by a fundus camera. A, Under white light illumination with a 10 × 2-mm strip as a calibration scale on the lower lid. B, Photograph with a scale under blue light through a fluorescein filter showing the area of the tear meniscus. C, Area corresponding to tear meniscus is shown in red, and the average height of a selected area of 5 mm width was calculated.

Topcon). The area corresponding to the tear meniscus was outlined (Fig. 1C), and the number of pixels in the selected central 5-mm-wide region was counted to calculate the TMH by NIH image software (NIH, Bethesda, MD). To reduce the bias, 1 masked examiner (MK) performed the whole image analysis. The upper and lower TMH was measured, and the values for healthy subjects were compared with those for patients diagnosed with dry eye. The Pearson correlation coefficient was calculated between mean TMH (upper and lower TMH) and values of the Schirmer test (Schirmer 1 test with anesthesia) or the cotton-thread tests to determine whether they were related in normal subjects and patients with dry eye.

RESULTS

TMH Values in Healthy Subjects

The TMH of the upper tear meniscus (upper TMH) and that of the lower meniscus (lower TMH) was measured on the same image in all subjects. The means of the upper and lower TMH in both eyes of healthy subjects were 0.22 ± 0.06 and 0.24 ± 0.08 mm, respectively. The mean upper TMH in the right eyes was 0.24 ± 0.06 (SD) mm, and the lower TMH was 0.25 ± 0.07 mm (Fig. 2). The comparable values for the left eyes were 0.20 ± 0.04 and 0.23 ± 0.09 mm, respectively. The upper TMH was significantly higher than the lower TMH in each eye (right eye, $P = 0.03$; left eye, $P = 0.02$; paired t test).

TMH Values in Patients With Dry Eye

The mean upper TMH was 0.17 ± 0.04 mm and the mean lower TMH was 0.17 ± 0.07 mm in the patients with dry eye. The difference between the upper and lower TMH was not significant in patients with dry eye ($P = 0.85$, paired t test). However, both of these values were significantly lower than the comparable values in healthy subjects (Fig. 3; upper TMH, $P = 0.01$; lower TMH, $P = 0.04$; unpaired t test).

Correlation Analysis

The coefficient of correlation between mean TMH (upper and lower TMH) and the Schirmer test values in patients with dry eye was significant ($r = 0.72$, $P = 0.01$; Fig. 4), but the correlation between TMH and the cotton-thread test values in dry eye patients was not significant ($r = 0.10$; $P = 0.75$; Fig. 5). In healthy subjects, the correlations of the mean TMH to these 2 values were also not significant.

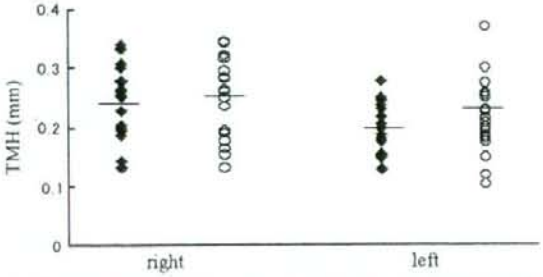


FIGURE 2. Values of TMH in healthy subjects. Closed diamonds are the upper TMH, and open circles are the lower TMH. The mean upper TMH is 0.24 ± 0.06 (SD) mm, and the lower TMH is 0.25 ± 0.07 mm in right eyes of healthy subjects and 0.20 ± 0.04 and 0.23 ± 0.09 mm in left eyes, respectively. These mean TMH values are not significantly different.

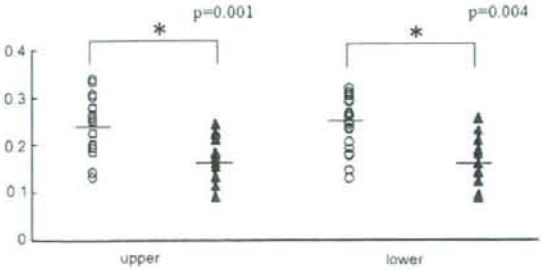


FIGURE 3. Comparison of TMH in healthy subjects and in patients with dry eye. ○, values of TMH in healthy subjects; ▲, TMH in patients with dry eye. The upper and lower TMHs in healthy subjects are significantly higher than those in patients with dry eye.

DISCUSSION

The results of this study showed that the mean upper and lower TMHs in patients with dry eye were significantly smaller than those in healthy subjects, and the TMH values were correlated significantly with the Shirmer test values in patients with dry eye. This simple method is valuable to evaluate dry eye because values of the Schirmer test with anesthesia represent the volume of tear reservoir and basic tear secretion. In addition, the upper and lower TMHs can be measured individually on the same photograph, and all subjects and patients can be measured to allow the quantification of the entire meniscus, not only the lower TMH as in earlier studies.[1–9] Another advantage of this technique is that it requires only a conventional fundus camera to photograph the anterior ocular surface and a personal computer without any specialized equipment.

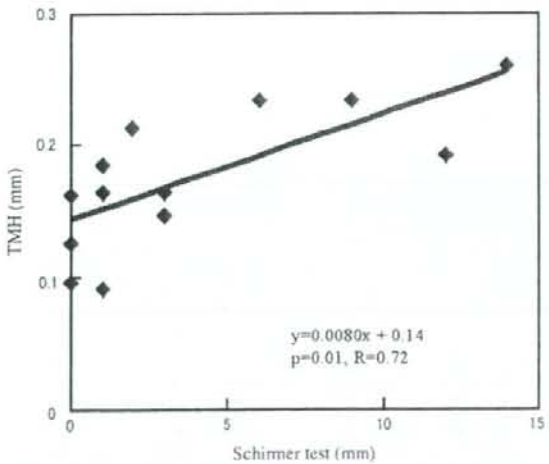


FIGURE 4. Correlation between mean TMH and values of the Shirmer test in patients with dry eye. A significant correlation was observed between mean TMH and values of the Schirmer test in patients with dry eye.

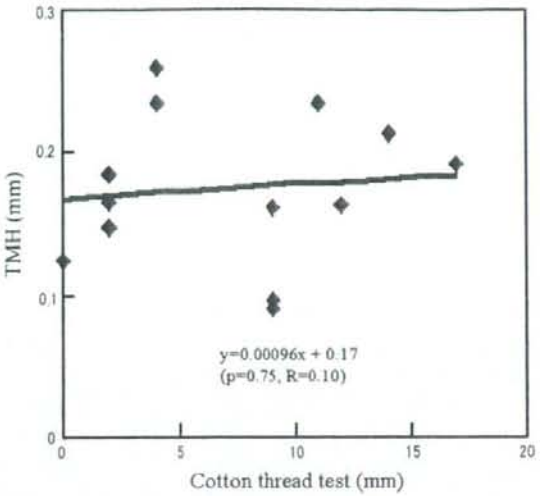


FIGURE 5. Correlation between mean TMH and values of the cotton thread test in patients with dry eye. There was a lower, but not significant, correlation between mean TMH and values of the cotton-thread test in patients with dry eye.

A low supply of tears has been suggested to play a role in certain types of dry eye. For example, patients with superior limbic keratoconjunctivitis (SLK) have been reported to have a low level of tears. The degrees of Rose Bengal and fluorescein staining are reduced, accompanied by an improvement of subjective symptoms after lacrimal punctal occlusion in the upper and lower sides or even after upper lacrimal punctal occlusion without lower occlusion.[10] Thus, it was suggested that SLK might be caused by lack of upper tear meniscus. Our method should be able to quantify the therapeutic values before and after lacrimal punctal occlusion by evaluating the upper or lower TMH separately.

This method also has disadvantages; it requires topical fluorescein solution, which may alter the characteristics and volume of the tear film. However, Oguz et al[9] evaluated the tear meniscus of the lower central lid with a meniscometer with and without fluorescein, and they concluded that there was a minimal effect of the small amount of fluorescein. Another disadvantage is that the TMH values cannot be obtained immediately but require offline analysis with a personal computer.

This technique probably will be valuable in the diagnosis of dry eye and determining the effectiveness of treatment of dry eye. In addition, this technique can be used to define the role played by the upper and lower TMHs in patients with dry eye.

REFERENCES

1. Mishima S, Gasset A, Klyce SD Jr, et al. Determination of tear volume and tear flow. *Invest Ophthalmol.* 1966;5:264–276.
2. Doughty MJ, Laiquzzaman M, Button NF. Video-assessment of tear meniscus height in elderly Caucasians and its relationship to the exposed ocular surface. *Curr Eye Res.* 2001;22:420–426.

3. Nichols KK, Nichols JJ, Mitchell G. The relation between tear film tests in patients with dry eye disease. *Ophthalmic Physiol Opt*. 2003;23:553–560.
4. Mainstone JC, Bruce AS, Golding TR. Tear meniscus measurement in the diagnosis of the dry eye. *Curr Eye Res*. 1996;15:653–661.
5. Golding TR, Bruuce AS, Mainstone JC. Relationship between tear-meniscus parameters and tear film breakup. *Cornea*. 1997;16:649–661.
6. Maruyama K, Yokoi N, Nishii M, et al. Evaluation of canalization of the canaliculus with digital photo system for treating dry eye. *Nippon Ganka Gakkai Zasshi*. 2003;107:526–529.
7. Horimoto K, Hamano T. Differences in tear meniscus height with age. *Folia Ophthalmol Jpn*. 1995;46:687–689.
8. Yokoi N, Bron A, Tiffany J, et al. Reflective meniscometry: a non-invasive method to measure tear meniscus curvature. *Br J Ophthalmol*. 1999;83:92–97.
9. Oguz H, Yokoi N, Kinoshita S. The height and radius of the tear meniscus and methods for examining these parameters. *Cornea*. 2000;19:497–500.
10. Yang HY, Fujishima H, Toda I, et al. Lacrimal punctual occlusion for the treatment of superior limbic keratoconjunctivitis. *Am J Ophthalmol*. 1997;124:80–87.

New Grading System for the Evaluation of Chronic Ocular Manifestations in Patients with Stevens–Johnson Syndrome

Chie Sotozono, MD, PhD,[1] Leonard P. K. Ang, FRCS, MRCOphth,[1] Noriko Koizumi, MD, PhD,[1] Hisayo Higashihara, MD,[1] Mayumi Ueta, MD, PhD,[1] Tsutomu Inatomi, MD, PhD,[1] Norihiko Yokoi, MD, PhD,[1] Minako Kaido, MD,[2] Murat Dogru, MD, PhD,[2] Jun Shimazaki, MD, PhD,[2,3] Kazuo Tsubota, MD, PhD,[2] Masakazu Yamada, MD, PhD,[4] Shigeru Kinoshita, MD, PhD[1]

Purpose: To evaluate and grade the extent and severity of chronic ocular manifestations in Stevens–Johnson syndrome (SJS).

Design: Prospective multicenter case series.

Participants: We enrolled 73 patients (138 eyes) with SJS seen between April 2003 and March 2005 at 3 tertiary referral centers.

Methods: Patients with a confirmed history of SJS and chronic ocular complications that persisted for at least 1 year from the onset of SJS were included. Their detailed medical history and ophthalmic examination results were recorded on an itemized data collection form. Complications were categorized as corneal, conjunctival, and eyelid complications, and 13 components were evaluated and graded on a scale from 0 to 3 according to their severity.

Main Outcome Measures: These were broadly classified as corneal (superficial punctate keratopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, keratinization), conjunctival (hyperemia, symblepharon formation), and eyelid (trichiasis, mucocutaneous junction involvement, meibomian gland involvement, punctal damage) complications.

Results: The most severely affected complication components were loss of the palisades of Vogt (114 eyes; 82.6%) and meibomian gland involvement (102 eyes; 73.9%). Visual acuity in 74 of the 138 eyes (53.6%) was worse than 20/200. The severity of corneal, conjunctival, and eyelid complications was significantly correlated with visual loss. All 13 complications were correlated significantly with logarithm of the minimum angle of resolution (logMAR) visual acuity; the correlation coefficient (R) ranged from 0.359 to 0.810 ($P<0.0001$); for corneal epithelial defects, R was 0.169 ($P = 0.0473$). Eyes with a higher total score for the 3 complication categories had poorer vision ($R = 0.806$; $P<0.0001$). Multivariate regression analysis showed that corneal neovascularization, opacification, keratinization, and cataracts significantly affected logMAR visual acuity ($P<0.0001$, $P<0.0001$, $P = 0.0142$, $P = 0.0375$, respectively).

Conclusions: The authors describe a new method for grading the extent and severity of ocular involvement in patients with SJS and demonstrate that the severity of ocular involvement is correlated significantly with the final visual outcome. This new grading system provides a more objective method for evaluating SJS patients and may be adapted for use in other cicatricial ocular surface diseases. *Ophthalmology 2007;114:1294–1302* © *2007 by the American Academy of Ophthalmology.*

Stevens–Johnson syndrome (SJS) is an acute, self-limiting disease of the skin and mucous membranes that predisposes patients to life-threatening complications such as sepsis, respiratory dysfunction, and multiorgan failure. In the acute stage, more than 50% of patients experience ocular complications ranging from minimal (e.g., mild conjunctival hyperemia) to very severe (e.g., corneal melting and perforation).[1–4] Inflammation and epithelial erosion of the ocular surface often persist beyond the acute stage and the resolu-

Originally received: May 25, 2006.
Accepted: October 26, 2006. Manuscript no. 2006-570.

[1] Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

[2] Department of Ophthalmology, School of Medicine, Keio University, Tokyo, Japan.

[3] Department of Ophthalmology, Tokyo Dental College, Chiba, Japan.

[4] National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo, Japan.

Supported in part by grants-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan, and grants from the Ministry of Health, Labor, and Welfare, Tokyo, Japan.

The authors have no financial interest in this work.

Correspondence to Chie Sotozono, MD, PhD, Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-0841 Japan. E-mail: csotozon@ophth.kpu-m.ac.jp.

ISSN 0161-6420/07/$–see front matter
doi:10.1016/j.ophtha.2006.10.029

tion of skin eruptions, leading to ocular complications and scarring in the chronic stage. Severe ocular surface disease arising from SJS encompasses a spectrum of ocular manifestations and complications that often is associated with significant visual morbidity. Visual impairment and ocular discomfort continue throughout life and patients usually require long-term medication for disease control.

Over the past 40 years, it has been widely accepted that erythema multiforme (EM), SJS, and toxic epidermal necrolysis (TEN) are part of a single EM spectrum.[5–7] However, because no clear diagnostic criteria have been established, reaching a definitive diagnosis can be difficult. Roujeau,[6] who performed a retrospective analysis of the type and distribution of skin lesions and the extent of epidermal detachment, concluded that EM major (EMM) and SJS were 2 separate clinical entities that differed with respect to histopathologic changes and cause. A large international case-control study, called the Severe Cutaneous Adverse Reaction study, prospectively evaluated the validity of this clinical distinction; its results strongly support the hypothesis that EMM is different from SJS and TEN, and that SJS and TEN are severity variants of a single entity.[5] The classification was based on the clinical appearance and pathologic results of skin lesions present in the acute stage. However, patients often seek treatment from ophthalmologists in the late stage of the disease with chronic cicatricial complications, after resolution of the dermatologic changes, and it can be difficult to elicit the original clinical manifestations used to distinguish between EMM and SJS or TEN from patients seen many years after disease onset. Therefore, from the ophthalmologist's perspective, ocular surface diseases arising from EM, SJS, or TEN often are regarded collectively as SJS.

Corneal transplantation in SJS patients with severe ocular surface disease is associated with a poor prognosis. Persistent epithelial defects occurring after penetrating or lamellar keratoplasty often progress to corneal melting and perforation. Transplanted limbal stem cells or keratoepithelioplasty in these chronically inflamed eyes often elicit graft rejection and loss of donor epithelial cells, resulting in progressive conjunctivalization, scarring, and visual loss.[8,9] Over the past decade, new ocular surface reconstructive procedures such as amniotic membrane and cultivated epithelial transplantation have yielded promising results for the treatment of SJS.[10,11] However, despite its potentially devastating nature and the increasing indications for ocular reconstructive surgery, there is currently no standardized method for evaluating the spectrum of ocular manifestations and the severity of ocular complications in this blinding disease.

The aims of this study were to elucidate the profile of chronic ocular manifestations in SJS patients and to develop an objective method for grading the extent and severity of ocular complications in patients with cicatricial ocular surface diseases. Three large tertiary referral ophthalmic centers participated in this multicenter study; to our knowledge, it represents the largest series of SJS patients with ophthalmic complications studied to date. Because it provides a common platform for the discussion and management of these patients, this study has important clinical implications for the diagnosis, treatment, and the prediction of visual outcomes in patients with SJS.

Patients and Methods

Patients

The 3 ophthalmic centers that participated in this multicenter study are Kyoto Prefectural University of Medicine, Keio University, and National Tokyo Medical Center. All patients with chronic ocular complications from SJS who were referred to these centers between April 2003 and March 2005 were evaluated prospectively in this study. Patients with a confirmed history of SJS and chronic ocular complications that persisted for at least 1 year from the onset of SJS were included. The diagnosis of SJS was based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least 2 mucosal sites including the ocular surface. Eyes with a past history of ocular surface surgery were excluded from this study. The study was approved by the ethics committee and institutional review boards of each institution; the guidelines of the Declaration of Helsinki in Biomedical Research Involving Human Subjects were followed, and written informed consent was obtained from each patient.

The symptomatology, physical findings, detailed ophthalmic examination results, and ocular complications were recorded on an itemized data collection form. The detailed ophthalmic examination included an assessment of visual acuity, tonometry, slit-lamp examination, fluorescein staining, and anterior segment photography. A careful drug history also was obtained by the attending physician. A drug was considered a possible etiologic agent if it had been taken shortly before the onset of symptoms, that is, within 2 weeks of disease onset. If the reaction showed signs of regression during the continued administration of the drug, a causal relationship was considered unlikely.

Classification and Grading of Ocular Involvement

We considered 13 components of 3 categories of ocular complications to be important in the assessment of the 138 eyes; each component was graded on a scale from 0 to 3, depending on the severity of involvement. The complications were classified broadly as corneal complications, comprised of superficial punctate keratopathy (SPK), epithelial defect, loss of the palisades of Vogt (POV), conjunctivalization, neovascularization, opacification, and keratinization components; conjunctival complications with hyperemia and symblepharon formation as the components; and eyelid complications consisting of trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage as the evaluated components. The following classification and grading systems were used to evaluate the nature of the ocular complications in these patients.

Corneal Complications

Severity of Superficial Punctate Keratopathy. We used fluorescein staining and a simplified method of Miyata et al[12] to grade SPK based on the area and density of the lesions. The area was graded as A0 when there was no punctate staining and as A1, A2, or A3 when the area occupied less than one third, one third to two thirds, or more than two thirds of the cornea, respectively. Density was graded as D0 when there was no punctate staining and as D1,