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A New Potential Cause in the Development of Toxic Anterior Segment Syndrome: Fibrin Glue

Toksik Ön Segment Sendromu için Yeni Bir Etken: Fibrin Yapıştırıcı

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Summary

Objectives: To present a potential cause for toxic anterior segment syndrome (TASS).

Materials and Methods: We report 4 cases of TASS that occurred following uneventful phacoemulsification and intraocular lens implantation.

Results: The 4 cases were the first consecutive 2 cases of 2 different surgery days, 5 months apart. The most prominent sign of TASS was limbus-to-limbus corneal edema. Pain and/or intraocular pressure rise were also common. All surgical and presurgical procedures were checked after the first outbreak, whereas the second outbreak required further investigation. Fibrin glue remnants from preceding pterygium surgery with conjunctival autografting were found to be the potential cause. Despite intensive corticosteroid therapy, corneal edema did not resolve in 2 patients who underwent keratoplasty.

Conclusion: TASS is a sight-threatening condition which requires thorough investigation for prevention of new cases. All steps must be carefully revised. (Turk J Ophthalmol 2014; 44: 280-3)

Key Words: Toxic anterior segment syndrome, fibrin glue, corneal edema, corticosteroid

Özet

Amaç: Toksik ön segment sendromuna (TÖSS) yol açan olası bir etkeni sunmak.

Gereç ve Yöntem: Komplikasyonsuz fakoemülsifikasyon ve göz içi lensi yerleştirilmesi sonrasında TÖSS gelişen 4 olgu sunulmaktadır.

Bulgular: Olgular, 5 ay ara ile iki ayrı ameliyat gününün ilk iki olgusu idi. TÖSS'nin en belirgin bulgusu limbustan limbusa uzanan kornea ödemiydi. Ağrı ve/veya göz içi basınç artışı da diğer sık bulgulardı. İlk olaydan sonra tüm cerrahi ve cerrahi öncesi basamaklar gözden geçirildi; ikinci olaydan sonra daha detaylı araştırma gerekti. Önceki ameliyat gününün son vakası olan otogreftli piterjiyum cerrahisinden arta kalan fibrin yapıştırıcı artıklarının sorumlu etken olduğu bulundu. Yoğun kortikosteroid tedavisine rağmen 2 hastada kornea ödemi düzelmedi ve hastalara keratoplasti yapıldı.

Sonuç: TÖSS görmeyi tehdit eden bir durumdur ve yeni olguların önlenebilmesi için etkene yönelik yoğun araştırma gerektirir. Tüm basamaklar dikkatlice gözden geçirilmelidir. (Turk J Ophthalmol 2014; 44: 280-3)

Anahtar Kelimeler: Toksik ön segment sendromu, fibrin yapıştırıcı, kornea ödemi, kortikosteroid

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Introduction

Cataract surgery has improved tremendously over the last couple decades. However, postoperative inflammation, even minor, remains to be a problem for visual recovery. Toxic anterior segment syndrome (TASS) was first described by Monson and co-workers[1] in 1992. This syndrome clinically presents with blurred vision, red eye, and occasional pain. Examination reveals limbus-to-limbus corneal edema, flare, fibrin deposits, and an unresponsive and irregular pupil. Symptoms particularly occur within the first 24 hours of surgery and progress to severe sight-threatening complications such as permanent corneal edema, secondary glaucoma, and chronic macular edema.[2-4] Several potential causes have been proposed to be responsible for the etiology of TASS: preservatives used in topical medication, residual denatured ophthalmic viscosurgical devices (OVD), remnants of sterilizing detergents, endotoxin-contaminated balanced salt solution, talc from surgical gloves, and antibiotic or steroid ointments used to patch the operated eye.[2,5-8]

Literature search reveals that TASS tends to occur as outbreaks.[3,7] The condition may happen in two or more consecutive patients operated on the same day. In case of a TASS outbreak, all potential causes must be questioned and eliminated.

Materials and Methods

This is a retrospective case series of 4 patients who developed TASS. All patients were operated by the same surgeon (CK) using the same routine phacoemulsification and intraocular lens (IOL) implantation technique for age-related cataract. The first 2 patients were the initial consecutive cases of the day, and the second outbreak also followed the same pattern 5 months later.

The surgical technique was the same in all patients. Routine phacoemulsification and IOL implantation through 3.2 mm clear corneal incision was performed. Foldable hydrophilic acrylic posterior chamber IOL was inserted into the capsular bag, and the OVD was removed meticulously as described previously by Zetterström et al.[9]. The whole procedure was conducted with sterile balanced salt solution (BSS plus, Alcon Lab, Tx, USA) as irrigation solution, and no other chemicals like antibiotics or epinephrine were added. All eyes were patched at the end of the surgery without using any antibiotic or steroid ointment.

Each surgery reported in this study was completed free of complications. All of the four patients were discharged an hour after the completion of the surgery as usual, disclosing no problems.

Case Report

Case 1

This 53-year-old female patient suffered from blurred vision and pain in her operated left eye at postoperative first day. Biomicroscopic examination revealed limbus-to-limbus corneal edema, which made the anterior chamber details hard to assess. The intraocular pressure (IOP) was measured to be 30 mmHg with applanation tonometer. Prednisolone acetate drops q1hr, ofloxacin drops 5 times daily, NaCl 5% drops TID, and acetazolamide TID per os were prescribed. The clinical presentation was unchanged the next day. For the following three days, subconjunctival injection of dexamethasone (0.2 mL, 4 mg/mL) was administered. However, there was minimal improvement in corneal edema, and band-like fibrin formations became evident in the anterior chamber, along with a mid-dilated, unresponsive pupil. The IOP was measured as 12 mmHg, and the oral acetazolamide therapy was discontinued. Despite intensive anti-inflammatory therapy, corneal edema did not resolve and the patient required penetrating keratoplasty 5 months after the cataract surgery. The patient's visual acuity was 0.5 at the last examination with moderate complaint of glare due to fixed mid-dilated pupil.

Case 2

The second patient was a 66-year-old man, who again presented with limbus-to-limbus corneal edema on the first day after surgery in his operated left eye. He was the second patient who was operated on the same day after Case 1. The patient reported pain that started 12 hours after surgery. The conjunctiva was hyperemic, and the pupil was dilated with no response to light. The IOP of the operated eye was unelevated. The patient was immediately started on prednisolone acetate eye drops q1hr, ofloxacin eye drops q3hrs, and NaCl 5% drops TID. The next day, despite the persistence of corneal edema, the patient reported no pain. Despite subconjunctival injection of dexamethasone (0.2 mL, 4 mg/mL) for consecutive 5 days, corneal edema did not resolve. The patient undergone penetrating keratoplasty after 2 months, and his visual acuity increased to 0.6.

Case 3

This patient was a 63-year-old woman. The patient complained of postoperative pain that started 8 hours after surgery. Anterior segment examination at that time revealed limbus-to-limbus corneal edema, dilated pupil, and a red eye without any significant chemosis. The IOP was measured to be 42 mmHg with applanation tonometer. The IOP was immediately lowered by anterior chamber decompression and oral acetazolamide 3x1 were given. Additionally, prednisolone acetate drops q1hr was prescribed, and subconjunctival dexamethasone (0.2 mL, 4 mg/mL) was injected daily for 3 consecutive days. Having the diagnosis of TASS, an additional subconjunctival triamcinolone (0.2 mL, 40 mg/mL) was administered into the lower conjunctival fornix. The corneal edema showed minimal clearance, however, the IOP was in normal range during the first postoperative week. Topical steroid treatment was maintained for another 3 weeks with gradual improvement in corneal edema that totally has cleared at the 4th postoperative week visit. Although the pupil was responding sluggish to light stimulus, the patient's visual acuity was 20/20 without any complaint at 3rd month follow-up.

Case 4

Our last patient was a 61-year-old male, who again showed up with limbus-to-limbus corneal edema on the first postoperative day. He did not suffer from any pain, however, the pupil was dilated and unresponsive to light. The IOP in the operated eye

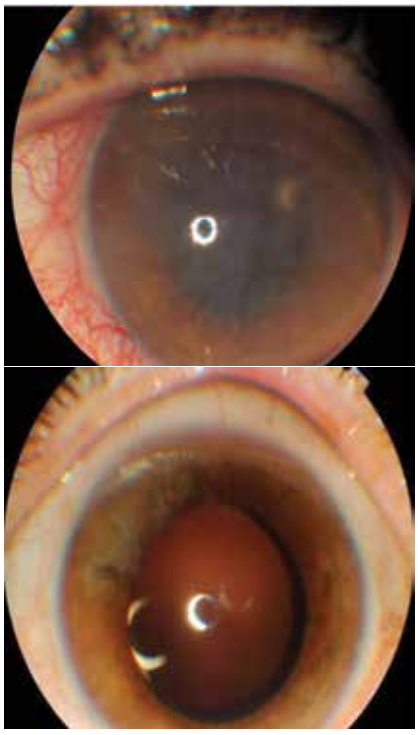

Figure 1. Anterior segment photograph of a patient who revealed limbus-to-limbus corneal edema which made anterior chamber details hard to assess, and an unresponsive mid-dilated pupil on the first postoperative day (upper). The photograph of the same patient after intensive topical and subconjunctival steroid therapy showed a clear cornea at postoperative 2nd month follow-up (lower). Note the pupillary sphincter sclerosis between 10 and 12 clock meridians.

was measured to be 30 mmHg using applanation tonometer. The same treatment as in Case 3 was started which consists of subconjunctival dexamethasone for 3 consecutive days followed by subconjunctival triamcinolone (0.2 mL, 40 mg/mL) injection. Topical prednisolone acetate q1hr was started immediately after the diagnosis of TASS was established as well as systemic acetazolamide given BID. The corneal edema persisted for 2 weeks on this regimen, and after that, the patient showed significant improvement. At his last examination on postoperative 2th month, he had a clear cornea and a visual acuity of 20/25. However, the patient showed pupillary sphincter sclerosis (Figure 1) and he had to use topical antiglaucomatous agent, dorzolamide/timolol combination (BID), to control the IOP.

Discussion

Prolonged inflammation and complications leading to permanent visual loss has caused TASS to become a major concern for cataract surgeons. TASS is an unpleasant complication of cataract surgery usually with good prognosis, as in two of our cases (cases 3 and 4). However, it may rarely present as severe endothelial toxicity which may result in devastating complications.[10] Ünal and co-workers[6] reported 5 of 6 TASS patients undergoing penetrating keratoplasty. Our cases 1 and 2 were such cases that required PK. In addition, refractory glaucoma may require filtrating surgery.[6] Glaucoma was controlled with medication in all our cases including the severe ones, and no case required glaucoma surgery. There is no exact data on the incidence of TASS.[5] Choi and Shyn[3] reported a rate of 1.87% with little variance among 5 surgeons, although they did not report any statistical analysis for the surgeon preference.

Diagnosis of TASS may be challenging since it is rare and the clinical picture may be confusing for the inexperienced eye. An important key point in diagnosis is to differentiate TASS from endophthalmitis. The clinical presentation of TASS occurs particularly within the first 24 hours of surgery, whereas endophthalmitis develops 4-7 days following surgery. Eye redness and blurry vision are the common symptoms for both entities. Pain may not always accompany TASS, while it is common in endophthalmitis. Fibrin formation and hypopyon are frequently present in both conditions, thus they are not useful signs in delineating the two conditions. Chemosis and eyelid swelling are generally present in endophthalmitis as indicators of infection, whereas these signs do not occur in TASS. The most common finding of TASS is limbus-to-limbus corneal edema.[2] Moreover, TASS only involves the anterior segment and Gram staining and cultures are always negative. Response to steroids is another differentiating factor of endophthalmitis and TASS; as this is only present in the latter.[2-4] The most prominent clinical finding in our cases was extensive corneal edema in all patients. Pain and secondary glaucoma were the next common features, as both were present in 75% of cases. Considering the clinical presentation, we could exclude endopthalmitis, so we did not need to take any cultures or to analyze the anterior chamber fluid.

Avoiding TASS depends on familiarity with the condition. Hence, in case of an outbreak, the cause must be identified. Preservatives, detergents, denatured OVDs, incorrect chemical composition or pH, bacterial endotoxins, sterilizing agents, ophthalmic ointments have all been reported as responsible factors for the development of TASS.[2,10] A multicenter report has declared intrinsic endotoxin contamination of a particular balanced salt solution product to be the source of an outbreak of TASS.[5] Glutaraldehyde and EO gas sterilization were two other etiologic agents reported.[3,6] The first two TASS cases reported in this study has alerted the authors to identify an underlying cause. The operating team was well-trained and had significant experience in phacoemulsification surgery for many years without a single TASS case. All the phacoemulsification surgeries have been conducted with the same brand of OVDs, disposable surgical knives, operating solutions and IOLs for several years, and no ointment was ever used intra- or post-operatively. An interesting fact was the absence of a single anterior segment inflammation sign in the rest of the cases operated on that same day.

The next 2 TASS cases occurred 5 months after the initial outbreak. The patients again were the first 2 cases operated on the same day, and similarly, the remaining cases of the session showed no signs of inflammation. Further research was conducted to identify the cause of these 2 outbreaks. A careful observation revealed the fact that all the cases preceding the surgeries complicated with TASS without exception had undergone pterygium surgeries with autografts involving the use

of fibrin glue (Tisseel VH, Baxter, USA). Tisseel, composed of purified fibrinogen and human thrombin, has gained popularity recently in pterygium surgery with advanced patient comfort and lack of suture-related complications.[11,12] We had started to use the glue in pterygium surgeries shortly before the TASS outbreak. Although it has a special designed application device (Duploject), we prefer to use separating cannulas to apply each component which allow us to administer adequate amount of glue to the recipient bed and conjunctival graft; we believe that the adhesive is more properly applied over the surface with these cannulas. After further investigation, we found out that the operation nurse did not dispose the irrigating cannulas and she sent them to sterilization unit. She had only flushed the cannulas with BSS which may have not cleaned the remnants of fibrin glue components thrombin and fibrinogen. In the light of these findings, we hypothesize that the retained tissue adhesive in the cannulas were denatured during sterilization and were introduced into the anterior chamber during the next surgery day causing TASS. Chen and co-workers[13] reported minimal cytotoxicity of fibrin glue in cultured bovine corneal cells. In a recent study, intracameral injection of fibrin glue showed no toxicity or structural damage to the corneal endothelium in rabbits.[14] Por and co-workers reported the use of intracameral fibrin tissue sealant in tectonic lamellar keratoplasty. The authors noticed no signs of endothelial cell damage or anterior chamber inflammation, although they proposed that it would not be surprising.[15] However, we believe that not the glue itself but the denatured remnants might act adversely and could be responsible for the TASS we observed in our cases. The amount of the retaining tissue adhesive must have been sufficient enough to contaminate two cases in a row, and with repeating sterilization procedures, the material was probably washed out, as the third and following cases of the sessions remained TASS-free.

It is well-known that corneal endothelial cells have limited reproduction rate and cellular density goes down every year with increasing age. Moreover, endothelial cells are particularly vulnerable to toxic substances, in which case, endothelial cellular damage might lead to decompensation and persistent corneal edema.[16,17] There is extensive insult to the corneal endothelial cells in cases of TASS. Rate of penetrating keratoplasty in TASS was reported as 33.3% and 83.3% in 2 previous studies.[3,6] This rate was 50% in our study. To our opinion, the difference in the reported keratoplasty rates implies to the clinical variability of TASS. Moreover, corneal edema completely healed with treatment in the remaining 50% of our cases and did not require corneal transplantation. Therefore, we believe that aggressive steroid therapy, including immediate and repeating subconjunctival injections of short-acting agents such as dexamethasone which should be followed by a long-acting triamcinolone injection, is mandatory in the treatment of TASS. Although 2 patients presented with elevated IOP levels, none of our cases required glaucoma surgery.

To the best of our literature search, this is the first report on tissue adhesive and TASS relationship. We also believe that our 4 cases of TASS will remind and educate the reader of the importance in urgent analysis of the condition by careful work-up of key symptoms and the need for immediate proper treatment to avoid devastating complications. Prevention of TASS is the key for a safe surgery, however when it happens, the surgeon should be equipped with the knowledge to identify the causing factor to avoid outbreaks. From our experience with the 4 cases, we would suggest the use of disposable surgical instruments instead of the reusable ones as much as possible for the prevention of TASS. In case of an outbreak, all preoperative, operative and postoperative steps should be revised and the routine behaviors of the staff should be questioned. The nurses and technicians should be educated and reminded of the possible causes periodically, even if no TASS case occurs.[18] In the unlikely event that TASS occurs after all the preventive measures taken, our experience with these 4 cases implied that the most important prognostic steps in the treatment of the condition include early diagnosis and the use of repeating subconjunctival steroid injections as soon as possible.

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