



Brief Report

Late-onset bleb-associated endophthalmitis and continuous positive airway pressure

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ARTICLE INFO

Keywords:

Endophthalmitis
Bleb
Mitomycin C
Express trabeculectomy
Continuous positive airway pressure
Streptococcus mitis

ABSTRACT

Purpose: To raise awareness of a possible association between continuous positive airway pressure (CPAP) devices and postoperative bleb-related infection.

Observations: A 57-year old patient on CPAP presented with unilateral bleb-associated endophthalmitis 32 months after routine ExPress Trabeculectomy with mitomycin C. The offending organism, *Streptococcus mitis*, is a nonmotile and generally non-virulent pathogen which predominates in the normal human respiratory flora.

Conclusions and importance: This conceptual report underscores a potential relationship between CPAP use and bleb-associated endophthalmitis. Streptococcal species are the most commonly reported causative organisms in bleb-associated endophthalmitis, and *S. mitis* is of particular concern as the most abundant microbe among all human oral flora. A logical risk factor for infection, the CPAP device may inadvertently deliver such organisms to the vulnerable conjunctival filtering bleb.

1. Introduction

Trabeculectomy has been the time-tested gold standard surgical procedure to reduce intraocular pressure (IOP) in the eye(s) of patients with high-risk glaucoma not controlled by medications and laser^{1–3}. Trabeculectomy is a type of glaucoma filtration surgery to drain aqueous from the anterior chamber of the eye into a subconjunctival pocket created during surgery known as a filtering bleb. The bleb acts as a reservoir for aqueous to be shunted to prevent ocular hypertension and progressive damage to the optic nerve. Mitomycin C (MMC) is a cytotoxic antifibrotic agent delivered intraoperatively to the subconjunctival space in glaucoma filtration surgery to avoid or reduce scar tissue formation within the bleb and to prevent bleb compromise or failure⁴. The conjunctival thinning effects of intraoperative anti-fibrotic agents such as MMC or 5-fluorouracil persist for years and increase the risk of postoperative bleb-related infection^{5,6}. The average onset of bleb-related infection is 3.1 years after trabeculectomy⁷ and cases of late-onset endophthalmitis have been reported 1 month to 60 years after trabeculectomy.^{8,9}

Streptococcus mitis is a Gram-positive species of viridans-group streptococci (VGS) which asymptotically dominate the normal microbiological flora within the mouth, respiratory tract, and oropharynx of healthy humans¹⁰. The *S. mitis* bacterium is a nonmotile facultative anaerobe which grows best in environments between 20 and 45 degree

Celsius. *S. mitis* has generally low pathogenicity but is associated with infective endocarditis¹¹ and particularly guarded clinical outcomes in endophthalmitis compared to other organisms, including vision loss or globe loss^{12,13}. Without considering CPAP use, streptococcal species such as *S. mitis* have been validated as the most commonly-reported causative organisms in delayed-onset bleb-related endophthalmitis^{14–16}. In this report, *S. mitis* is of particular concern as the source of infection in bleb-associated endophthalmitis given it is the most abundant microbe among all human intraoral flora.^{17,18}

Continuous positive airway pressure (CPAP) devices are an effective first-line therapy to treat obstructive sleep apnea (OSA) by delivering a steady stream of air through tubing and a mask to prevent airway collapse during sleep. Obstructive sleep apnea has a reported prevalence of 9–38% and is more common in men, obese persons, and the aging population.

The authors present the possibility that a CPAP device may inadvertently spread oral bacteria to the vulnerably thinned conjunctival bleb, increasing the risk of bleb-related endophthalmitis. This notion is an especially important consideration as the patient's fellow eye also has a thin conjunctival bleb. To date, no cases of bleb-associated endophthalmitis have been linked to a CPAP machine.

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Received 12 June 2017; Received in revised form 4 February 2018; Accepted 7 February 2018

Available online 08 February 2018

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2. Case report

2.1. Case presentation

A 57-year-old man complained of pain in the left eye that began two days prior to clinical presentation at a Minneapolis eye clinic. Visual acuity remained stable until the morning of presentation when his ocular pain increased and vision quickly deteriorated. The patient rated his ocular pain a 9 out of 10 and complained of a headache. Except for OSA, the patient reported no active or chronic medical conditions and was not using any systemic medications, supplements, or topical eye drops in the affected eye. He was using Durezol twice a day in the fellow eye.

On exam, corrected visual acuity was 20/25 in the right eye and light perception only in the left eye. Goldmann tonometry revealed right- and left-eye IOP of 22 and 54 mmHg, respectively. External examination of the left eye revealed a minimally reactive pupil, severe conjunctival injection, and an opaque Seidel-negative bleb. Slit lamp biomicroscopy showed mild corneal edema with keratic precipitates, a severe anterior chamber cellular reaction, and a fibrinous pupillary membrane. View to the posterior segment was limited with only a red reflex visible.

At a routine visit seven weeks before the onset of endophthalmitis, the patient was phakic and his corrected visual acuity in the affected eye tested 20/25. IOP in the affected eye was 11 mmHg, and the Seidel-negative bleb was lightly vascularized and nicely elevated.

The patient's ocular history includes two previous selective laser trabeculoplasty procedures in 2011 and 2005 on both eyes. Due to uncontrolled glaucoma, he underwent routine uncomplicated ExPress trabeculectomy in the affected eye in 2013 and the right eye in 2016. During each trabeculectomy procedure, 0.2 mL of a 50:50 mixture of lidocaine and 0.4 mg/mL MMC was injected into the superior subconjunctival space. The patient underwent a suture lysis procedure on the right eye three months prior to presentation.

The patient first experienced sleep difficulty in the 1980s and underwent uvulopalatopharyngoplasty in 1990 which did not resolve his symptoms. In 2010 he experienced a motor vehicle collision related to drowsiness and subsequently sought a sleep consult on suspicion of OSA. Polysomnography confirmed moderate OSA and the patient was recommended to begin using CPAP set at seven centimeters of water pressure. The patient reported that he was using CPAP as directed four nights per week when the bleb-related endophthalmitis developed.

2.2. Management and outcome

Initial management consisted of oral acetazolamide, topical antibiotics, and pressure-lowering eye drops. An emergent referral was made to a retinal specialist for additional treatment where severe corneal edema and inflammatory debris were present on exam. The patient underwent same-day anterior chamber paracentesis, aqueous culture and Gram stain, and intravitreal injections of vancomycin and ceftazidime. He was also started on topical steroids, antibiotics, and atropine.

The patient was evaluated daily for two additional days. Due to the extensive corneal edema, presence of cells in the anterior chamber, keratic precipitates on the endothelium, and inflammatory reaction, the retinal specialist determined the poor internal view precluded a safe vitrectomy. The patient underwent a second anterior chamber paracentesis and was given intravitreal injections of vancomycin and ceftazidime. Four days after his initial presentation, the patient was treated with additional intravitreal injections of vancomycin, ceftazidime, and triamcinolone. Around this time the result of the original aqueous culture showed heavy growth of *S. mitis* sensitive to vancomycin, penicillin, ceftriaxone, clindamycin, and ampicillin. Seven weeks after diagnosis, the retinal consultant performed a pars plana vitrectomy and pars plana lensectomy with intravitreal antibiotics. There was no bleb leakage between initial diagnosis and this procedure.

Due to the possibility that the CPAP device had spread this common oral bacterium from the patient's respiratory tract to his eye via the mask or tubing, he was asked to consider other treatment modalities for sleep apnea. This measure was recommended out of concern that his better-seeing right eye also underwent a prior ExPress trabeculectomy and may have been at risk for bleb-associated endophthalmitis as well. Despite close follow up, the patient's visual acuity in the affected eye has remained at hand motion. The authors recognize that an immediate vitrectomy could not be performed; unfortunately, the view to the posterior segment was limited by the severity and extent of infection which made the procedure technically unfeasible.

3. Discussion

In considering the origin of this specific case of delayed-onset microbial bleb infection, it was regarded as a possibility that the CPAP machine harbored the generally non-virulent organism and/or served as its transmission vector to the patient's eye where infection arose in the thin-walled bleb formed by intraoperative MMC 32 months prior. This idea was plausible as the patient reported CPAP use at the time of infection and the *S. mitis* microbe lacks the ability to move on its own, predominates in normal oral flora, and colonizes the saliva and soft tissues of the human mouth and respiratory tract.

VGS organisms have low virulence unless presented with an opportunity to become pathological, but unfortunately several noteworthy examples of such infections exist. *S. mitis* has been isolated from purulent meningitis following lumbar puncture procedures¹⁹ and inoculation was attributed to inadvertent droplet dispersal from the upper respiratory tract of medical staff²⁰. In one instance of meningitis, analysis of the offending VGS isolate from the patient's cerebrospinal fluid was compared with an oropharyngeal swab from the treating neurologist which produced an identical microbiological profile²¹. *S. mitis* has also been implicated in endophthalmitis sustained from penetrating ocular injuries with used instruments during dental cleanings²², reaffirming the typical residence of this pathogen. In patients undergoing chemotherapy, iatrogenic mucositis permits *S. mitis* access from oral flora into the bloodstream where seeding onto cardiac valves is made possible²³. It has not escaped notice that two devastating cases of globe loss due to endophthalmitis each involved opportunistic invasion of culture-proven VGS following routine procedures. In the first occurrence, ocular access was obtained through an exposed suture which eroded through the conjunctiva²⁴. The second case presented in association with a phenomenon now accepted as vitreous wick syndrome²⁵ in which normal bacterial flora communicate with the interior eye. There was no contribution of medical history provided in these two reports, including CPAP use or OSA.

The idea that CPAP devices can be a source of bacterial contamination has been researched and described. Studies of patients using CPAP have shown that a wide array of microbes, including VGS species²⁶, can be cultured from a CPAP mask, tubing, or reservoir²⁷. Whether a CPAP device is capable of delivering organisms to the human respiratory tract has also been previously confirmed. Among 167 premature infants using CPAP, nasal colonization with a potential pathogen was significantly increased among subjects using CPAP compared to subjects without CPAP ($P < 0.001$)²⁸. Additionally, a study of 246 subjects with OSA demonstrated that CPAP usage was linked to an increased risk of upper respiratory infections compared to patients without CPAP treatment ($P < 0.05$)²⁹. One notable instance of bilateral conjunctivitis occurred eight days after the onset of CPAP therapy³⁰; the offending organism was determined to be *Hemophilus influenzae*, a dominant microbe within normal human oral flora³¹. While an increased frequency of infection in the presence of CPAP has been disputed,^{25,26} in each study of morbidity and CPAP the number of at-risk subjects with a vulnerable bleb was not discussed. CPAP use has been associated with ocular infection, dryness, and irritation³², and previous authors have even considered that bacteria may be introduced

to the mucous membranes of the eye by forced air from a CPAP device³³. Yet, no discussions in the literature associate CPAP use with opportunistic infections of the susceptible bleb. Interestingly, even in the absence of detectable mask leaks, CPAP-associated retrograde air flow via the nasolacrimal system (CRANS) may be evident by a saline bubble test during CPAP use³⁴, a mechanism previously suggested to have implications in dry eye and conjunctivitis.^{31,35}

OSA is well known to be a risk factor in glaucoma³⁶ and in a 2008 study, CPAP use was observed to elevate nocturnal IOP and induce larger night-time IOP fluctuations compared to subjects with OSA who did not use CPAP³⁷. Therefore, there is a concern that CPAP users may be at a greater risk to develop glaucoma-induced optic neuropathy³⁸, increasing the likelihood of undergoing surgical procedures such as trabeculectomy.

The authors recognize the importance of comparing an original ocular isolate with the CPAP isolate for whole-genome sequencing to show a clonal match of the exact same strain. Unfortunately, the original aqueous and vitreous isolates were destroyed soon after laboratory identification and the authors first considered culturing the CPAP mask and tubing months after the subject stopped using the device. The inability to demonstrate cause and effect is one limitation to this report. To that end, the authors suggest culturing the CPAP mask, tubing, and reservoir when the device is suspected to be a source of infection in future cases of bleb-related endophthalmitis. Notably, the swabbing of CPAP devices may result in a false negative culture due to sampling error, a low degree of inoculation, or location of the organism in a confluent area of the device not swabbed with culture materials.²²

Alternative theories for transmission of the *S. mitis* organism to the eye include contaminated water, eye rubbing, or delivery of the microbe onto the face or hands from respiratory or nasal discharge, or via the nasolacrimal duct. The patient did not use oral dentures but did report the feeling of air blowing onto his face and eyes routinely during the night from the CPAP machine.

Given the concern for a potential bleb-related infection in the patient's remaining sighted eye, the patient was referred to a sleep specialist and otolaryngologist for consultation of other sleep apnea treatments. As OSA is implicated in other chronic health affairs, the authors supported the patient in seeking hypoglossal nerve stimulation to maintain airway patency while asleep. This modality would mitigate the risk of microbe delivery to the eye by propelled air and obviate the patient's responsibility to maintain a clean CPAP device. A recent study indicated a poor frequency of device cleaning by the majority of CPAP users,²⁶ yet in published literature few guidelines exist regarding CPAP maintenance. One recommendation is to clean the device with distilled water daily and allow it to air dry³⁹; even so, unpressurized water alone may not suffice to disperse bacteria which have settled on the small and uneven surfaces of the facemask or within the ribbed tubing. Thus, the efficacy of adequate device cleaning appears complex as the internal surfaces are possible sites for microorganism adherence and colonization.

Another alternative for OSA management is the less invasive nasal pillow CPAP headgear device which minimizes a bulky facial mask over the nasal bridge. This device consists of a small headpiece placed at the base of the nose and two nasal cushions inserted into the anterior nares which deliver continuous air. The nasal pillows decrease direct contact between the apparatus and ocular adnexa and may reduce air leakage compared to a standard CPAP mask. Prospective study of patients using the nasal pillow CPAP may rule out competing hypotheses of direct contact or mask leakage as routes of microbial transmission to the eye and leave retrograde CRANS as the most likely source of bacterial exposure.

This concept paper is the first documented case of bleb-associated endophthalmitis in a patient using CPAP, and the authors suggest a potentially unrecognized pathological association between such devices and filtering blebs formed by anti-fibrotic agents such as MMC. A logical risk factor for ocular surface infection, it stands to reason that oral-

or respiratory-based microorganisms delivered to the eye with CPAP assistance may opportunistically invade conjunctival tissue which lacks its full ability to act as a barrier against bacterial penetration. A critically important question to research and consider, the authors hope to raise awareness of this possibility and advocate close monitoring of patients with conjunctival filtering blebs who also use CPAP devices. Additional cases of bleb-associated endophthalmitis among patients using CPAP must be examined to substantiate this hypothesis. In the meantime, patient education regarding the risk of bleb infection remains vital. Other sleep apnea treatment modalities such as upper airway stimulation or nasal the pillow device may be better options than pressurized air delivered by a face mask in patients with thin-walled blebs, but further prospective study is necessary to determine if CPAP devices increase the frequency or risk of bleb-related infections.

Patient consent

The patient provided written and informed consent to the publication of this report.

Funding

No funding or grant support.

Conflicts of interest

The authors have no financial disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgements

None.

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