Abstract

Fungal infections are commonly resistant to treatment, penetrate deep into the cornea, take days to culture and extended periods of time to heal. This case report discusses the management of fungal keratitis.

I. Case History
a. Patient SB, a Caucasian 29 year old male was referred to our clinic for a corneal ulcer OD.
b. Chief Complaint: Decreased distance VA and significant pain OD. No problems or complaints OS.
c. Past Ocular History: SB scratched his OD two weeks before presenting to our clinic while power washing a hog confinement. He does not wear contact lenses only spectacles.
d. Past Medical History: Unremarkable

e. Medications – Referring OD started gatifloxacin q1h OD and loteprednol 0.2% 2 x a day OD
f. Family Medical History: Diabetes

g. Allergies: amoxicillin

II. Pertinent findings
a. Distance Visual Acuity w/ specs: 20/400 OD and 20/20 OS. Pinhole acuity OD – 20/100
b. No manifest refraction performed due to the intense pain and photophobia experienced by the patient.
c. Pupils were equally round and reactive to light, no afferent pupil defect was noted OU. Confrontation fields were not tested. Extraocular muscles were unrestricted in all gazes.
d. IOP: 14mmHG OD and 10 mmHG OS

e. Anterior Segment OD – 4 x 4 mm central, mildly opaque corneal ulcer. No satellite lesions present, but the edges appeared “feathery” (Image available). 2+ conjunctival injection. AC was deep and quiet. Lens was clear. Evaluation OS was normal.
f. Undilated Fundus Examination – difficult due to intense pain and photophobia
   i. C/D Ratio: OD 0.20/0.20 OU with normal neuroretinal rims.
   ii. A/V ratio: 2/3
   iii. Macula: Flat and intact

III. Differential Diagnosis
a. Primary/Leading
   i. Bacterial Corneal Ulcer OD
b. Others
   i. Fungal Corneal Ulcer
   ii. Herpes Simplex Virus Keratitis
   iii. Acanthamoeba Keratitis

IV. Diagnosis and discussion
a. Diagnosis
   i. Culture of ulcer was obtained – sabouraud, chocolate, blood agar, and thioacrylate broth medium.
   ii. Initial Diagnosis – Bacterial Corneal Ulcer/Infectious Bacterial Keratitis OD

V. Treatment, management
a. Treatment and response to treatment
   i. The decision was made to start fortified vancomycin and tobramycin q1h OD during the day and q2h OD throughout the night until culture results were obtained. All other drops were stopped. Follow-up in 48 hours.
ii. Follow-up #1 - SB states that he is starting to feel better and could actually open his eye a little today. SB is applying one drop of fortified vancomycin and tobramycin every two hours OD during the day and during the night. Uncorrected VA – CF @ 3ft. A stable 4 x 4 mm central, mildly opaque corneal ulcer. It appeared slightly improved as the edges of the ulcer appeared less “feathery”. The conjunctiva had 2+ injection OD. His IOP was 14 OD. SB was instructed to continue the vancomycin and tobramycin every hour and the importance was stressed to him of using it every hour. He was asked to return to our clinic two days later for re-evaluation.

iii. Follow-up #2 – SB states that he is starting to see a little better. SB is applying one drop of fortified vancomycin and tobramycin every one hour OD during the day and every two hours during the night. His uncorrected visual acuity OD is 20/400 with no improvement with pinhole. Slit lamp examination OD showed a stable 4 x 4 mm central, mildly opaque corneal ulcer. No improvement was noted from two days earlier. The conjunctiva had 2+ injection OD. The remainder of the slit lamp examination was normal OD. His IOP was 9 OD. A positive growth of Fusarium was noted on one of the bacterial cultures. SB was instructed to stop the vancomycin and tobramycin. He was prescribed natamycin 5% and instructed to apply one drop every hour OD during the day. He was asked to return to our clinic three to five days later for re-evaluation.

iv. SB states things are going a lot better. He states his vision is better and he is not as light sensitive. SB is applying one drop of natamycin 5% every one hour OD during the day. His corrected visual acuity OD is 20/40. Slit lamp examination OD showed a 4 x 4 mm central, mildly opaque corneal scar. The tissue appeared re-epithelialized. The conjunctiva had 1+ injection OD. The remainder of the slit lamp examination was normal OD. His IOP was 11 OD. SB was instructed to taper the natamycin 5% to one drop every two hours OD. A prescription for difluprednate 0.05% was given and SB was instructed to apply one drop one time a day only OD. He was asked to return to our clinic in one week for re-evaluation.

v. SB states his vision is better and things continue to improve. SB is applying one drop of natamycin 5% every two hours OD during the day and one drop of difluprednate 0.05% one time a day OD. His corrected visual acuity OD is 20/25. Slit lamp examination OD shows a stable 4 x 4 mm central, mildly opaque corneal scar. The conjunctiva has no injection OD. The remainder of the slit lamp examination was normal OD. His IOP was 13 OD. SB was instructed to taper the natamycin 5% to one drop four times a day OD. He was instructed to continue the difluprednate 0.05% one drop one time a day OD. SB was asked to return to our clinic in one week for re-evaluation.

vi. SB states his vision is a little blurry, but the eye is comfortable. SB is applying one drop of natamycin 5% four times a day OD and one drop of difluprednate 0.05% one time a day OD. His corrected visual acuity OD is 20/40. Slit lamp examination OD shows a stable 4 x 4 mm central, mildly opaque corneal scar. The conjunctiva has no injection OD. The remainder of the slit lamp examination was normal OD. His IOP was 14 OD. SB was instructed to taper the natamycin 5% to one drop two times a day OD. He was instructed to continue the difluprednate 0.05% one drop one time a day OD. SB was asked to return to our clinic in one week for re-evaluation.

vii. SB states his vision is great and the eye is comfortable. SB is applying one drop of natamycin 5% two times a day OD and one drop of difluprednate 0.05% one time a day OD. His corrected visual acuity OD is 20/25. Slit lamp examination OD shows a stable 4 x 4 mm central, mildly opaque corneal scar. The conjunctiva has no injection OD. The remainder of the slit lamp examination was normal OD. His IOP was 15 OD. SB is instructed to stop the natamycin 5% and the difluprednate 0.05%. SB was asked to return to our clinic in one week for re-evaluation. SB was lost to follow-up after this visit.
Discussion

1. In order to make a diagnosis of fungal keratitis it is important to understand the risk factors associated with it and how it presents. The location of the eye care provider’s clinic or where a patient has traveled recently are significant risk factors.\(^1\)\(^,\)\(^2\) It is much more common to see fungal keratitis in hot and humid areas. Three other significant risk factors are trauma involving vegetative or agricultural material, contact lens use or abuse, and immunocompromised individuals.\(^1\)\(^,\)\(^2\)

Fungal infections take time to get worse. The condition typically will build for weeks before becoming debilitating to the patient.\(^3\) In comparison bacterial infections will present as normal one day, and the next day the eye is painful with significant inflammation.\(^4\) It is common to see satellite lesions with fungal infections, which surround the main lesion. Fungal ulcers will usually go deeper into the cornea than bacteria, and also have feathery borders compared to more distinct borders seen with bacterial infections.\(^3\)\(^,\)\(^4\) Finally, another feature of fungal infections is that the eye can be relatively quiet compared to bacterial keratitis.\(^3\)\(^,\)\(^4\) Culturing or a biopsy are crucial to make a definitive diagnosis of fungal keratitis.

Filamentous fungi are treated with natamycin every one hour. Previously, filamentous fungal infections of the cornea were treated with voriconazole, until the results of the Mycotic Ulcer Treatment Trial (MUTT).\(^5\) In this trial natamycin outperformed voriconazole. Patients on natamycin in the MUTT were less likely to suffer a perforation or need a therapeutic penetrating keratoplasty compared to patients on voriconazole.\(^5\)

Patients should be followed daily or every other day while hourly treatment is being initiated. Once the ulcer responds to treatment and begins to improve, less frequent follow-up is possible, and a tapering schedule is begun. Patients should be educated that treatment could last many months.

References:


Conclusion

a. This case demonstrates the options and the thought process that a clinician considers when managing a patient with a fungal keratitis. Treatment of a fungal keratitis can be very challenging for an eye care provider if a prompt diagnosis isn’t made and quick treatment is not started. Adding to this challenge is the poor corneal penetration and the limited commercial availability of antifungal agents. There is a need for better antifungal agents that work quicker, penetrate more efficiently into ocular tissue, and have fewer medical failures. It is important to treat corneal ulcers of all natures aggressively, culture any large and any centrally located ulcers, and monitor these patients often. Many times the cornea can be saved if these steps are taken.
American Academy of Optometry - Grand Rounds

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PSEUDOEXFOLIATION SYNDROME BEYOND THE EYE

Abstract
This case report reviews a less common form of glaucoma, emphasizing the key role that optometry plays in the healthcare team when co-managing systemic manifestations, which in this case may have been life-saving.

I. Case History

Patient demographics: 63 year old caucasian female (mixed European descent)

Chief complaint: Stable blurry vision distance and near. No ocular health complaints. Here for routine eye exam.

Ocular history: Unremarkable.

Medical history: Borderline hypercholesterolemia. No previous surgeries.

Medication: None; red yeast rice dietary supplements only.

Other Salient Information: Strong family history cerebrovascular accidents (CVA) in both parents and grandparents, most resulting in sudden death. No history of smoking. No known drug allergies. Blood pressure in office 113/77.

II. Pertinent Findings

Clinical:
- BCVA: 20/20 OD, OS distance and near.
- Preliminary testing (pupils, EOMs, CVFs): all normal and unremarkable OU.
- IOPs: 18mmHg OD, 24mmHg OS on Goldmann applanation.
- Slit lamp exam: Trace corneal endothelial pigment OU. No krukenberg spindles nor transillumination iris defects OU.
- Gonioscopy (4-mirror): Open angles to ciliary body band 360°. Unevenly distributed grade 2-3+ trabecular meshwork pigment and marked sampaolesi lines 360° OU. No synechiea OU.
- Dilated fundus exam: Classic “three ring sign” of pseudoexfoliation (PXF) material on the anterior lens capsule centrally and peripherally OS only. Early nuclear sclerotic cataracts OU. No phacoedonesis or subluxation OU. No frank signs of glaucomatous cupping OU. C/Ds 0.35R and pink/distinct OU. No drance hemorrhages OU. No frank retinal nerve fiber layer (RNFL) defects funduscopically. No apparent maculopathy, vasculopathy, or retinopathy OU.
- Optical Coherence Tomography (OCT): Unremarkable OD. Early RNFL thinning superiorly and inferiorly OS.
- Humphrey Visual Field (HVF) SITA FAST 24-2: Generally clean fields OU. No frank glaucomatous defects OU.
- Pachymetry: 566 OD, 575 OS.

Assessment/Plan: Pseudoexfoliation syndrome and ocular hypertension OS. Concern for possible systemic correlation to strong family history CVA-related deaths. Glaucoma risks were reviewed over the next several follow up eye exams and patient eventually elected for prophylactic treatment with Latanoprost 0.005% ophthalmic drops QHS OS. Patient was referred to primary care physician (PCP) for physical, bloodwork, and cardiovascular work up.

Physical and Laboratory Studies:
- PCP's physical exam report generally unremarkable. Blood pressure stable and non-elevated. Bloodwork confirmed elevated LDL cholesterol and high triglycerides despite normal diet and healthy weight / body mass index.

Others:
- PCP felt red yeast rice and omega-3 supplements were NOT adequately controlling patient’s cholesterol and triglyceride levels over the past two medical visits.
- Given blood work results, strong family history of CVA-related deaths, and diagnosis of PXF syndrome, PCP prescribed atorvastatin and referred the patient to cardiology to rule out other cardiovascular co-morbidities.
- Cholesterol and triglyceride levels normalized and ultimately risk for cardiovascular complications decreased.

III. Differential Diagnosis

Primary/Leading: Pseudoexfoliation syndrome / glaucoma

Others: • Pigmentary dispersion syndrome / glaucoma • Narrow angle / angle closure / phacomorphic glaucoma • Capsular delamination / true exfoliation • Primary open-angle glaucoma (POAG) • Primary Familial Amyloidosis • Fuch’s heterochromic iridocyclitis
IV. Diagnosis and Discussion

Definition. Pseudoexfoliation (PXF) Syndrome is an age-related systemic disease characterized by accumulation of fibrillar proteinaceous extracellular fibers in the ocular tissues. PXF syndrome is a risk factor for developing PXF glaucoma. These fibers impede aqueous outflow and gradually cause a secondary rise in intraocular pressure.

Epidemiology. Studies vary worldwide.
- Among patients with glaucoma, PXF accounts for 12% (Roth and Epstein) vs 1.8% (Framingham Study) vs 2.3% (Australian Blue Mountains Eye Study)
- 50% incidence of PXF in certain Scandinavian countries
- Prevalence of PXF 0.6% age 52-64, 2.6% age 65-74, 5% age 75-85 (Framingham Study)

Genetics. Lysyl oxidase-like 1 (LOXL 1) gene has been referenced in recent studies in the biogenesis of connective tissue and cross-linking of elastin. Studies suggest that genetic alterations in LOXL 1 lead to excess production of extracellular material among other genetic catalysts like contactin-associated protein-like 2 (CNTNAP2) and clusterin (CLU).

Pathophysiology. Multifactorial including genetic mutation, oxidative stress (UV light), inflammation, hypoxia, and age.
- Microfibrillar PXF material produced by epithelium in the iris pigment, ciliary, and peripheral anterior lens.
- PXF material moves into aqueous humor and deposits into trabecular meshwork.
- Over time, PXF material accumulates and degenerates Schlemms canal and juxtacanaliclar area.
- Aqueous outflow becomes impeded, leading to increased IOP and secondary glaucoma.

Risk Factors. Family history of PXF, female, >50 years old, Scandinavian, living higher altitudes / greater UV exposure.

Diagnostic Factors. Primarily diagnosed on slit lamp biomicroscopy. The following diagnostic signs to not miss include:
- **White fibrillar deposits on anterior lens capsule and/or pupillary margin.** Perhaps the most pathognomonic sign. Look for “3-ring sign” of PXF material on the anterior lens capsule (central disciform ring, peripheral ring, and clear zone separating the two). Rings have well-demarcated borders and look “curled up” on the edges.
- **Peripupillary atrophy.** Transillumination iris defects (TIDs) observed at the pupil margins. Mid peripheral transillumination defects are more associated with pigmentary dispersion syndrome (PDS).
- **Atypically high trabecular meshwork pigment on gonioscopy.** ≥ Grade 2+ pigment and uneven Sampaolesi’s line raises suspicion for PXF and PDS. Other signs must be taken into account in the differential diagnosis.
- **Poor pupillary dilation.** Structural damage to the iris from PXF material may be the cause.
- **Asymmetric signs.** Each matching correlation should raise PXF suspicion (example: the eye with larger C/D also has more pigment on gonioscopy, more pupillary TIDs, dilates poorly, and has higher IOP than the fellow eye).
- **Phacodonesis or subluxation.** Zonular weakness from PXF deposits make lens more prone to subluxation.

Systemic Implications. PXF material has been identified outside of the ocular tissues via autopsy and electron microscope studies in multiple visceral organs (heart, blood vessels, lungs, kidneys, liver, skin, etc). Currently, there’s mixed consensus in the medical literature about its implications for cardiovascular disease but note the following:

**Studies supporting PXF association with cardiovascular risk**
- PXF significantly associated with hypertension, angina, acute myocardial infarction, and/or stroke in large population study (Australian Blue Mountains Eye Study 1997)
- PXF significantly associated with various stages of ischemic heart disease, cardiomyopathy, aortic aneurysm in national cross-section comparison study (French, 2012)
- PXF associated with and may be risk factor for peripheral vascular disease (Praveen 2011)
- PXF correlated to high incidence of transient ischemic attacks (Repo 1995)
- PXF associated with higher homocysteine levels, which is risk factor for cardiovascular disease (Roedl 2007)

**Studies NOT supporting PXF association with cardiovascular risk**
- PXF not associated with cardiovascular or cerebrovascular mortality in smaller population study (Shrum 2000)
- No increased risk of mortality in patients with PXF in 30 year follow up study (Svensson 2014)
- No significant relationship between PXF and coronary artery disease, aortic aneurysm, or peripheral artery disease (Emiroglu 2010)

There is also mixed medical opinions on PXF as risk factor for **Alzheimer disease** and **sensorineural hearing loss**.

**Conclusion:** More population based studies must be done. Current overall consensus is that there continues to be growing evidence that patients with PXF have increased cardiovascular risk in general, which may lead physicians to investigate other cardiovascular co-morbidities.
V. Treatment and Management

Topical Agents. Same topical medications for treating POAG, but tend to be less effective in PXF. These include prostaglandin analogs, beta blockers, alpha-2 adrenergic agonists, carbonic anhydrase inhibitors, and sympathomimetics.

Surgical. Laser trabeculoplasty has proven effective for treating PXF glaucoma in many studies. Both selective and argon laser trabeculoplasties (SLT and ALT) have proven equally effective in recent studies (Kent 2015) at lowering IOP at 6 months post treatment. Some ophthalmologists favor SLT for being able to repeat treatment when its effect wears off.

Treatment Considerations. PXF syndrome may NOT need to be treated until there is high risk or strong evidence of conversion to PXF glaucoma. Risk increases significantly with age, so baseline HVFs and OCT of the optic nerves are indicated upon diagnosis of PXF syndrome in order to monitor for glaucomatous changes. Gonioscopy should also be performed regularly in PXF syndrome due to elevated risk for secondary angle closure. This may be due to loose zonules, shallowing of the lens over time, or iris synechial changes. Co-management with PCP should also be considered upon diagnosis of PXF syndrome in order to screen for cardiovascular disease.

Treatment and Management Approach. Many doctors of optometry and ophthalmology start with topical agents and monitor IOPs closely since PXF is often less stable and less predictable than POAG. Once two agents are on board, it may be time to consider SLT/ALT options. Once patients have maxed out on topical agents and repeat laser trabeculoplasties, it’s time for glaucoma specialist referral to consider other surgical options including trabeculectomy, stents, etc.

Cataract Surgical Considerations. Zonular weakness and poor pupillary dilation significantly increase risk for surgical complications. Doctors of optometry should note any phacodonesis (indication of zonular instability) or poor dilation to alert the surgeon in the cataract surgical referral. Some ophthalmologists may combine cataract and glaucoma surgeries.

Case Treatment and Management Summary. Diagnosis was straight forward. Unilaterally elevated IOP OS led to further investigation with gonioscopy. The initial diagnostic impression was PDS, but dilated view of the lens uncovered pathognomonic signs for PXF. Patient was followed 1-2 weeks later for repeat IOP check, HVF, OCT, and pachymetry. Stable asymmetrically high IOP OS correlated to OCT’s vertical RNFL thinning OS and unilateral PXF lenticular signs OS. Risk factors were reviewed and patient elected for treatment with latanoprost 0.005% QHS OS. At 6 week follow up, IOP OS reduced >20% lower than IOP max from 24mmHg to 16mmHg OS. She is currently being followed every 4-6 months by both primary care optometry and cardiology.

VI. Conclusion

Pseudoexfoliation syndrome continues to be an evolving area of scientific and clinical research on its systemic manifestations.

Aside from mixed medical opinions in the current literature, this patient’s strong family history of CVA-related deaths was of serious concern, especially with potential increased risk for cardiovascular complications in PXF syndrome. The patient’s family may have all had PXF, possibly predisposing them to elevated risk for CVA.

Doctors of optometry continue to play an integral role in interdisciplinary healthcare. When PXF syndrome is diagnosed, it’s critical for eye doctors to evaluate the systemic history for cardiovascular risk factors (systemic hypertension / elevated blood pressure in office, metabolic syndrome, family history of cardiovascular disease, smoking, etc) and refer for further medical evaluation where indicated.

This patient’s ophthalmic diagnosis not only led to timely preventative treatment against glaucomatous vision loss, but it also helped justify the referral for cardiovascular work up and systemic medications that may have been life-saving.
Retinitis Pigmentosa: Novel Treatment Using Microcurrent for Visual Field Expansion
Laurie Chalkin, OD

Abstract: 59-year-old patient with retinitis pigmentosa with 15 degree visual fields initially, receives seventeen weekly treatments of microcurrent. Visual fields expand to 50 degrees with concurrent improvements in contrast sensitivity, color vision and functional mobility.

I. Case History

- Patient is a 59-year-old African-American female.
- Chief complaint: Patient is having difficulty navigating, tripping and stumbling frequently.
- Ocular, medical history: Abnormal retinal findings first noted in 2009, she was initially diagnosed with Pigmentary Degeneration, then formally diagnosed with Retinitis Pigmentosa in 2013 at UCSF. Medical history positive for HIV. She is fifteen years status post brain injury from an arterial venous malformation hemorrhage, and has type II diabetes.
- Medications: Isentriss, preziztra, intence, norvir, viread, atorvastatin, nadalol, multi vitamin.

II. Pertinent findings

- Clinical: pre-treatment findings:
  o Visual fields were measured on a stereo campimeter (tangent screen type of field). Right eye horizontal field was 12°, vertical was 8°. Left eye visual field was 24° horizontal and 12° vertical.
  o Visual acuity was OD 20/30-2, OS: 20/30+2.
  o Stereopsis was 200 arc seconds
  o Contrast sensitivity: significantly depressed at low and medium spatial frequencies, absent at high spatial frequencies
  o Color vision: abnormal
- Treatment: consisted of dual channel frequency specific microcurrent where electrodes were placed within a damp cloth and applied trans-palpebrally and sub-occipitally. There were 17 weekly treatments with a duration of about 30 min.
- Post treatment findings:
  o Tangent screen visual fields expanded in the right eye horizontally from 12° to 50° and vertically from 8° to 42°. In the left eye fields expanded horizontally from 24° to 46°, and vertically from 12 to 22°. Expansion was non-uniform.
  o Visual acuity increased to 20/20 in each eye
  o Stereopsis increased to 63 arc seconds
  o Contrast Sensitivity: completely normalized.
  o Color vision: significantly improved
- Independently tested Goldman visual fields supported this change, showed significant improvement.

III. Differential diagnosis
• Primary/leading: initially diagnosed as pigmentary degeneration, then in 2013 by UCSF ophthalmologist as atypical retinitis pigmentosa.
• Others: choroidal degeneration.

IV. Diagnosis and discussion

• Elaborate on the condition: diagnosed as atypical retinitis pigmentosa: genetic testing did not reveal the usual markers and there was no family history, plus late onset.
• Unique features: there is extensive literature in animal research and human clinical trials that demonstrate visual change (increased visual acuity) as well as measurements of possible mechanisms of action. Measurements include increases in ATP production to provide the energy for cellular processes such as trans-membrane transport, reduction in inflammatory markers and alterations of gene transcriptase factors. It is thought that microcurrent may be operating on a tissue resonance effect which may enhance blood flow and nerve signal conduction as well as slow down cell apoptosis.

V. Treatment, management

• Treatment and response to treatment: dual channel frequency specific microcurrent was applied via electrodes inserted in a wet cloth, and placed in trans-palpebral application and sub occipital application. Subjective response to treatment over the 17 weeks was an increasing confidence in ambulation, greater speed during movement and feeling like she can see better on the side and below.
• Research by the following have demonstrated significant clinical visual improvements: Anastassiou, Chaikin, and Shinoda. Below are a number of studies of microcurrent effecting vision in a variety of eye diseases, followed by animal studies done to investigate effects on cellular level.

Bibliography, literature:


Animal Studies:


VI. Conclusion

- Clinical pearls, take away points if indicated:
  - frequency specific microcurrent is a treatment modality which bears further investigation both within the primary eye care and low vision settings. Microcurrent has been FDA approved to treat pain and as physicians we are permitted to use it off label.
  - Research supports that it is safe and efficacious, many documented cases of wound healing.
  - Double-blind controlled studies and long term studies would be recommended
  - On-going treatment is likely to be needed in the case of degenerative conditions.