American Academy of Optometry: Case Report Sample

Atypical Thygeson Superficial Punctate Keratitis: Advances in Treatment and Management

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Abstract

Thygeson superficial punctate keratitis is a rare, bilateral, epithelial keratitis of unknown etiology commonly confused with other clinical entities. This case outlines a discussion of treatment and management for this elusive disease characterized by exacerbations and remissions.

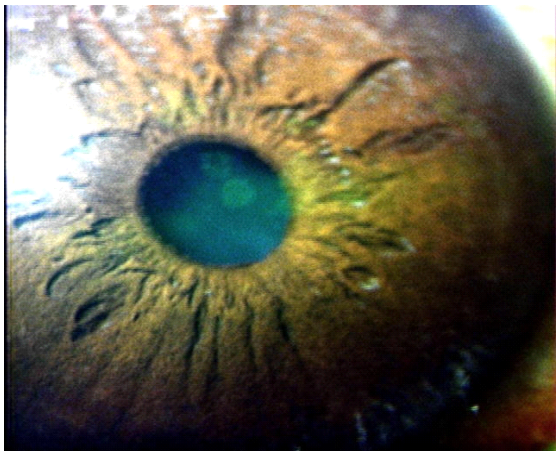
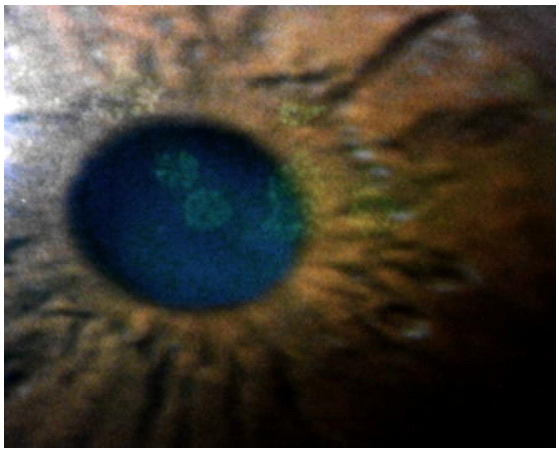
Key words: *Thygeson superficial punctate keratitis, herpes simplex virus, acanthamoeba, cyclosporin A, corticosteroids*

Introduction

Case Report

A 43 year old African American male presented for examination with the complaint of a foreign body sensation in the left eye when blinking. He denied ocular hyperemia, lacrimation, discharge, pain, or changes in visual acuity. He recalled similar symptoms in the past affecting both eyes. His last ocular examination was 3 months earlier with an outside provider but he admitted to non-compliance with the recommended follow-up. His ocular history included presbyopia and suspicion of glaucoma. He denied past ocular surgery or trauma. Family ocular history was positive for glaucoma (mother). The patient's medical history was positive for coronary artery disease, cardiac stents (four placed one year earlier), orthostatic hypertension, neurotic depression, and cervical radiculopathy. He could not recall his systemic medications. Social history was negative for tobacco, alcohol, or recreational drug abuse. He had no known drug allergies. He was oriented to time, place, and person and his mood was appropriate.

Uncorrected distance visual acuity was 20/20 OD and 20/20 OS. Habitual spectacle correction measured via lensometry was plano sphere OD, plano sphere OS, with an add of +2.50 OU. Manifest spectacle correction revealed the same powers. Near visual acuity with correction was 20/20 OD and 20/20 OS. Pupils were equal, round and reactive to light; no afferent pupillary defect was noted. Confrontation fields were full to finger counting in both eyes. Extraocular muscles were unrestricted in all gazes without pain or diplopia. Cover test was orthophoric at distance and near. There was no evidence of preauricular lymphadenopathy. Cotton wisp test was negative for decreased corneal sensitivity. Goldmann applanation tonometry measured 12 mmHg OD, OS at 11:18 am. Slit lamp biomicroscopy revealed normal adnexae, lids, lashes, puncta, and palpebral and bulbar conjunctivae in both eyes. The right cornea was normal, however, the left eye demonstrated multiple, conglomerate, white, stellate, superficial, punctuate, epithelial corneal lesions. Sodium fluorescein staining was positive in the left eye. Both anterior chambers appeared quiet without evidence of cell or flare; estimation of the chamber angles was 4/4 via the Von Herrick method. Both irides were flat and brown. Pupils were dilated using one drop 1% Mydriacyl® and one drop 2.5% phenylepherine. Evaluation of the posterior segment revealed 1+ nuclear sclerosis of the lens in both eyes with peripheral cortical spoking in the right eye. Fundus assessment revealed optic nerves with a cup-to-disc ratio of 0.80/0.85 OD and 0.70 (0.10 superior rim, 0.20 inferior rim)/0.65 OS. The cups were deep; there was no evidence of pallor or edema of the neuroretinal rim. The right macula showed trace hard drusen; both maculae were flat. The vitreous was optically clear in both eyes. The vasculature was normal and the retinal periphery was flat without breaks in both eyes.

Figures 1 & 2
Anterior segment photographs of the corneal lesions stained with sodium fluorescein in the left eye: 10x magnification (left); 16x (right).

The differential diagnoses considered at this point included:

Herpes simplex viral (HSV) keratitis
Herpes zoster viral (HZV) keratitis
Epidemic keratoconjunctivitis (EKC)
Acanthamoeba keratitis (AK)
Bacterial keratitis
Corneal ulcer
Dry eye syndrome (DES)
Thygeson superficial punctate keratitis (TSPK)

- HSV keratitis typically presents as a unilateral 'red eye' with variable degrees of pain or ocular irritation often associated with lacrimation, photophobia, and decreased corneal sensitivity. Epithelial corneal lesions, termed dendrites, often present in a punctate or tree-branching pattern and stain with sodium fluorescein.
- HZV keratitis often presents unilaterally with similar symptoms as described above; corneal pseudodendrites are typically seen. Symptoms may also include facial pain and skin lesions in the region along the branches of cranial nerve V particularly affecting the V_1 and V_2 dermatomes.
- EKC presents as an acute follicular conjunctivitis with a watery discharge, hyperemia, chemosis, preauricular lymphadenopathy, and non-staining, subepithelial corneal infiltrates. Pseudomembranes are sometimes observed.
- AK is a parasitic infection of the cornea presenting with severe pain, hyperemia, photophobia, infiltrates or ulceration, and in advanced cases, radial neurokeratitis.
- Bacterial keratitis generally presents with acute pain, photophobia, hyperemia and a thick, ropy, mucopurulent discharge. A focal, stromal infiltrate with an overlying epithelial excavation may be present.
- A corneal ulcer often presents with hyperemia, photophobia, and pain with minimal to severe discharge and reduced visual acuity depending on the location of the lesion.

Corneal lesions stain with sodium fluorescein and may include infiltration and edema with or without an anterior chamber reaction.

- DES can present with burning, irritation, foreign body sensation, lacrimation, and blurred vision that improves or fluctuates with blinking. Moderate to severe cases may include positively staining corneal punctate epithelial erosions.
- TSPK involves a mild to moderate foreign body sensation, minimal lacrimation, and occasional photophobia. Numerous round or stellate areas of coarse, gray, slightly elevated intraepithelial corneal opacities are observed in one or both eyes with an asymmetric presentation.

The appearance of the corneal lesions in the left eye suggests a diagnosis of TSPK based on the following: multiple, superficial, slightly elevated, stellate lesions that stain with sodium fluorescein dye; no conjunctival involvement; no anterior chamber reaction; and a history of recurrence. The patient was started on a maintenance dose of Vexol® (rimexolone) 1% ophthalmic suspension, one drop daily in the right eye and four times daily in the left eye; and Restasis® (cyclosporine A) 1% ophthalmic emulsion, one drop three times daily in both eyes. He was scheduled to follow-up in one week. In addition, he was diagnosed as a glaucoma suspect secondary to a large cup-to-disc ratio and family history of glaucoma. A Humphrey visual field 30-2 SITA standard test, Cirrus OCT of the optic nerves and pachymetry were ordered to further evaluate the risk of glaucoma; past eye records were also requested. Macular drusen in the right eye, non-visually significant cataracts in both eyes, and presbyopia were also assessed. These findings would be monitored at future visits. The patient chose to use over the counter readers for near.

Follow up #1

The patient returned one week later for an anterior segment evaluation. He reported complete resolution of symptoms in the left eye and compliance with the recommended medical therapy. Visual acuity remained stable with uncorrected distance acuities of 20/20 OD, OS. Slit lamp biomicroscopy of both eyes revealed normal lids, lashes, conjunctivae, corneas, anterior chambers and irides. The corneal lesions noted previously in the left eye resolved completely. Intraocular pressure measured 10 mmHg OD, OS at 1:18 p.m. via Goldmann applanation tonometry.

To avoid recurrence, the patient was instructed to continue the present medications consisting of Vexol® and Restasis® as previously instructed for an additional week and follow-up for an anterior segment evaluation.

The patient presented with his past eye records which were reviewed at the time of this visit. The following is a summary of his ocular history starting 7 years prior to this presentation:

- 36 year old male presented to an outside eye clinic with complaints of intermittent episodes of mild distance blur, foreign body sensation, and epiphora for two years. A description of the corneal findings noted "+ Rose Bengal and NaFl staining of

superficial, white, snowflake opacities with a question of terminal end bulbs and associated stromal haze OU." The patient was diagnosed with probable HSV keratitis. Acanthamoeba was considered but felt to be less likely. The patient was started on Viroptic® ophthalmic solution, one drop nine times per day in both eyes. A consultation with a corneal specialist was placed.

- Cornea consultation: Culture for acanthamoeba was negative. The records indicated the patient responded poorly to Viroptic®. The diagnosis of atypical Thygeson SPK was assessed. He initiated treatment with Pred Forte® 1% ophthalmic suspension, one drop every two hours in both eyes. The patient responded well to this medication.
- A series of exacerbations and remissions followed with documentation of 11 episodes in the right eye and 22 in the left eye over the course of seven years.

Follow-up #2

The patient returned 2 weeks later for an anterior segment evaluation. He reported a reactivation of symptoms in the left eye and admitted to poor compliance with his medications. His visual acuity remained stable with uncorrected distance visual acuities of 20/20 OD, OS. Slit lamp biomicroscopy revealed normal lids, lashes, conjunctivae, anterior chambers and irides in both eyes. The right cornea was clear, however, there were seven, white, stellate, circular areas of peripheral, coalescent SPK in the left eye. Intraocular pressure measured 11 mmHg OD and 13 mmHg OS at 11:34 a.m. via Goldmann applanation tonometry.

Given the worsening corneal signs as compared to the initial presentation, the patient was instructed to increase the Vexol® dosage to one drop every 3 hours in the left eye while maintaining a once daily dosage in the right eye. Restasis® 1% ophthalmic emulsion, one drop in both eyes 3 times a day in both eyes was continued. He was instructed to return to the clinic in one week. Medication compliance was stressed.

Follow-up #3

The patient returned one week later for an anterior segment evaluation. He reported complete resolution of symptoms and compliance with all medications. His visual acuity remained stable with uncorrected distance visual acuities of 20/20 OD, OS. Slit lamp biomicroscopy revealed normal lids, lashes, conjunctivae, corneas, anterior chambers and irides in both eyes. Intraocular pressure measured 13 mmHg OD and 12 mmHg OS at 11:00 a.m. via Goldmann applanation tonometry.

Given the previous reactivation in such a short period of time, the patient was asked to remain with the same medication dosage; compliance was stressed. He was asked to return in one week.

Follow-up #4

The patient returned in one week for an anterior segment evaluation. He reported no symptoms and compliance with all medications. His visual acuity remained stable with uncorrected distance visual acuities of 20/20 OD, OS. Slit lamp biomicroscopy revealed normal lids, lashes, conjunctivae, corneas, anterior chambers and irides in both eyes. Intraocular pressure measured 13 mmHg OD and 12 mmHg OS at 11:40 a.m. via Goldmann applanation tonometry.

The patient was instructed to continue the maintenance dose of Vexol® one drop daily in the right eye while tapering to one drop 4 times a day in the left eye. Restasis® was maintained at three times a day in both eyes. He was instructed to return to the clinic in one week for a completion of the glaucoma work-up and anterior segment evaluation.

The patient was lost to follow-up as he transferred his care out of state.

Discussion

P. Thygeson, M.D. first described the clinical entity known as Thygeson Superficial Punctate Keratitis in 1950.[1] Noted as a transient, most commonly bilateral disease exhibiting coarse corneal epithelial opacities without evidence of stromal involvement or corneal edema, TSPK remains a diagnosis of unclear etiology. Gross inspection of the eyes appears essentially normal with little or no evidence of eyelid swelling or conjunctival injection. Biomicroscopy shows multiple, round or stellate areas of whitish-gray, slightly elevated intraepithelial opacities which stain brightly with sodium fluorescein.[2] The opacities are evanescent and often change in pattern over time.[3] The lesions may resemble subepithelial infiltrates or pseudodendrites. Corneal sensation is normal. Inspection of the anterior chamber reveals the absence of cell or flare.

Visual acuity may be unaffected or mildly reduced (typically better than 20/50) depending on the density and location of the corneal lesions.[1] Given the chronic nature of the disease and its insidious onset, patients often report a history of similar symptoms primarily including mild to moderate irritation or foreign body sensation, tearing, occasional photophobia, mildly blurred vision, dryness, and rarely, hyperemia or diplopia. Bilateral involvement is most common although corneal signs may not occur simultaneously; fewer cases have remained unilateral. Typically, there is no history of recent ocular inflammation or association with systemic illness.[2]

The age of onset of symptoms has been documented as young as age 2 and as old as age 71.[1] The duration of the disease may extend up to 41 years characterized by exacerbations and remissions.[4] As symptoms resolve, visual acuity returns to normal with minimal, if any, visual sequellae.

In 1961, Thygeson[5] presented five diagnostic criteria that he felt differentiated the disease from other forms of epithelial keratitis: 1) a chronic, bilateral punctate epitheliopathy, 2)

a long duration of exacerbations and remissions, 3) corneal epithelial healing without scars, 4) no response to antibiotics, and 5) a remarkable response to corticosteroids.

Several ideas have been proposed to explain the etiology of TSPK. A primary hypothesis suggests an autoimmune mechanism. Darrell[3] reported a highly significant association with Human Leukocyte Antigen DR3 (HLA DR3), which he stated may alter the immune response of individuals presenting with TSPK to viral infections (exogenous or endogenous) thereby resulting in the prolonged duration of disease with characteristic exacerbations and remissions. Several mechanisms have been postulated to explain the HLA system and its role in various diseases.[6-9] It is suggested that molecular mimicry occurs when an infectious agent has a similarity to a normal tissue antigen. As a result, the infectious agent will stimulate a weak immune response as compared to a stronger immune response if the agent were inherently different than normal tissue. The HLA type may determine cell surface receptors that enhance the attachment of viral particles to the cell and increase its ability to transport the virus across the cell membrane thereby increasing susceptibility to a particular disease. This modified cell theory concludes that viruses could alter antigens coded for by the HLA D and DR regions; hence, these antigens would be thought of as foreign by the host and cause an autoimmune reaction. HLA DR3 is increased in patients with TSPK and is known to correlate with other autoimmune disorders such as celiac sprue, chronic hepatitis, Addison's disease, Sjögren's syndrome, Graves' disease, insulin-dependent diabetes mellitus, and systemic lupus erythematosus.[10-16] Darrell[3] reports further evidence for an immune mechanism given the lymphocytic response within the corneal epithelial lesions, response to corticosteroids, and the chronicity of the disease.

Another potential etiology widely explored is a viral cause. During the same year Thygeson described his personal accounts of patients with TSPK, Braley[17] described one case of SPK from which a virus had been isolated. Jones[1] unsuccessfully attempted to isolate a virus from corneal scrapings but reported that the previously mentioned isolation of a virus by Braley had not been accomplished by controls and the methodology of using intracerebral inoculations of mouse brain was known to potentiate latent mouse viruses. Jones subsequently confirmed the benefit of corticosteroids that controlled the signs and symptoms in the majority of his clinical cases. In 1974, Lemp *et al.*[18] presented the first successful isolation of a virus by tissue culture. The testing was positive for varicella zoster virus. Lemp *et al.* reported that the exacerbations and remissions of TSPK were exhibitions of latent viral infections of the herpes group of viruses which might represent sporadic spread of varicella zoster virus from deeper corneal sensory ganglia. The chronicity of the epithelial lesions might be a hypersensitivity reaction. Additional research by Darrell and Iwamoto[3] failed to uncover reproducible viral isolation. Using modern molecular genetic techniques, Reinhard *et al.*[19] attempted to isolate VZV from patients with corneal epithelial lesions consistent with TSPK without success. Given the resemblance of corneal epithelial lesions of TSPK to that of adenoviral infections, Ostler *et al.*[20] described a case where adenovirus had been isolated from a patient diagnosed with TSPK. No other studies were found to duplicated these findings successfully.

The diagnosis of TSPK relies largely upon clinical presentation and response to corticosteroids. More recent research has been completed to describe the corneal lesions of TSPK via confocal microscopy. Watson *et al.*[21] noted irregular nerve fibers masked by significant haze located in the subepithelial nerve plexus just anterior to Bowman membrane in TSPK cases. Diffuse haze in the anterior stroma associated with areas of high reflectivity, microdots, and reflective bodies were also noted. Changes in keratocytes resulted in highly reflective nuclei and irregular size, orientation, and shape of cell bodies. The modifications found to be associated with the chronicity of TSPK were not seen in normal eyes and were also noted in areas without active lesions. Similarly, corresponding changes have been noted in patients with a variety of other corneal diseases as well as following laser corneal surgery. TSPK has traditionally been described as a disease of the corneal epithelium; however, confocal results indicate involvement of the anterior stroma as well. The images also suggest that both wound healing and cell death are occurring in the anterior stroma. Watson *et al.* postulated that cell death predominated during active disease whereas wound healing occured during times of quiescence.

A single clinical case of TSPK examined with *in vivo* confocal microscopy was reported by Cheng *et al.*[22] The superficial corneal epithelial cells showed a loss of intracellular adhesions, cell size enlargement and hyper-reflectivity all of which were speculated to represent signs of epithelial edema and desquamation. It is suggested that the white, punctate corneal lesions of TSPK represent desquamating epithelium as seen on biomicroscopy. Highly reflective linear filamentary lesions are hypothesized to represent devitalized epithelial cells. Cheng *et al.* suggest that monitoring with confocal microscopy may be advantageous in following patients for therapeutic improvement.

TSPK has been described as a self-limiting disorder with therapeutic treatment thought to speed resolution of signs and symptoms versus exacerbating the chronicity of the disease. Several methods of treatment have been proposed including non-preserved artificial tears, bland ophthalmic ointments, topical corticosteroids, topical cyclosporine A, topical antivirals, soft bandage contact lenses, and corneal surgeries. Treatment is only indicated in patients with significant blurred vision or irritation as therapeutic side effects may occur, which include glaucoma and cataracts.

Nagra *et al*[1] support a stepwise approach to medical treatment starting with low-dose steroids (*i.e.* fluorometholone 0.1% or similar low-dose steroid) in symptomatic patients with TSPK followed by a stronger steroid and then extended-wear bandage contact lenses or topical cyclosporine for severe cases. They also advocate for a slow steroid taper over the course of months with some patients requiring weekly or bi-weekly regular use to prevent symptoms. It has been speculated that patients who are not treated with corticosteroids might have a shorter disease course; however, further research is needed to validate this claim.

Topical cyclosporine A was introduced in 1994 as a potential treatment option for patients diagnosed with TSPK.[23] Cyclosporine reduces interleukin-2 production by T-lymphocytes.[24] Del Castillo *et al.* found that 2% topical application of cyclosporine A in

olive oil was sufficient to alleviate corneal lesions from TSPK in eight patients with a follow-up period from one to two years.[25] Dosages started at one drop q.i.d. for three months, one drop b.i.d. for one month and then discontinued. Reinhard and Sundmacher[26] published results of 52 eyes treated with topical cyclosporine A 2% for TSPK in 1997. The emulsion was compounded using Sandimmun and oleum arachidis. They started with one drop t.i.d. for one month, tapered to one drop b.i.d. for one month, one drop daily for one month, one drop every other day for three months, and then discontinued treatment at the conclusion of six months. Complete suppression of corneal lesions was achieved in 71.5% of adult cases and 40% of pediatric cases. Forty point five percent of the adult cases and 40% of the pediatric cases did not experience recurrence during the tapering period. Recurrence occurred at the b.i.d. dose, daily dose, every other day dose or within 6 weeks after cessation of therapy. Higher dosages up to five times per day did not show improved efficacy. The primary side effect noted was burning upon instillation of the medication. The support for such therapy stems from no risk for glaucoma, cataract, and surface disorders, including infection. Given therapy for such TSPK cases is often frequent over the course of months or years, safer therapies are warranted.

Bandage soft contact lenses have been cited to have beneficial effects on the symptoms of TSPK without altering the appearance of the corneal lesions. First described by Sundmacher *et al.*[27] in 1977, bandage contact lenses were reported to alleviate symptoms in three of ten patients. In 1979, Forstot and Binder[28] confirmed and published a report that three of their patients benefited from relief of symptoms with a bandage soft contact lens. Similar support for such treatment was advocated by Goldberg *et al.*[29] in a report published in 1980 describing relief of symptoms in four patients. Given the absence of corneal lesion resolution, it is merely thought that corneal exposure and friction are reduced to provide relief in symptoms.

Fite and Chodosh[30] reported a case of TSPK treated successfully with rimexolone 1% ophthalmic suspension, 1 gtt q.i.d. OU for one week and then tapered without exacerbation of corneal lesions. The patient underwent photorefractive keratectomy (PRK) for myopia; recurrence was noted outside the laser ablation zone suggesting that an inflammatory signal in the anterior stroma may be responsible for the pathogenesis of TSPK. The patient was treated with cyclosporine A 2% drops with rapid resolution of signs and symptoms. A similar case of a patient diagnosed with TSPK underwent PRK combined with phototherapeutic keratectomy (PTK) without recurrence of symptoms during an eight-month follow-up.[31] Seo *et al.*[32] refuted the claim described by Fite and Chodosh in 2000[30] reporting a case of TSPK recurrence within the ablation zone of a patient status post PRK. Netto *et al.*[33] reported a case of a patient previously diagnosed with TSPK who underwent PRK in the right eye and LASIK in the left eye for correction of myopia. Recurrence was noted in the left eye ten months after ablation with corneal lesions manifesting within the central cornea. Similarly, Jabbur and O'Brien[34] of the Wilmer Eye Institute reported a case of recurrent bilateral TSPK in a patient status post LASIK.

Conclusion

This case illustrates the challenges in the diagnosis and treatment of TSPK. The choice of corticosteroid therapy was based on previous successes published by Fite and Chodosh[30] with rimexolone 1% ophthalmic suspension where corneal lesions resolved quickly and improved patient comfort. Prolonged use of such medications, however, can pose an increased risk for glaucoma and cataracts. Compliance and patient education become an important issue in preventing such complications and avoiding disease recrudescence. For maintenance therapy, Restasis® 1% ophthalmic emulsion was used based on previous studies[25,26] published prior to the commercial launch of the current pharmaceutical drug. Compounded cyclosporine A 2% ophthalmic emulsion at a t.i.d. dosage was maintained as an alternative to the traditionally prescribed b.i.d dosage. This therapy may offer a safer alternative to chronic corticosteroid use.

Further research is warranted to elucidate the exact etiology of TSPK. Given the chronicity of treatment, great care must be taken to prevent long term complications of the current treatment alternatives for this disease. Where appropriate, lubricant eye drops alone may offer relief. A careful case history and analysis of the corneal signs as well as presenting symptoms will assist the clinician in making the correct diagnosis at presentation. Ancillary testing such as cornea culture or confocal biomicroscopy may also aid in correct diagnosis. Patients should be educated about the recurrent nature of TSPK, the need for continued follow-up, and the importance of therapy compliance.

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