A Title: Successful Off-Label Treatment of Limbal Vernal Keratoconjunctivitis (VKC) with Tacrolimus

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Abstract: A 10 year old male who recently emigrated from a country endemic for trachoma presents with Limbal vernal keratoconjunctivitis (VKC). This case highlights the variable presentations of VKC and efficacy of treatment with Tacrolimus.

Outline:

I. Case History
   a. 10 year old African male. Emigrated from Mali 1 year ago.
   b. Complains of redness OU since age 3. Redness has become intermittent over the past 3 months but worsening and is associated with mucus. Symptoms were constant in Mali, but improves in the winter months in the US.
   c. Patient has no other significant ocular history
   d. Medical history:
      i. Erythema Multiforme
      ii. Positive PPD 9 months earlier; did not finish course of Isoniazid due to an allergic reaction
   e. No current Medication

II. Pertinent findings
   a. Uncorrected VA OD: 20/20, OS: 20/20
   b. Pupils, EOMS, CVF full
   c. Anterior segment:
      i. Lashes are clear
      ii. Bulbar conjunctiva:
         1. OU: Injection
         2. OU: Interpalpebral gelatinous limbal nodules
      iii. Palpebral conjunctiva:
         1. OU: 2+ papillary reaction
         2. OS: subtle scar inferior temporal to caruncle
      iv. Cornea: clear OU (-) scarring
      v. Lens: clear OU
   d. Posterior segment: unremarkable OU

III. Ancillary Testing
   a. External Photodocumentation
   b. Chlamydia trachomatis viral culture

IV. Differentials
   a. Vernal keratoconjunctivitis
   b. Chlamydia trachomatis conjunctivitis
   c. Atopic keratoconjunctivitis
   d. Bacterial conjunctivitis
   e. Seasonal allergic conjunctivitis
   f. Viral conjunctivitis
   g. Perennial allergic conjunctivitis
V. Diagnosis and Discussion

a. Diagnosed with vernal keratoconjunctivitis (VKC)
   i. VKC is a bilateral, chronic inflammation of the conjunctiva
   ii. Onset usually occurring in the first decade of life and usually resolves around puberty (this patient was 10 years old)
      1. Initial presentation usually between 1 to 22 years old
      2. Resolution typically seen between the ages of 8 and 22
   iii. VKC persists throughout the year, worsens during the spring
   iv. Most common and most severe in hot, arid environments such as the Mediterranean basin, West Africa (this patient is from Mali), and the Indian subcontinent
   v. Symptoms include intense itching, tearing, mucous secretions, blepharospasm, redness and photophobia
   vi. Divided into 3 subtypes: limbal, palpebral, and mixed
      1. Limbal:
         a. Elevated gelatinous nodules, papillae, Horner-Trantas’ dots surrounding the limbus
            i. This patient presented with limbal nodules without the classic cobblestone papillae
            ii. Limbal VKC is more often seen in patients of African or Asian descent and those who have migrated to more temperate locales which is consistent with this patient
            iii. Atypical presentation: Limbal nodules were located in the interpalpebral area in this patient when typically they are located superior
            iv. Disease severity seems milder in limbal VKC
      2. Palpebral:
         a. Classic giant papilla upper tarsal conjunctiva
      3. Mixed:
         a. Presents with findings of both limbal and palpebral
   vii. Corneal complications
      1. Superficial punctate keratitis, abrasion, shield ulcers, keratoconus, pseudogerontoxon, and corneal opacification
      2. No corneal complications were exhibited in this patient
   viii. Risk factors include personal or family history of atopy (allergic rhinitis, atopic dermatitis or asthma)
      1. Not present in this patient
b. Differential diagnoses
   i. Chlamydia trachomatis conjunctivitis
      1. Top differential due to patient emigration from endemic country
         a. Geography of VKC disease prevalence overlaps with the distribution of trachoma, so patients will often have these two eye diseases simultaneously - Mali is endemic for both conditions
      2. Ruled out by negative culture
      3. Presentation not typical of trachoma
         a. No presence of follicles or scarring on superior palpebral conjunctiva, no Herbert’s pits
   ii. Atopic keratoconjunctivitis (AKC)
      1. Symptoms and signs were consistent with AKC, but AKC usually has a peak incidence of ages 30 to 50
iii. Bacterial conjunctivitis/ Seasonal allergic conjunctivitis/ Perennial allergic conjunctivitis
1. Unlikely - limbal findings are not characteristic of these conditions

iv. Viral conjunctivitis
1. Unlikely since patient had limbal findings and no follicles

VI. Treatment and Management
a. Treatment options for VKC include:
   i. Cold compresses, artificial tears, ocular corticosteroids, ocular mast cell stabilizers, antihistamine/ mast cell stabilizer combo drops, cyclosporine, mitomycin C, surgical excision for giant papillae, cryotherapy, amniotic membrane, NSAID

   1. Corticosteroids are first line therapy in moderate and severe cases
      a. Typically unsatisfactory results with topical antihistamines, mast cell stabilizers, and NSAIDs alone
      b. Steroids are fast acting potent anti-inflammatory agents
      c. Avoided in this patient due to concern with compliance and reliability with follow up
         i. Aimed to avoid adverse side effects of steroids such as glaucoma, cataracts, susceptibility to herpetic eye infection
         ii. VKC patients may have PSC cataract (14%) and glaucoma (2-7%) due to prolonged topical steroid use

   2. Immunomodulators
      a. Cyclosporine
         i. Inhibit T-cell activation and reduce inflammation
         ii. 0.05% cyclosporine emulsion was shown to be effective in AKC and VKC patient but failed to exhibit clinical efficacy in some steroid-dependent cases
         iii. High-concentration cyclosporine results in intense stinging sensation and blurred vision upon instillation, leading to poor compliance
      b. Tacrolimus
         i. Currently topical tacrolimus is FDA approved for atopic dermatitis, therefore off label for ophthalmic use
         ii. Tacrolimus is a nonsteroidal immune suppressant which inhibits calcineurin activity and histamine release from mast cells
         iii. According to one study, severe VKC responds promptly to topical 2% cyclosporine A and 1% tacrolimus ointment within 1 month of therapy and without significant side effects
         iv. Tacrolimus 0.1% is up to 100 times stronger than cyclosporine with less side effects
         v. Tacrolimus 0.1% ointment treatment in VKC showed significant improvement in signs and symptoms after 6 weeks of treatment but recurred in all patients who attempted to discontinue treatment
When comparing tacrolimus ophthalmic suspension 0.01%, 0.03%, and 0.1% showed stronger improvement and similar safety profile compared with 0.01% and 0.03%. (6)

b. Day 1 and 2
   i. Start tacrolimus 0.02% QID OU, then tapered to TID OU on one day follow up
   ii. No change in clinical signs or symptoms on 1 day follow up
   iii. External Photography on day 2
   iv. Chlamydia culture sent

c. Day 9
   i. Improved symptoms and flattened limbal nodules OU
   ii. Negative chlamydia cultures
   iii. Continue Tacrolimus 0.02% TID OU

d. Week 7
   i. No symptoms
   ii. Minimal papillary reaction, limbal nodules flattened and resolved
   iii. Taper tacrolimus 0.02% to BID OU
   iv. RTC 2 months

VII. Conclusion

a. VKC can have a variety of presentations and available treatment options
b. Atypical presentations should encourage the clinician to rule out other etiologies, in this case, chlamydia trachomatis conjunctivitis was a differential primarily due to patient demographics

c. Subtypes of VKC can be specific to patient demographics

d. Evidence is provided for safe and successful treatment of VKC by using topical tacrolimus solution to avoid serious side effects of topical steroids

e. Adequate follow up is necessary to ensure efficacy of treatment and monitor for recurrence which is common in this condition

VII. References: