Darier`s Disease: A corneal Conundrum

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Abstract: This case reviews the rare ocular complications of Darier's Disease and also suggests novel therapeutic approach for a better management of poorly responsive corneal lesions.

I. Case History
   A. 47 year old, Caucasian female
   B. Chief complaint: Follow up on presumed herpes simplex (HSV) keratitis OD
      1. Onset 1 week prior, when checked into ER
      2. Patient reports she had redness, pain & lower lid swelling OD at that time
      3. Notes improvement in symptoms
      4. Treated with oral Acyclovir, erythromycin ointment, Viroptic and Gentamicin drops for a week
   C. Ocular History
      1. HSV keratitis (2005, 2015) OS
      2. Recurrent corneal ulcer OS
      3. Marginal keratitis OU
      4. Glaucoma suspect secondary to large C/D Ratio
      5. Mild nonexudative age-related macular degeneration OU
   D. Medical History
      1. Darier's disease (DD)
      2. Irritable bowel syndrome
      3. Migraine
      4. Vitamin D deficiency
      5. Hyperlipidemia
      6. Post-traumatic stress disorder
      7. Gastroesophageal reflux disease
   E. Medications
      1. Vitamin D3 2000 IU BID
      2. Erythromycin 0.5% ointment QHS OU
      3. Gentamicin sulfate 0.3 % sol. QID OU
      4. Ocuvite Preservison AREDS II, 2 softgels/day PO
      5. Artificial Tears – Polyvinyl Alcohol 1.4 % QID OU
      6. Cyancobalamin 1000mcg QDay
   F. Adverse Reactions
      1. Sumatriptan
      2. Hydrocodone
      3. Omeprazole
G. Family ocular history
   1. Insignificant

H. Family medical history
   1. (-) Darier’s Disease

I. Social history
   1. (+) tobacco use
   2. (-) alcohol or recreational drug abuse

II. Pertinent Findings
   A. Clinical
      1. Ocular motilities and confrontation fields: Unremarkable
      2. Cover test: Ortho’, Ortho
      3. Color vision (HRR plates): normal OU
      4. Pupils: PERL OU, (-) APD
      5. IOP (GAT): 12/13 mmHg at 13:57
      6. Cotton wisp test: (-) OU
      7. (-) Preauricular lymphadenopathy

     8. Anterior Segment:
        a. Non-ulcerative warty hyperkeratotic plaque, upper eyelid OD
        b. Madarosis and seborrhea-like debris, eyelid margins OU
        c. Cicatricial changes and several small follicles OU
        d. OD: Trace scattered conjunctival injection, trace scattered punctate keratitis, corneal scar tissue inferior temporally (-) fluorescein staining
        e. OS: Infiltrate sized 1.0 x 1.0 mm with trace overlying epithelial defect superior nasally with 1+ adjacent sectoral conjunctival injection.
        f. Mild sup-nasal epithelial irregularities similar to microcystic edema OS
        g. Peripheral epithelial nebular opacities without fluorescein staining OS
        h. Anterior chamber was deep and quiet OU

     I. Anterior chamber angles: 1/4 by VonHerrick

   9. Posterior Segment
      a. Lens: 1+ nuclear sclerotic cataract OU
      b. Vitreous: Mild syneresis OU
      c. ONH: Normal size with enlarged cupping ratio of 0.70/0.70 OU
      d. Macula: More than five 63-micron hard drusens OU
      e. Vasculature: Normal, A/V 2/3 OU
      f. Retinal periphery: Intact OU

   B. Imaging
      1. Optical coherence tomography (OCT):
         a. ONH: (-) thinning OD, (+) thinning sup-nasal OS
         b. Anterior segment: CCT 578/580 microns OD, OS
      2. Anterior segment photos taken
      3. Fundus photos taken

   C. Lab work: To rule out adult inclusion conjunctivitis
      1. Chlamydiazyme test
2. IgG titers to *chlamydia*

### III. Differential Diagnosis

**A. Primary: Ocular complications of DD**
1. Recurrent marginal keratitis
2. Corneal epithelial lesions
3. Recurrent HSV keratitis

**B. Secondary:**
1. Herpes zoster (HZV) keratitis
2. Adult inclusion conjunctivitis
3. Neurotrophic ulcer

*Marginal keratitis* presents with singular or multiple peripheral sterile infiltrate with sectoral conjunctival injection. Scaly lid margins 2 to hyperkeratosis in DD causes chronic blepharitis. *Corneal epithelial lesions* in DD are caused by defective local immune responses on top of impaired desmosome function. Loss of epithelial barrier makes the cornea more susceptible to infections such as recurrent HSV.

### IV. Diagnosis and Discussion

**A. DD is a rare (4 in 1 million) AD genodermatosis characterized by scaling papules.**\(^{1,2}\)

**B. Prevalence:**
1. 1:36,000 in north east England and 1:100,000 in Denmark
2. The largest pedigree in the US is from southern Pennsylvania and upstate NY.\(^1\)

**C. Precipitating factors:**\(^{2,3}\)
1. Mechanical trauma
2. Heat/ humidity/ UVB light during summer
3. Oral lithium, Azathioprine, Diltiazem

**D. Histopathology:**\(^{1-3}\)
1. Premature keratinization (dyskeratosis)
2. Hyperkeratosis
3. Suprabasal clefts in the epithelium
4. Intra and extracellular edema of all corneal epithelial layers
5. Presence of dendritic cell in corneal epithelium (Immune activity model)

**E. Etiology:**\(^{1-3}\)
1. Mutation in the ATP2A2 gene on chromosome 12 results in abnormal function of endoplasmic reticulum Ca\(^{2+}\) ATPase only on skin and mucosa.
2. Elevated cytosolic Ca\(^{2+}\) level propagates an abnormal desmosome tonofilament complex leading to the loss of cellular adhesion and apoptosis.

**F. Ocular manifestations:**\(^{1-3}\)
1. Eyelid: Lesions parallel the cutaneous findings
   a. Warty hyperkeratotic plaques; Rarely similar to BCC lesions
b. Scaly hyperkeratotic lid margins result in chronic blepharitis and marginal keratitis.
c. Trichiasis and madarosis

2. Conjunctiva: Follicles, cicatricial changes in mucocutaneous junction
   a. Unchecked chronic inflammation:
      I. Anomalous marginal keratinocytes: Lack of regulating cytokines release
      II. Chronic blepharitis
   b. Increased sensitivity of conjunctival nonkeratinized epithelium to decreased number of tonofilaments in the disease process

3. Cornea: Different from cutaneous lesions
   a. Cornea is not a keratinized epithelium
   b. Peripheral nebular opacities
   c. Recurrent corneal ulcer
   d. Central epithelial irregularities/edema.

   Ocular toxicology model:  
   a. Elevated Ca\(^{2+}\) in cornea activates phospholipase and releases arachidonic acid (AA) from membrane phospholipids.
   b. AA is metabolized to PGI\(_2\) initiating inflammatory cascade.
   c. Prednisolone acetate (1% topical, QID x 2 Ws): Does not improve nebular opacities nor central epithelial irregularities

   Immune activity model:  
   a. Dendritic cell impairment results in a defective local immune response & an increased CD4+ T lymphocytes
   b. CD4+ T cells produce interferon-\(\delta\) (IFN-\(\delta\)) resulting in corneal epithelial apoptosis.

4. Associated conditions:
   a. Concomitant retinitis pigmentosa in 2 cases
   b. Possibility of proximity of their genes loci.

V. Treatment and Management

A. Systemic therapy
   1. Retinoids
      a. Most effective in flattening the hyperkeratotic papules.
      b. Does not alter the corneal epithelial lesions.
      c. Side effects: Mucosal dryness, photosensitivity, teratogenicity
   2. Cyclosporines
      a. Up-and-coming approach in treatment of recalcitrant DD
      b. Inhibit proliferation & activation of CD4+ T lymphocytes by suppressing, IFN-\(\delta\), cytokines IL-2, and IL-4
B. Topical therapy
   1. Corticosteroids
   2. 5-fluorouracil
C. Photodynamic therapy.
D. Tx of marginal keratitis (MK):
   1. Tobradex ophthalmic solution (0.3% tobramycin and 0.1% dexamethasone) QID OS
   2. lid hygiene via lid scrub only. Stop using warm compress as it exacerbate the outbreak of DD
   3. Scheduled to follow-up in 4 days
F. Tx of Recurrent HSV keratitis:
   1. Maintenance dose of Acyclovir 400mg tab PO BID
G. Follow-up #1:
   1. BCVA: 20/20 OD, 20/25 OS
   2. IOP (GAT): 13/13 mmHg at 14:18
   3. Infiltrate 2° to MK OS: resolved to a 0.25 mm round infiltrate, (-) epithelial defect or sectoral conjunctival injection.
      a. Hx of recurrent MK
      b. Tx: Tapered Tobradex OS to QID x 2 days, BID x 2 days Qday x 2 days, then D/C.
   5. No improvement of sup-nasal epithelial irregularities OS.
      a. Restasis (cyclosporine A) 1% emulsion BID OU.
      b. She was asked to return in two weeks.
H. Follow-up #2:
   1. BCVA: 20/20 OD, 20/20 OS
   2. IOP (GAT): 12/12 mmHg at 14:18
   3. Infiltrate 2° to MK OS: resolved, (-) epithelial defect or sectoral conjunctival injection.
   5. Sup-nasal epithelial irregularities OS, resolved.
      a. Restasis (cyclosporine A) 1% emulsion BID OU.
      b. She was asked to return in two weeks.
      Will monitor cornea for epithelial irregularities OU at the upcoming follow-up visits (4, 6 weeks after Restasis therapy initiation)
      c. Follow-up visit in 4 months for a completion of the glaucoma work-up
Restasis (cyclosporine A) ophthalmic emulsion14-16
   1. Has anti-inflammatory, immunomodulatory pharmacokinetics.
   2. Causes a decrease in the number of CD4+ T lymphocytes
3. Tx effect can be observed as early as 1-2 weeks of Tx, contrary to general belief that Restasis works 4-6 weeks after treatment initiation.

IV. Conclusion
A. There is an increased risk of ocular complications in keratosis follicularis due to impaired functionality of corneal epithelium desmosomes and defected local immunity.
B. The natural history of DD fluctuates in severity, so it necessitates a maintenance therapeutic approach to subside it’s devastating corneal recurrences.
C. Needs novel therapeutic approach for a better management of poorly responsive corneal lesions
   1. Cyclosporine A inhibits proliferation and activation of CD4+ T lymphocyte and also decreases their numbers, targeting the disease etiopathogenesis
   2. Many studies report successful treatment of conditions with similar immunomodulatory etiology applying Restasis.
D. Further studies are needed to elucidate the prolong impact of cyclosporine in recurrence rate of this complicated disease.
E. Clinical Pearls: It is more effective to address etiopathogenesis rather than symptomatically treating ocular conditions.

Bibliography


