CASE REPORT

Recurrent presumed herpes simplex keratitis and episcleritis in keratosis follicularis (Darier's disease)

Meera Radia, Michael James Gilhooley, Chris Panos, Charles Claoué

Department of Ophthalmology,
Queen's Hospital, Romford,
London, UK

Correspondence to
Dr Michael James Gilhooley,
mjg93@doctors.org.uk

Accepted 2 July 2015

SUMMARY

Keratosis follicularis (Darier's disease) is an autosomal dominant dermatological disorder characterised by abnormal epidermal differentiation and loss of normal cell-to-cell adhesion. Cardinal features include diffuse hyperkeratotic warty papules with scaly plaques in seborrhoeic regions with associated mucous membrane changes. Darier's disease is rare (prevalence 2.7 in 100 000), with few ocular sequelae reported: commonly dry eye with or without Sjögren's syndrome. This is the first report, to the best of our knowledge, to describe a case of recurrent herpes simplex virus (HSV) keratitis and episcleritis in a 47-year-old man suffering from Darier's disease. The patient's condition predisposed him towards developing ocular complications due to several factors: impaired desmosome function leading to poor cell-to-cell adhesion in the corneal epithelium, dry eye and HSV invasion of inflamed periocular skin presumably combining to allow viral colonisation of a poorly protected cornea.

BACKGROUND

Keratosis follicularis (Darier's disease), is an autosomal dominant disorder of the epidermis characterised by abnormal epidermal differentiation and loss of normal cell-to-cell adhesion.¹ Cardinal features on clinical examination of the skin include diffuse hyperkeratotic and warty papules with scaly plaques in the seborrhoeic regions along with mucous membrane changes. Characteristic histological findings include focal clefting of dyskeratotic round epidermal cells on light microscopy, known as 'corps ronds'.² Darier's disease is rare (prevalence 2.7 in 100 000)³ and ocular sequelae have been reported in a few cases. This is the first report, to the best of our knowledge, to describe a case of recurrent herpes simplex virus (HSV) keratitis and episcleritis in Darier's disease. The case illustrates several useful learning points for the management of keratitis in patients with a weakened corneal epithelium for any reason (not just Darier's).

CASE PRESENTATION

A 47-year-old man with no ophthalmic history and a confirmed diagnosis of keratosis follicularis was referred to our ophthalmic clinic during an inpatient dermatology admission for Darier's herpeticum with secondary staphylococcal cellulitis in November 2012.

The presenting ophthalmic symptom was of bilateral conjunctival injection, increasing pain and blurred vision (logMAR acuity (VA) R=0.24 and L=0.10) (figures 1 and 2). Slit lamp biomicroscopy

Figure 1 Initial presentation of Darier's herpeticum, December 2013: multiple pustules in seborrhoeic distribution.

revealed hyperkeratotic lesions contiguous with the patient's forehead rash extending over the eyelids without frank cellulitis. In addition, there was a small right-sided corneal ulcer with adjacent subconjunctival haemorrhage and mild, bilateral episcleritis. The tear break up time was shortened (<5 s), with a low tear meniscus and punctate staining of the cornea corresponding to clinically moderate dry eye.⁴ There was no history of contact lens use.

Figure 2 Right eye on presentation: global subconjunctival haemorrhage. Note surrounding orbital *Staphylococcus aureus* crusting.

CrossMark

To cite: Radia M, Gilhooley MJ, Panos C, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210772

INVESTIGATIONS

Corneal scrapes were taken and empirical treatment started with g. ofloxacin (initially 2 then 4 hourly), as clinically there was a suspicion of microbial keratitis. Oc. acyclovir four times a day was also started to complement the systemic acyclovir and flucloxacillin required for the patient's dermatological manifestation.

The clinical picture improved at reviews over the following 2 weeks, at which point examination in early December 2012 revealed a VA of right (R)=0.12 and left (L)=0.04 with a clear cornea but thickened, irregular right conjunctiva without papillae, follicles, subconjunctival haemorrhage or episcleritis. Oc. lacrilube was started prn in place of Oc. acyclovir, and g. ofloxacin was tapered and stopped. The corneal scrapes showed no organism on Gram stain or culture growth after 2 weeks.

DIFFERENTIAL DIAGNOSIS

In March 2013, a recurrence of Darier's herpeticum occurred, manifesting again as a pustular facial eruption; this time, a clinically typical corneal dendritic ulcer on the right was seen associated with limbal injection. The clearer clinical picture and earlier ophthalmic examination in this second episode narrowed our differential greatly—the impression was now of epithelial herpes simplex keratitis rather than an atypical bacterial keratitis. VA was good on this presentation (R=0.04 and L=0.02) and the flare was managed with acyclovir and flucloxacillin orally for the dermatological manifestations with Oc. chloramphenicol four times a day as prophylaxis and Oc. acyclovir five times daily for 10 days for the herpetic keratitis.

TREATMENT

Three weeks later, in early April 2013, the patient returned with continued right eye pain and injection. VA was R=0.12 and L=0.04. Slit lamp biomicroscopy revealed severe, sectoral, superficial injection, with no corneal or scleral involvement. He was treated for severe right eye episcleritis with flurbiprofen 100 mg orally two times a day, g. dexamethasone 0.1% 2 hourly to the right eye and prophylactic acyclovir 400 mg orally two times a day. Symptomatically, he improved over 2 weeks, so at review, flurbiprofen could be stopped and dexamethasone tapered, as the episcleritis had resolved on examination. Long-term prophylactic acyclovir orally was recommended given the patient's recurrences of herpetic skin and eye disease, and started in mid April 2013.

OUTCOME AND FOLLOW-UP

This relief was short lived and in July 2013, a further, less severe episode of right episcleritis occurred, initially contained with lubricants. Two weeks later, however, a full recurrence of Darier's herpeticum with herpetic keratitis prompted representation with a painful red, weeping right eye. VA was R=0.10 and L=0.00. Oc. acyclovir (five times daily for 10 days) was started with g. dexamethasone 0.1% 2 hourly, tapered over the following 2 months to alternate days as symptoms resolved by October 2013. This treatment was continued until January 2014, before being withdrawn without event. Prophylactic acyclovir orally has been continued and there have been no further episodes with 12 months of follow-up.

DISCUSSION

Darier's disease is caused by mutations in the ATP2A2 gene (12q23-24.1), which encodes the sarcoplasmic/endoplasmic reticulum ATP-dependent calcium pump (SERCA2).¹ Loss of function in this gene leads to impaired desmosome function,

especially in ectodermal tissues. Clinically, the condition rarely remits but can be controlled with acitretin orally.⁵

Cutaneous herpetic infections with or without secondary bacterial/fungal overgrowth (usually *Staphylococcus aureus*) in Darier's disease, as described here, are widely reported and are thought to be opportunistic: the result of an epithelium weakened by poor desmosome function in combination with a mild inflammatory insult (eg, hyperhydrosis, trauma, infection or sun exposure).⁶⁻⁸

Ocular involvement is relatively rare, commonly manifesting as dry eye and occasionally Sjögren's syndrome secondary to poor function of ectodermal adnexal tissues including conjunctiva, lacrimal and tarsal glands.⁹ This poor tear film combined with a similarly weakened epithelium presumably leave the cornea vulnerable to recurrent microbial and herpetic keratitis,⁵ even without the use of contact lenses (which are known to increase the risk of microbial keratitis).

Other corneal findings previously described, but not found in this case, include arcus lipoides-like opacifications, asymptomatic nebular dot-like opacities of the peripheral corneal epithelium and central epithelial surface irregularities.⁵⁻⁷ The skin of the eyelids can also be affected by the skin changes described above. Associations with retinitis pigmentosa, suboptimal dark adaptation and postcataract extraction staphylococcal endophthalmitis have additionally been reported.⁹⁻¹¹

Episcleritis is a very common ocular condition, which, although usually idiopathic, can be associated with systemic disease in around 30% of cases: including herpetic infections. This in itself may have predisposed the patient to recurrent episcleritis, however, the context of his Darier's disease cannot be ignored. Certainly, a combination of weak cell-to-cell adhesion in a pro-inflammatory environment may have again led to a self-perpetuating inflammatory cycle in the episclera as well as on the skin and cornea. As reported clinically, this could only be broken with pharmacological intervention in the form of topical steroid therapy.

In conclusion, this case of a 47-year-old man presenting with recurrent HSV epithelial keratitis and episcleritis in the context of active keratosis follicularis is, to the best of our knowledge, unique in the literature.

Learning points

- ▶ Darier's disease is a rare genetic disease altering cell-to-cell adhesion in ectodermal tissue.
- ▶ Darier's disease may be complicated by herpetic infections both on the skin and eye.
- ▶ Prompt examination of painful red eyes in the context of herpetic skin infection is important to optimise management.
- ▶ Where there is doubt, corneal scrapes should be sent for culture at the first presentation and empirical antimicrobial therapy started with expedient clinical review.

Contributors MR and MJG collated the clinical case from notes, prepared first draft of the manuscript. CC, CP and MJG were involved with the clinical care of the patient. All the authors reviewed the manuscript critically for important intellectual content before submission.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Puri N. A clinical and histopathological study of Darier's disease. *J Pak Assoc Dermatol* 2011;21:230–4.
- 2 Ringpfeil F, Raus A, DiGiovanna JJ, *et al.* Darier disease—novel mutations in ATP2A2 and genotype-phenotype correlation. *Exp Dermatol* 2001;10:19–27.
- 3 Berg D, Bassett AS. Darier's disease: current understanding of pathogenesis and future role of genetic studies. *Int J Dermatol* 1993;32:397–400.
- 4 Baudouin C, Bron A, Dogru M, *et al.* Report of the International Dry Eye Workshop (DEWS). *Ocular Surf* 2007;5:65–204.
- 5 Mielke J, Grub M, Besch D, *et al.* Recurrent corneal ulcerations with perforation in keratosis follicularis (Darier-White disease). *Br J Ophthalmol* 2002;86:1187–95.
- 6 Daicker B. Ocular involvement in keratosis follicularis associated with retinitis pigmentosa. *Ophthalmologica* 1995;209:47–51.
- 7 Blackman HJ, Rodriguez MM, Peck G. Corneal epithelial lesions in keratosis follicularis (Darier's disease). *Ophthalmology* 1980;87:931–43.
- 8 Macsai MS, Agarwal S. Staphylococcal endophthalmitis following cataract extraction in a patient with Darier's disease. *Cornea* 1998;17:335–7.
- 9 Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol* 1992;27:40–50.
- 10 Yang J, Kim K, Lee G, *et al.* Eczema herpeticum in Darier's disease. *Ann Dermatol* 1998;10:32–4.
- 11 Liaw F, Huang C, Hsueh J, *et al.* Eczema herpeticum: a medical emergency. *Can Fam Physician* 2012;58:1358–61.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow