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In-vivo confocal microscopy of the cornea in Darier-White disease

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Darier-White disease (also known as Darier's disease or keratosis follicularis spinulosa decalvans) is a rare, dominantly-inherited skin disorder characterized by firm, scaly cutaneous papules and plaques distributed over various regions of the body.¹ Histopathologic and electron microscopic studies of biopsied skin specimens have revealed a loss of cell-to-cell adhesion and abnormal differentiation of the epidermis.¹ Ocular involvement in Darier-White disease has been observed, with eyelid and corneal abnormalities being reported.²⁻⁵ To date, however, examination of corneal abnormalities in Darier-White disease has been limited to slit lamp observation²⁻⁵ and microscopic examination of superficial, peripheral biopsy samples in cases with confirmed corneal abnormalities.^{2,3}

In this report we use in-vivo confocal microscopy to describe the general corneal morphological features present in five members (4 affected and 1 unaffected) of a 5-generation, 32-member Swedish family with Darier-White disease, 15 of whom are affected. All five individuals had good vision without ocular symptoms or history of contact lens wear, and no corneal abnormalities were apparent upon slit lamp examination. Using in-vivo laser-scanning confocal microscopy (HRT3-RCM; Heidelberg Engineering, Heidelberg, Germany), irregularities in the epithelium, nerves, and anterior stroma were observed in all affected individuals. Documenting corneal abnormalities, which on occasion have been associated with severe photophobia² and corneal clouding³, may be useful in elucidating the pathogenesis of corneal changes in this rare disease.

Case 1. In-vivo confocal microscopy in the central cornea of a 67-year-old affected woman (MT) revealed basal epithelial cells with an abnormally dark cytoplasm and reflective nuclei, invading the intermediate epithelial layers (Fig 1). Oblique sections indicated an indistinct demarcation between basal epithelium and Bowman's membrane, while thick, beaded, subbasal nerve fibers invaded the epithelial compartment. Numerous reflective, punctate deposits were observed in the anterior stroma.

Case 2. In a 41-year-old affected daughter of MT, in-vivo confocal microscopy revealed a basal epithelial cell layer with abnormally reflective nuclei physically separated from Bowman's layer and folded upwards into the wing cell layers (Fig 2). Thick, beaded, reflective subbasal nerves were observed, however they did not appear to invade the epithelium. Punctate deposits were observed in the anterior stroma.

Case 3. A 33-year-old affected daughter of MT exhibited small intercellular inclusions throughout the epithelium (Fig 3). Beaded, abnormally tortuous subbasal nerves were interspersed among basal and wing cells, with regions of abnormally reflective cytoplasm or cell nuclei appearing to be demarcated by the subbasal nerves, as in Case 1. In the underlying subbasal plexus, nerves were thickened. As in Case 1, punctate deposits were present in the anterior stroma, while oblique sections revealed discontinuities in the basal and wing cell layers. No visible corneal changes were noted upon slit lamp examination, however, skin lesions and plaque-like material were observed in the eyelid margin and eyelids.

Case 4. A 44-year-old unaffected daughter of MT exhibited intercellular inclusions throughout the epithelium as in Case 3. Thickened subbasal nerves were present, while the remainder of the cornea appeared normal.

Case 5. A 51-year-old sister of MT exhibited intercellular epithelial inclusions as in Case 3, and fragmented 'islands' of wing and basal epithelial cells with either an abnormally bright cytoplasm or with dark cytoplasm and indistinct cell borders (Fig 4). Subbasal nerves were tortuous and a large population of dendritic cells was present. Oblique sections revealed discontinuities in the various epithelial cell layers and punctate deposits in the anterior stroma.

Comment

Previously reported slit lamp findings of corneal involvement in Darier-White disease have included punctate epithelial opacities,^{2,4} peripheral intraepithelial opacities,³ faint lines of central epithelial irregularity,³ and prominent corneal nerves.² Histopathological and ultrastructural analysis of biopsy samples revealed intracellular and extracellular epithelial edema in basal and wing cell layers, separation of basal epithelium from Bowman's layer, a deficit of desmosomes and hemidesmosomes at the basement membrane, cellular debris and a 'granular substance' below the epithelium, and an almost total absence of epithelial basement membrane.^{2,3}

Abnormalities in the cytoplasm, nuclei, and homogeneity of epithelial wing and basal cells as well as morphology consistent with an absent or abnormal epithelial basement membrane were prominent corneal features of Darier-White disease observed by in-vivo confocal microscopy. These findings are suggestive of abnormal cellular adhesion and differentiation, which are hallmarks of the condition. The punctate anterior stromal deposits (reminiscent of the 'microdot' deposits seen in long-term contact lens users) may correspond to the cellular debris or granular substance observed by electron microscopy³; however, the origin and composition of this substance remains unknown.

Corneal subbasal nerve involvement was noted in the present family. Perpendicular penetration of thick, beaded subbasal nerve fiber bundles into the epithelium suggests that in the absence of an intact basement membrane (providing both a physical and biochemical barrier between epithelium and stroma), thicker subbasal nerve fiber bundles may proceed unimpeded into the more superficial wing cell layers before branching into thinner nerve strands. Additionally, nerves observed within the epithelium appeared to follow a course adjacent to areas of basal and wing cells with abnormally reflective cytoplasm; extracellular edema or a breakdown of intercellular adhesion may have provided a further path of decreased resistance to direct aberrant nerve growth. Dendritic cells in the basal epithelium appeared in two of four affected individuals, indicating possible immune activity. As the small, intercellular epithelial deposits observed in the present family were not visible with the slit lamp, it is unclear whether these corresponded to the 'punctate epithelial opacities' observed by others.^{2,4} Interestingly, the deposits were also found in the unaffected individual. It is suspected that these 'deposits' may be dendritic cells additionally present within the wing cell layers, however, it is unclear whether their presence is disease-related, as a sparse distribution of dendritic cells is sometimes observed in the central cornea of normal, healthy individuals. Notably, we did not detect peripheral corneal opacities or the 'cornea verticillata' observed by Blackman et al.³; nevertheless, the epithelial edema and abnormal cellular adhesion they found in biopsy samples is consistent with the (somewhat milder) epithelial pathology and lesions observed within the central and peripheral cornea in the present family.

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Figure legends

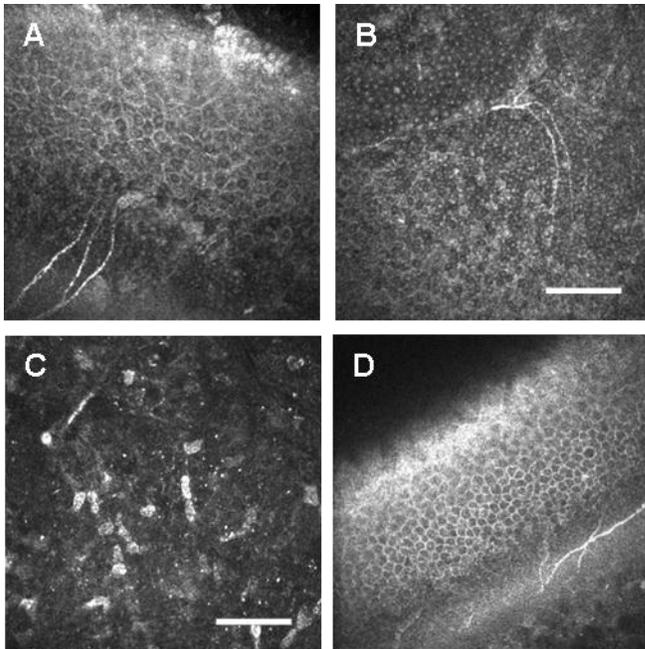


Figure 1. Corneal images in MT. A, Oblique section of epithelium with abnormal basal cells and epithelial invasion by subbasal nerves. B, Abnormally tortuous, branching subbasal nerve in the basal/wing cell layer (depth 39µm from epithelial surface). C, Bright, punctate anterior stromal deposits (depth 69µm). D, epithelium of a normal, healthy 60-year-old male subject. Scale bar = 100µm.

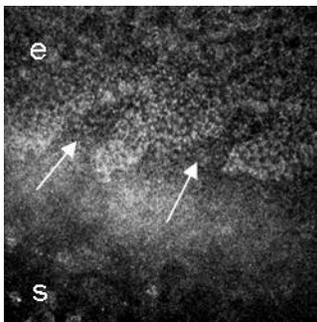


Figure 2. Oblique section of corneal epithelium (e) and anterior stroma (s) in a daughter of MT. Basal epithelium is separated from Bowman's layer and protrudes upwards into the epithelium (arrows).

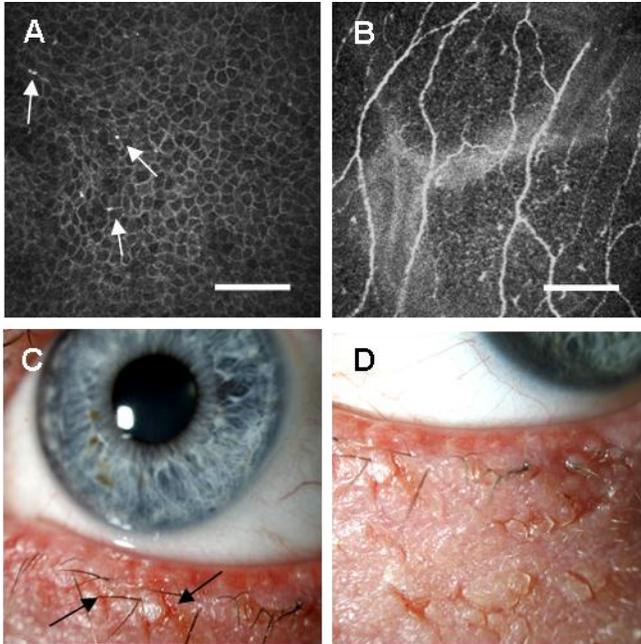


Figure 3. Daughter of MT. A, bright, intercellular deposits (arrows) in epithelial wing cell layer (depth 36 μ m). B, subbasal plexus with prominent nerves (depth 57 μ m). C, slit lamp photograph without visible corneal changes but with lesions at the eyelid margin. D, keratotic lesions of the lower eyelid. Scale bar = 100 μ m.

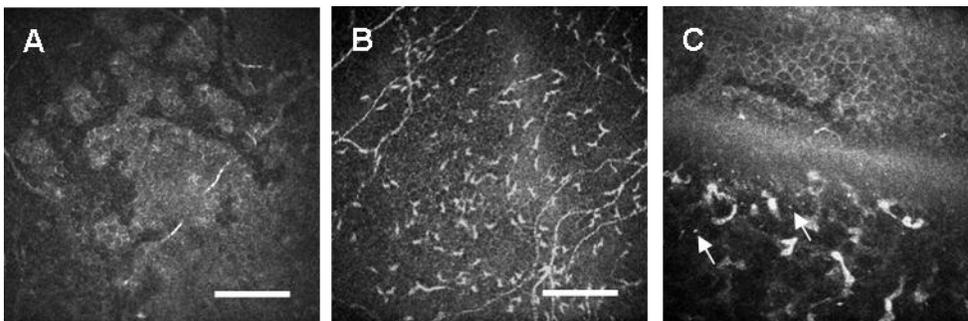


Figure 4. Corneal microstructure in a sister of MT. A, fragmented basal and wing cell layers with beaded subbasal nerves present (depth 33 μ m). B, subbasal nerve plexus with tortuous nerves and dendritic cells (depth 45 μ m). C, oblique section indicating epithelial lesions (dark areas). Note the punctate anterior stromal deposits (arrows). Scale bar = 100 μ m.