In Vivo Confocal Microscopy of the Cornea in Darier-White Disease

Darier-White disease (also known as Darier 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.\(^2,3\) To date, however, examination of corneal abnormalities in Darier-White disease has been limited to slitlamp observation\(^2,3\) and microscopic examination of superficial peripheral biopsy samples in cases with confirmed corneal abnormalities.\(^2,3\)

In this article we use in vivo confocal microscopy to describe the general corneal morphological features present in 5 members (4 affected and 1 unaffected) of a 5-generation, 32-member, Swedish family with Darier-White disease, 15 of whom are affected. All 5 individuals had good vision without ocular symptoms or history of contact lens wear, and no corneal abnormalities were apparent on slitlamp 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 that, on occasion, have been associated with severe photophobia\(^2\) and corneal clouding\(^2\) may be useful in elucidating the pathogenesis of corneal changes in this rare disease.

**Report of Cases.** Case 1. In vivo confocal microscopy in the central cornea of a 67-year-old affected woman revealed basal epithelial cells with an abnormally dark cytoplasm and reflective nuclei invading the intermediate epithelial layers (Figure 1). Oblique sections indicated an indistinct demarcation between the basal epithelium and the Bowman layer 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 case 1, in vivo confocal microscopy revealed a basal epithelial cell layer with abnormally reflective nuclei physically separated from the Bowman layer and protrudes upward into the wing cell layers (Figure 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 case 1 exhibited small intercellular inclusions throughout the epithelium (Figure 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 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, peripheral intraepithelial opacities, faint lines of central epithelial irregularity, and prominent corneal nerves. Histopathological and ultrastructural analysis of biopsy samples revealed intracellular and extracellular epithelial edema in basal and wing cell layers, separation of basal epithelium from the Bowman 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.

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 micro dot deposits seen in long-term contact lens users) may correspond to the cellular debris or granular substance observed by electron microscopy; however, the origin and composition of this substance remains unknown.

Case 4. A 44-year-old unaffected daughter of case 1 exhibited intercellular epithelial inclusions, as in case 3, and fragmented islands of wing and basal epithelial cells with either an abnormally bright cytoplasm or a dark cytoplasm and indistinct cell borders (Figure 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.

Case 5. A 51-year-old sister of case 1 exhibited intercellular epithelial inclusions, as in case 3, and fragmented islands of wing and basal epithelial cells with either an abnormally bright cytoplasm or a dark cytoplasm and indistinct cell borders (Figure 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.

Figure 3. Daughter of case 1. A, Bright intercellular deposits (arrows) are seen in the epithelial wing cell layer (depth, 36 µm). B, Confocal microscopy shows subbasal plexus with prominent nerves (depth, 57 µm). C, Slitlamp photograph shows cornea without visible changes, but with lesions at the eyelid margin (arrows). D, Keratotic lesions of the lower eyelid are seen. Scale bars, 100 µm.

Figure 4. Corneal microstructure in a sister of case 1. A, Beaded, subbasal nerves are present in the fragmented basal and wing cell layers (depth, 33 µm). B, The subbasal nerve plexus contains tortuous nerves and dendritic cells (depth, 45 µm). C, Oblique section shows epithelial lesions (dark areas). Note, punctate anterior stromal deposits (arrows) are apparent. Scale bars, 100 µm.
Nerve fiber bundles may proceed unimpeded into the more superficial wing cell layers before branching into thinner nerve strands. Additionally, nerves observed in 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 2 of 4 affected individuals, indicating possible immune activity. As the small intercellular epithelial deposits observed in the present family were not visible with the slitlamp, it is unclear whether these corresponded to the “punctate epithelial opacities” observed by others. 

Interestingly, the deposits were also found in the unaffected individual. 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 healthy individuals.

Notably, we did not detect peripheral corneal opacities or the “cornea verticillata” observed by Blackman et al; nevertheless, the epithelial edema and abnormal cellular adhesion they found in biopsy samples is consistent with the (somewhat milder) epithelial pathology and lesions observed in the central and peripheral cornea in the present family.

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OBITUARY

Rocko Fasanella, MD (1916-2009)

Rocko Fasanella, MD, the first full-time chief of ophthalmology at Yale University, has died at age 92 years. His textbook, Complications in Eye Surgery, was required reading in the 1960s and 1970s, and his Fasanella-Servat procedure for minimal ptosis remains a standard operation to this day.

As a native of Trenton, New Jersey, Dr Fasanella assumed he would attend nearby Princeton University, until a Yale representative visited his high school and “the rest is history.” He graduated from Yale College in 1939 and Yale Medical School in 1943. During medical school, he was part of a team that successfully administered penicillin for the first time in the United States. The patient was a young woman dying of septicemia following childbirth, and the irony is that she was the wife of the man who brought Dr Fasanella to Yale.

Following medical school, Dr Fasanella served in the medical corps of the US Army in France during World War II. He then returned to Yale for his ophthalmology residency; in 1951 at the age of 35 years, he was appointed chief of the Section of Ophthalmology, the youngest chief of any section at that time. Dr Fasanella laid a firm foundation for ophthalmology at Yale during his 10-year tenure, not only in his dedication to the finest qualities of our profession but also in the compassion and work ethic that he exemplified in his life.

Dr Fasanella was truly a renaissance man. He spoke several languages, enjoyed opera and other cultural activities, celebrated the culture of Italy, was an enthusiastic fisherman, and took up golf after retirement. He was also a man of deep faith and was devoted to his wife Marion, who predeceased him, and their 6 children and 4 grandchildren.

He was kind, gentle, and humble, as befits a giant of our profession.

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