Anterior Corneal Pathology in Chronic Corneal Edema

We read with interest the recent article by Alomar et al., and would like to congratulate the authors for their detailed description of confocal microscopy observations in corneas with chronic edema and their excellent description of the correlation of these observations to histopathologic findings. We certainly appreciate the vast amount of time that was spent acquiring images of such excellent quality.

In their article, the authors suggested that subepithelial fibroblasts located between the epithelium and Bowman’s layer were “keratocyte-derived cells.” We have also observed by confocal microscopy this reticular network of cells located in the same region, as have other investigators, contrary to the authors’ claim of first publication. This subepithelial fibrosis is the primary reason for increased light scatter in corneas with chronic edema. The authors attempted a morphologic comparison of keratocyte and subepithelial fibroblast nuclei, but they did not convincingly demonstrate that these cells were derived from keratocytes. First, the morphologic size of the nuclei determined from light (or confocal) microscopy cannot conclusively determine the origin or similarity of cell types. Second, the authors attempted to show similarity between the cell types by measuring the average length of the nuclei from a few sagittal histologic sections. This is not an accurate quantitative method, as the authors pointed out in the Discussion, because the histologic sections may not have traversed the maximum length of all nuclei, and the shape of the nuclei was not considered. A more accurate quantitative approach would have been to examine multiple, serial sagittal histologic sections, or better, en face (coronal) histologic sections, to determine the maximum length of individual nuclei. An ideal approach, considering that these corneas were examined by using confocal microscopy, would have been to measure the dimensions and shape of the nuclei in the en face confocal images. This information was available to the authors, but surprisingly, they did not report the data. Confocal microscopy is a valuable quantitative tool that enables examination of the cornea in vivo, while avoiding artifacts created by tissue shrinkage during fixation for histologic examination. With this approach, the authors would have found that the maximum diameter of the nuclei was greater than that estimated by histology, which was predisposed to underestimating the diameter. The authors also did not discuss alternative origins of subepithelial fibroblasts, such as from epithelial cells.

Despite the lack of conclusive evidence of the origin of the subepithelial fibroblasts, it is certainly possible that these cells are derived from keratocytes. The authors alluded to the hypothesis that keratocytes may migrate through Bowman’s layer to transform into subepithelial fibroblasts, and indeed, Iwamoto and DeVoe examined multiple serial sections by electron microscopy and found one stromal cell traversing Bowman’s layer and concluded that this was a rare finding. As the authors found, and our experience supports, subepithelial fibroblasts are present in most corneas with chronic edema, although cells traversing Bowman’s layer are rarely found by light microscopy. In support of keratocytes as the origin of subepithelial fibroblasts, the authors alluded to the hypothesis that anterior keratocytes are depleted in corneas with chronic edema, a finding in a previous histologic validation of confocal microscopy observations (also contrary to the authors’ claim of first publication). Did Alomar et al. examine multiple serial sections by light microscopy to determine whether cells traversed Bowman’s layer and whether the presence of subepithelial fibroblasts was associated with anterior keratocyte depletion? If so, their observations would support this hypothesis.

As the authors discussed, understanding anterior corneal pathology in corneas with chronic edema will be helpful for understanding the long-term clinical outcomes of these eyes after endothelial keratoplasty. The detailed analysis provided by Alomar et al. is an important contribution to this topic.

Sanjay V. Patel
Jay W. McLaren

Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota.
E-mail: patel.sanjay@mayo.edu

References


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Author Response: Anterior Corneal Pathology in Chronic Corneal Edema

We are pleased to respond to the letter written by Drs. Patel and McLaren in relation to our paper correlating in vivo confocal microscopy (IVCM) findings with histologic findings in corneas with chronic edema. We thank them for their generous commendation of our work in their opening sentences. They have essentially raised two issues.

First, they contend that we have made “first claim” to the IVCM demonstration of subepithelial fibrosis. They challenged this by quoting their own work, which is unpublished, and providing another reference. The latter paper was designed to establish the normative database for corneal backscatter analysis by IVCM. They have included one patient, which was not normal, of Fuchs endothelial dystrophy where a reticular network of subepithelial fibrosis was demonstrated. This was a passing reference as it was not the main thrust of the paper. Moreover, the paper was published in August 2011, and our paper was published in September 2011. Clearly, there was