Final Remark

In the interpretation of in vivo ocular surface changes, whether in clinical setting or at higher magnification, a comparison between disturbances caused by various agents is indispensable. Finding common and diverging features is helpful not only in differential diagnostics but also in understanding of the mechanisms behind them. In adenovirus infections, it seems natural to compare the morphology with that due to infections with the two other major viruses causing human epithelial keratitis, HSV and VZV. A comparison, however, is only partly possible. The reason is that in adenovirus infections the route of virus access to the epithelium is external, corresponding to that of primary HSV and VZV infections; the problem is that these primary infections are rare in an adult, and thus the experience with a primary HSV infection captured by the same method is limited to one case [6] and that with VZV is, unfortunately, none. (In retrospective, referring to the only case of primary HSV infection, the initial confusion with adenovirus could have been avoided by paying attention to the early appearance and the composition of epithelial foci, neither of them compatible with adenovirus.) Still, keeping in mind that in recurrent HSV and VZV infections the virus reaches the corneal epithelium via the corneal nerves which results in a focal involvement, some comparison can be made.

The three infections differ in that the in vivo virus CPE is easily discernible in both HSV and VZV but, strangely enough, not so in adenovirus infections. It may be that in the latter, during the acute stage, a sure identification of the virus CPE comparable to that in vitro is hampered by a diffuse epithelial involvement per se also compatible with unspecific oedematous changes.

A feature all three have in common is the presence of rounded/abnormal cells which, as already mentioned (Chap. 1) may represent incipient cell swelling, cells with damaged membranes for other reasons, or invading inflammatory cells; by the present method, these alternatives are indistinguishable from each other. In HSV and VZV keratitisides, such cells are discernible in areas of a previous epithelial involvement after the disappearance of the overlying epithelial disturbance relatable to the virus CPE, and thus it seems reasonable to assume that they represent invading inflammatory ones. Because preceded by overlying changes disturbing their detection, the point of time when they start to appear cannot be determined. In adenovirus infections, the interpretation calls for prudence because in the absence of a preceding epithelial focus of infection there is nothing to relate their locations to, their visibility is undisturbed, and their appearance coincides with the infectious stage of the disease; it is possible but remains to be proven that in adenovirus epithelial keratitis invading inflammatory cells are a very early occurrence.

Connected with this question is another feature common to all the three infections – focal corneal epithelial involvement. In HSV and VZV, it is the first sign of the disease; it is related to the route of infection via the corneal nerves; it clearly shows the virus CPE; and it either disappears with treatment (HSV) or shows typical spontaneous changes (VZV). Nothing like that occurs in adenovirus epithelial infiltrates: they start to appear several days after symptom onset, form against a background of a diffuse epithelial involvement, lack features indicating the virus CPE, have a uniform appearance in which no signs suggestive of ongoing virus infection can be discerned, and persist after the acute stage had subsided. These diverging features
imply that HSV and VZV focal lesions and adenovirus epithelial infiltrates are of different origin. In adenovirus infiltrates, long-term observations of their dynamics in conjunction with comparison with TSPK shed some light on the possible mechanisms behind their development (below).

In all the three infections, as a sequela, subepithelial opacities may develop which later on, without knowledge on the cause, could be attributed to any of them.

The morphology of TSPK lesions highlights why the confusion with adenovirus infections is so common. If two comparable photographs – one showing an adenovirus epithelial infiltrate and the other a typical TSPK lesion – were put in front of you, I wonder if you could tell which is which. I do not think I could. As far as can be discerned, both contain many rounded/abnormal cells, concentrated in a small area and overlain by damaged superficial epithelial cells.

This similarity implies the same type of reaction. In TSPK, the situation is simple: The keratitis appears as if from nowhere and either persists indefinitely or disappears spontaneously only to recur later on or, hopefully, never. This behaviour, and the sensitivity to cortisone, implies an immunologic disorder. (In a way, the course of TSPK reminds of some cases of idiopathic anterior uveitis).

In adenovirus infections, on the other hand, the sequence of events can be followed, from the initial stage during which the presence of living virus on the ocular surface can be proven to the sequelae of the infection. This late stage shows subepithelial infiltrates the disappearance of which with topical steroids, and their reappearance after the treatment is stopped, is a well-known phenomenon that, similarly to TSPK, implies an involvement of immunologic factors. When exactly during the course of the disease they start to operate seems unknown, but tracing back the morphology hints at an early event. The development of epithelial infiltrates in the presence of living virus on the ocular surface does not necessarily indicate that they are the result of a direct virus impact on epithelial cells because there is a distinct possibility of an overlap of two events of which one (relatable to the action of infectious virus) is manifest while the other (relatable to immunologic responses) is starting to show. The sequence of events shows that, with time, the first ceases while the other continues. Indeed, this would explain why the morphology of adenovirus epithelial infiltrates is so dissimilar to focal lesions caused by living viruses (HSV and VZV) but so similar to TSPK. In both diseases, the morphology of the lesions is well compatible with heaping-up of extraneous material (rounded/abnormal cells) mixed with damaged epithelial cells proper. In TSPK, the presence of inflammatory cells has been shown in histological preparations.

In both adenovirus infections and TSPK, the lesions in question are only the tip of the iceberg. With the slit lamp, the in-between areas seem inconspicuous, but they also show rounded/abnormal cells yet without any other associated epithelial disturbance. Probably, these cells are eliminated by transportation towards the surface from which they are shed, and the epithelial architecture is visibly disturbed only in places in which, for some reasons, they are concentrated. That the distribution of the rounded/abnormal cells varies and occasionally shifts towards more diffuse patterns show the “atypical” TSPK cases. (Actually, “atypical TSPK” is a misnomer because doubtfully “punctate,” but unless some other important feature distinguishing it from typical TSPK is found, there is hardly a need for inventing a new terminology.)

Hence, it seems that corneal epithelial infiltrates in adenovirus infections and “coarse” TSPK epithelial lesions are the result of the same reactive process which, however, may be an unspecific one, i.e., provoked by different agents. In adenovirus infections, the virus antigen is the primary suspect; in TSPK, despite all efforts to identify it, the agent remains unknown. It may be that it is not to be found among the known ones, or it has never been there when tested.
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